

Aus der Klinik für Neurochirurgie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Predictors of outcome in neurosurgically treated patients
with spontaneous intracerebral hemorrhage

Einflussfaktoren auf das klinische Ergebnis von
neurochirurgisch behandelten Patienten mit spontaner
intracerebraler Blutung

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Contents

Contents	iii
List of Figures	v
List of Tables	vii
Abbreviations	ix
Abstract	xi
Background	xi
Methods	xi
Results	xi
Conclusions	xii
Abstrakt	xiii
Hintergrund	xiii
Methoden	xiii
Ergebnisse	xiii
Schlußfolgerungen	xiv
1 Introduction	1
1.1 Epidemiology of Spontaneous Intracerebral Hemorrhage	1
1.2 Anticoagulation Management after Spontaneous Intracerebral Hemorrhage	1
1.3 The Role of Surgery for Evacuation of Spontaneous Intracerebral Hemorrhage	3
1.4 Study Aims	4

2	Methods	5
2.1	Study Population and Ethics Approval	5
2.2	Diagnostics and Indication for Surgery	5
2.3	Data Acquisition	7
2.3.1	Sources of Demographic and Clinical Data	7
2.3.2	Prior Anticoagulant Medication and Hemostatic Therapy	8
2.3.3	Imaging Analysis	9
2.4	Outcome Parameters	9
2.5	Preparation of Data and Statistical Analysis	11
3	Results	13
3.1	Patient Characteristics	13
3.2	Anticoagulation and Antiplatelet Therapy	14
3.3	ICH Characteristics	14
3.4	Treatment	17
3.4.1	Preoperative Reversal of Anticoagulation	17
3.4.2	Hematoma Evacuation Efficacy	18
3.4.3	Hematoma Evacuation Efficacy in the Context of MISTIE III	21
3.5	Clinical Outcome	22
3.5.1	Overall Mortality	22
3.5.2	Patient Performance as Assessed by mRS	24
4	Discussion	29
4.1	Patient Characteristics	29
4.2	Perioperative Anticoagulation Management	30
4.3	Hematoma Characteristics	31
4.3.1	Supratentorial Hematoma Characteristics	31

4.3.2	Supratentorial Hematoma Evacuation Efficacy and Minimally Invasive Approach	32
4.3.3	Infratentorial Hematoma Characteristics	33
4.4	Limitations	35
4.5	Conclusion	37
	References	39
	Eidesstattliche Erklärung	55
	Lebenslauf	57
	Danksagung	59
	Bescheinigung statistische Beratung	61

List of Figures

1	3D-reconstruction of hematoma	10
2	CONSORT-diagram of the study	13
3	Hematoma volume and midline shift	18
4	Efficacy of neurosurgical evacuation in homogenous hematoma	19
5	Efficacy of neurosurgical evacuation in diffuse hematoma	20
6	Surgical performance and hospital death	23
7	Supratentorial hematoma volume and mRS	25
8	One-year mRS in supratentorial ICH	26

List of Tables

2	ICD and OPS codes used for identification of patients	6
3	Demographic and baseline characteristics of patients	15
4	Medication of patients	16
5	Treatment results in patients with supratentorial hematoma	21

Abbreviations

3D	3-dimensional
AF	atrial fibrillation
APT	antiplatelet therapy
ASS	acetylsalicylic acid
CAD	coronary artery disease
CBF	cerebral blood flow
CI	confidence interval
CT	computerized tomography
CTA	CT angiography
DALY	disability-adjusted life year
DSA	digital subtraction angiography
DVT	deep venous thrombosis
ED	emergency department
FFP	fresh frozen plasma
FXa	activated factor X
FXa-i	factor Xa-inhibitor
GFR	glomerular filtration rate
ICD	international classification of diseases
ICH	intracerebral hemorrhage
ICP	intracranial pressure
IQR	interquartile range
IVH	intraventricular hemorrhage
MEA	multiple electrode aggregometry

MIS	minimally invasive surgery
MLS	midline shift
NA	information not available, i.e., missing data
NOAC	non-vitamin K oral anticoagulant
OAC	oral anticoagulation
OPS	operations and procedures code
PAE	pulmonary artery embolism
PAOD	peripheral arterial occlusive disease
PCC	prothrombin complex concentrate
RCT	randomised controlled trial
ROTEM	rotational thrombelastometry
TXA	tranexamic acid
VKA	vitamin K antagonist
mRS	modified Rankin scale
nOAC	no oral anticoagulation

Abstract

Background

The role of neurosurgical hematoma evacuation in patients with spontaneous intracerebral hemorrhage (ICH) is still controversial. Patients on anticoagulant medication are a particularly contentious group because of their higher initial risk for spontaneous ICH as well as their potentially increased risk for postoperative hematoma enlargement with subsequent adverse clinical outcome. We investigated whether prior oral anticoagulation had an impact on the surgical result, overall mortality, and functional neurological outcome of the patients. Furthermore, we were interested in how surgical performance influenced patients' outcome.

Methods

We conducted a retrospective cohort study of all patients neurosurgically treated at our University Hospital for the diagnosis of spontaneous ICH from January 2008 to December 2018, as identified systematically from the clinical information system by ICD and OPS codes. History of prior oral anticoagulation, mortality, pre- and postoperative functional neurological status as well as relevant laboratory results were obtained. Preoperative and postoperative CT scans were analyzed regarding hematoma localization and hematoma evacuation efficacy.

Results

We identified 296 patients with pertinent diagnoses and procedures with a median age of 69 years and a slight preponderance of male sex (56%). The ratio of supratentorial to infratentorial hematoma localization was 207 / 81 with no information available

in 8 patients. Perioperative hemostatic management was clinically effective as the patients with prior anticoagulant therapy, who presented with a significantly higher median preoperative hematoma volume, showed similar hematoma evacuation efficacy to patients without anticoagulation in both supra- and infratentorial hemorrhage. Reduction of hematoma volume to ≤ 15 ml or $\leq 30\%$ of preoperative size was achieved in 129 / 176 patients with supratentorial hematoma ≥ 30 ml preoperatively, and associated with a lower in-hospital- as well as one-year mortality, both of which were also inversely correlated with hematoma evacuation efficacy in infratentorial hematoma. Low residual hematoma volume was also predictive of functional neurological status after twelve months in supratentorial hematoma.

Conclusions

Surgical hematoma volume reduction efficacy is associated with improved in-hospital- and one-year survival in both supratentorial as well as infratentorial spontaneous ICH. It also positively affects functional neurological outcome in supratentorial ICH. These results are similar for patients with and without prior oral anticoagulation, and despite higher initial hematoma volumes in patients with anticoagulation, surgical efficacy in them was not reduced. According to our results, patients on oral anticoagulants eligible for neurosurgical hematoma evacuation should not be denied a potentially lifesaving surgical intervention as perioperative hemostaseological management is effective in ensuring a safe surgical procedure.

Abstrakt

Hintergrund

Der Stellenwert neurochirurgischer Hämatomausräumung im Rahmen der Therapie spontaner intrazerebraler Blutungen (IZB) ist nicht abschließend geklärt. Patienten mit oraler Antikoagulation sind eine Risikogruppe, da sie sowohl ein höheres Risiko für das Auftreten einer spontanen IZB als auch ein möglicherweise erhöhtes postoperatives Nachblutungsrisiko haben. Wir untersuchten den Einfluss einer bestehenden Gerinnungshemmung auf chirurgisches Ergebnis, Gesamtmortalität und funktionelles neurologisches Ergebnis der Patienten. Weiterhin stellten wir uns die Frage der Auswirkung des chirurgischen Ergebnisses auf den klinischen Verlauf.

Methoden

Im Rahmen einer retrospektiven Kohortenstudie identifizierten wir anhand der ICD und OPS Codes alle an unserem Universitätsklinikum neurochirurgisch behandelten Patienten mit spontaner IZB von Januar 2008 bis Dezember 2018, erhoben die entsprechenden klinischen Daten, insbesondere bestehende orale Antikoagulation, Mortalität sowie prä- und postoperativen funktionellen neurologischen Status. Hämatomlokalisierung und chirurgische Hämatomreduktion wurden mittels prä- und postoperativer CT-Untersuchungen ausgewertet.

Ergebnisse

Wir identifizierten 296 Patienten mit einem medianen Alter von 69 Jahren und leicht überwiegendem männlichem Anteil (56%). Das Verhältnis von supra- zu infratentorieller Hämatomlokalisierung war 207 / 81 , bei 8 Patienten fehlte diese Information.

Das perioperative Gerinnungsmanagement war klinisch effektiv, da eine bestehende orale Antikoagulation zwar mit einem signifikant höheren medianen präoperativen, nicht jedoch postoperativem Hämatomvolumen korrelierte. Die Reduktion des präoperativen Hämatomvolumens von ≥ 30 auf ≤ 15 ml oder $\leq 30\%$ des präoperativen Volumens wurde in 129 / 176 Patienten mit supratentorieller spontaner IZB erreicht und korrelierte mit einer geringeren Krankenhaus- und 12-Monats-Sterblichkeit und einem besseren funktionellen neurologischen Ergebnis. Bei infratentoriellen Blutungen zeigte sich eine inverse Korrelation zwischen der Effektivität der chirurgischen Hämatomausräumung und der Krankenhaus- sowie der Einjahresmortalität.

Schlußfolgerungen

Das Ausmass der chirurgischen Hämatomreduktion geht sowohl bei supratentoriellen wie infratentoriellen IZB mit einem verbesserten Überleben während des Krankenhausaufenthaltes als auch nach einem Jahr einher. Es hat darüber hinaus bei supratentoriellen Blutungen einen positiven Einfluss auf das funktionelle neurologische Ergebnis. Das gilt in gleicher Weise für Patienten mit oder ohne bestehende orale Antikoagulation, deren chirurgische Ergebnisse sich trotz unterschiedlicher präoperativer Hämatomvolumina nicht unterschieden. Aufgrund unserer Ergebnisse sollte Patienten mit oraler Antikoagulation, die für eine neurochirurgische Intervention qualifizieren, ein potentiell lebensrettender chirurgischer Eingriff nicht verwehrt werden, da das perioperative hämostaseologische Management eine sichere Operation gewährleisten kann.

1 Introduction

1.1 Epidemiology of Spontaneous Intracerebral Hemorrhage

Hemorrhagic stroke caused by spontaneous intracerebral hemorrhage (ICH) accounts for 10 – 15% of strokes in developed countries and is the subtype of stroke with the highest burden in terms of deaths and disability-adjusted life years (DALYs) worldwide^{1,2}.

Brain damage in ICH can be divided conceptually into primary injury, which occurs rapidly and is mainly the result of a mass effect, and secondary injury, which is caused by a multifactorial cascade of pathophysiological processes that are related to hematoma degradation, oxidative stress, and subsequently developing perihematomal edema. Hematoma and edema lead to an increase in intracranial volume and, due to the confinement within the skull, to an increase in intracranial pressure (ICP) with the risk of life-threatening brain herniation. Even if herniation does not occur, increased ICP can result in a critical reduction of cerebral blood flow (CBF) below the level required for cellular survival. Consequently, although the volume of the hematoma was previously identified as one of the most important predictors of survival in ICH³⁻⁶, secondary brain injury from the toxic effects of blood degradation⁷, hypermetabolism⁸, oxidative stress⁹ and spreading depolarization¹⁰, among others, poses an additional life-threatening risk that may perhaps be reduced by surgical hematoma evacuation.

1.2 Anticoagulation Management after Spontaneous Intracerebral Hemorrhage

Among the main risk factors for ICH are advanced age, male sex, high blood pressure, drug use, excessive alcohol consumption, as well as dietary and genetic factors. As these risk factors also predispose for other cardiovascular diseases, a relevant subset

of the patients presenting with ICH have received oral anticoagulant treatment (OAC) and/ or antiplatelet therapy (APT). In this setting, spontaneous ICH represents a well-recognized and potentially fatal complication. Although non-vitamin K oral anticoagulants (NOACs) may have a reduced risk of severe bleeding if compared to vitamin K antagonists (VKAs)¹¹⁻¹³, once ICH occurs, hematoma characteristics are similar and ICH remains a life-threatening event. In retrospective analyses, both VKAs and NOACs have been reported to be associated with a higher risk of hematoma expansion, higher mortality and worse functional outcome compared to patients without prior oral anticoagulant medication (nOAC patients)^{14,15}. Moreover, there appears to be an additional detrimental effect of APT in patients receiving VKAs¹⁶.

As initial hematoma volume and hematoma growth are powerful predictors of clinical outcome³⁻⁶, prevention of hematoma growth by aggressive blood pressure management and quick restoration of normal hemostasis are considered to be main pillars in the management of ICH patients^{14,17}. While administration of prothrombin complex concentrate (PCC) in patients with VKA intake and administration of idarucizumab for dabigatran-associated hemorrhage are recommended^{18,19}, the appropriate hemostatic management of activated factor X (FXa)-inhibitors is still under discussion, as the use of PCC in these patients is gradually being replaced by andexanet alfa, which has been approved for apixaban and rivaroxaban reversal by the European Medicines Agency (EMA) as of April 2019. Given the decades of difference in clinical experience between VKA and NOAC treatment, there is an urgent need to collect further data on the clinical management and safety profile of NOAC-related ICH, particularly in the context of surgical hematoma evacuation and perioperative hemostatic management.

1.3 The Role of Surgery for Evacuation of Spontaneous Intracerebral Hemorrhage

Despite a number of randomized controlled trials (RCTs), the general role of surgical intervention for ICH still remains controversial. Largely, this is due to the fact that the randomized STICH trials^{20,21} failed to show a benefit of early surgical intervention but, on the other hand, a large meta-analysis that also included data from STICH I suggested a significant benefit for surgery over medical management for patients who had early surgery, hematoma volumes between 20 and 50 ml, a Glasgow coma scale (GCS) score between 9 and 12 and were aged between 50 and 69 years²². One possible explanation for this discrepancy compared to the RCT results from STICH I and STICH II could be the relevant crossover of patients from conservative treatment to delayed surgery, e.g. 21% in the STICH II trial²¹. On the other hand, the results from the meta-analysis²² indicate that patient selection in previous RCTs might not have been ideal, and they show that it remains a critical factor to reliably identify only those patients as surgical candidates that have the greatest potential to benefit from the procedure. Next to the factors mentioned above, this also includes the development and utilization of less invasive (minimally invasive, MIS) surgical approaches²³, which could help limit the collateral tissue damage when approaching deep but also superficial lesions²⁴ and benefit long-term functional outcome and survival²⁵.

Another important factor that may influence outcome and that is naturally affected by anticoagulation management seems to be the effectiveness of the surgical hematoma evacuation, in other words the surgical performance²⁶. In the context of anticoagulation management, this surgical performance can be negatively affected by an intraoperative difficulty of hemostasis or by postoperative hematoma (re)enlargement, which has been reported to occur particularly in patients with OAC-associated ICH²⁷

and likely contributes to unfavorable clinical outcome²⁸.

1.4 Study Aims

In order to

- a) systematically characterize the common practice of perioperative anticoagulation management in patients undergoing surgery for ICH evacuation in a large university hospital, and
- b) determine the effect of perioperative anticoagulation management on surgical performance and clinical outcome,

we performed a retrospective, single-center cohort study of all ICH patients that underwent microsurgical hematoma evacuation in our department.

2 Methods

2.1 Study Population and Ethics Approval

This study included all consecutive patients that underwent surgery for evacuation of spontaneous supra- or infratentorial ICH at the Department of Neurosurgery at the Charité Universitätsmedizin Berlin in Berlin, Germany, from January 2008 to December 2018. Patients were admitted through the emergency department (ED) or by external referral to our neuro-intensive care unit and retrospectively identified by searching the clinical patient information system for ICD-10 codes I61.0 through I61.9, and I62.9²⁹ and procedure codes OPS 5-010.00 through 5-010.0x , 5-013.40, and 5-013.4x³⁰ in order to identify combinations of diseases and procedures pertinent to the problem as shown in Table 2.

The study was conducted in accordance with the declaration of Helsinki and approved by the local Ethics Committee of the Charité-Universitätsmedizin Berlin (approval number: EA1/156/14). Informed consent was waived due to the retrospective nature of the study and anonymization of the data at the source before analysis, according to the requirements determined by the Ethics Committee.

2.2 Diagnostics and Indication for Surgery

All patients received non contrast computerized tomography (CT) and CT angiography (CTA) at the time point of admission. In cases of external referrals, the initial CT and occasionally the CTA were performed at the referring institution and additional imaging was obtained upon arrival in our department as needed. In patients under the age of 60 and/ or with atypical hematoma localization (i.e., lobar or primarily intraventricular), a digital subtraction angiography (DSA) was performed to rule out a

Table 2: ICD and OPS codes used for identification of patients

ICD codes	
I61.0	Intrazerebrale Blutung in die Großhirnhemisphäre, subkortikal
I61.1	Intrazerebrale Blutung in die Großhirnhemisphäre, kortikal
I61.2	Intrazerebrale Blutung in die Großhirnhemisphäre, nicht näher bezeichnet
I61.3	Intrazerebrale Blutung in den Hirnstamm
I61.4	Intrazerebrale Blutung in das Kleinhirn
I61.5	Intrazerebrale intraventrikuläre Blutung
I61.6	Intrazerebrale Blutung an mehreren Lokalisationen
I61.8	Sonstige intrazerebrale Blutung
I61.9	Intrazerebrale Blutung, nicht näher bezeichnet
I62.9	Intrakranielle Blutung (nichttraumatisch), nicht näher bezeichnet
OPS codes	
5-010	Schädeleröffnung über die Kalotte
5-010.00	Kraniotomie, Kalotte
5-010.01	Kraniotomie, Kalotte über die Mittellinie
5-010.02	Kraniotomie, bifrontal
5-010.03	Kraniotomie, temporal
5-010.04	Kraniotomie, subokzipital
5-010.0X	Kraniotomie, sonstige
5-013.4	Entleerung eines intrazerebralen Hämatoms
5-013.40	Entleerung eines intrazerebralen Hämatoms, offen chirurgisch
5-013.4X	Entleerung eines intrazerebralen Hämatoms, sonstige

structural vascular pathology (i.e., aneurysm, arteriovenous malformation or dural arterial-venous fistula) as the cause of hemorrhage.

As outlined in 1.3, the indication for surgery and general patient management was based on institutional and international guidelines that were pertinent during the period when the patients of the study were treated³¹⁻³³. Briefly, supratentorial microsurgical hematoma evacuation was considered if patients had a premonitory modified Rankin scale (mRS) grade ≤ 1 , a GCS score between 5 and 14, a hematoma volume between 20 and 90 ml, a superficial (lobar) hematoma localization and if possible, surgery within 72 hours of the hemorrhage. For infratentorial ICH, the indication for surgery was based on a GCS score below 15 or a subsequent reduction of >2 points of the GCS score in addition to the presence of a space-occupying hematoma in the posterior fossa with compression of the fourth ventricle and/ or brainstem with or without hydrocephalus. Patients with mesencephalic, thalamic, brainstem or mainly intraventricular hemorrhages (IVHs) were generally not considered suitable for microsurgical hematoma evacuation. Importantly, the use of OAC or APT did not affect the indication for surgery. All treatment decisions were made within a multidisciplinary context that involved the treating physicians (neurosurgeons, neurologists, neuro-interventionalists and neuro-intensivists) as well as the patient and next of kin or caregiver.

2.3 Data Acquisition

2.3.1 Sources of Demographic and Clinical Data

Information on diagnostic ICD and OPS codes were obtained from the clinical information system (i.s.h.med/IS-H, Cerner Corporation, North Kansas City, USA; SAP AG, Walldorf, Germany). Data on demographics, medical history, admission status,

indication for oral anticoagulation, type of oral anticoagulation as well as perioperative hemostatic management and laboratory results were obtained from the clinical records and patient data management systems (COPRA, COPRA System GmbH, Berlin, Germany, and MedVision, MedVision AG, Unna, Germany).

2.3.2 Prior Anticoagulant Medication and Hemostatic Therapy

We studied patient records for information on medication with VKAs or NOACs, the latter being further specified as being either a direct thrombin-inhibitor (dabigatran) or a FXa-inhibitor (FXa-i, i.e., apixaban, edoxaban, and rivaroxaban), and we determined the underlying medical condition [deep venous thrombosis (DVT), pulmonary artery embolism (PAE), atrial fibrillation (AF)] requiring OAC. Furthermore, data were collected regarding APT with acetylsalicylic acid (ASS) and/ or clopidogrel as well as the indication for APT [coronary artery disease (CAD) or peripheral arterial occlusive disease (PAOD)].

Data on hemostatic management were extracted from ED and anesthesiological protocols and included administration of prothrombin complex concentrate (PCC), fresh frozen plasma (FFP), tranexamic acid (TXA), vitamin K, fibrinogen, platelet concentrates, and desmopressin. The effectiveness of hemostatic treatment was evaluated using prothrombin time (PT/ INR) and activated partial thromboplastin time (aPTT) recorded at the time point of admission compared to PT/ INR and aPTT at the closest time point documented before the neurosurgical intervention. If needed and logistically available, anti-FXa activity was determined and platelet function was additionally quantified by the *in vitro* bleeding time (determined by PFA-100), multiple electrode aggregometry (MEA), and/ or rotational thrombelastometry (ROTEM).

To assess the risk of prolonged drug activity due to impaired renal function, the

glomerular filtration rate (GFR, Cockcroft-Gold formula) was determined in all patients.

2.3.3 Imaging Analysis

Non-contrast-enhanced CT scans obtained before surgery and within 24 hours after surgical intervention were retrospectively analyzed regarding the hematoma volume, localization, the degree of midline shift (MLS), the presence of intraventricular hemorrhage, and involvement of the basal cisterns. In the case of postoperative clinical deterioration or a refractory increase in ICP, CT imaging was performed immediately.

As shown in Figure 1, volumetric analysis was performed by manual, 3-dimensional (3D) hematoma segmentation according to the visually identifiable, hyperdense hematoma in the transverse, sagittal, and coronal CT imaging planes using the SmartBrush Tool of iPlan cranial image guidance software (iPlan cranial, Version 3.0, Brainlab AG, Munich, Germany).

Using the same image guidance software, MLS was measured in the transverse plane as the maximal perpendicular distance (in mm) between the septum pellucidum at the level of the foramen of Monro and a line drawn along the fronto-occipital midline of the skull.

2.4 Outcome Parameters

Primary outcome was defined as mortality during the initial period of hospitalization and functional clinical outcome (including mortality) after one year, as determined by the mRS grade³⁴. In studies on cerebral stroke, the mRS is a widely applied, validated tool to evaluate functional independence in activities of daily life, categorizing impairment from no (mRS grade 0) to severe disability in bedridden patients with constant need of nursing care (mRS grade 5) on an ordinal scale. The cutoff between an mRS

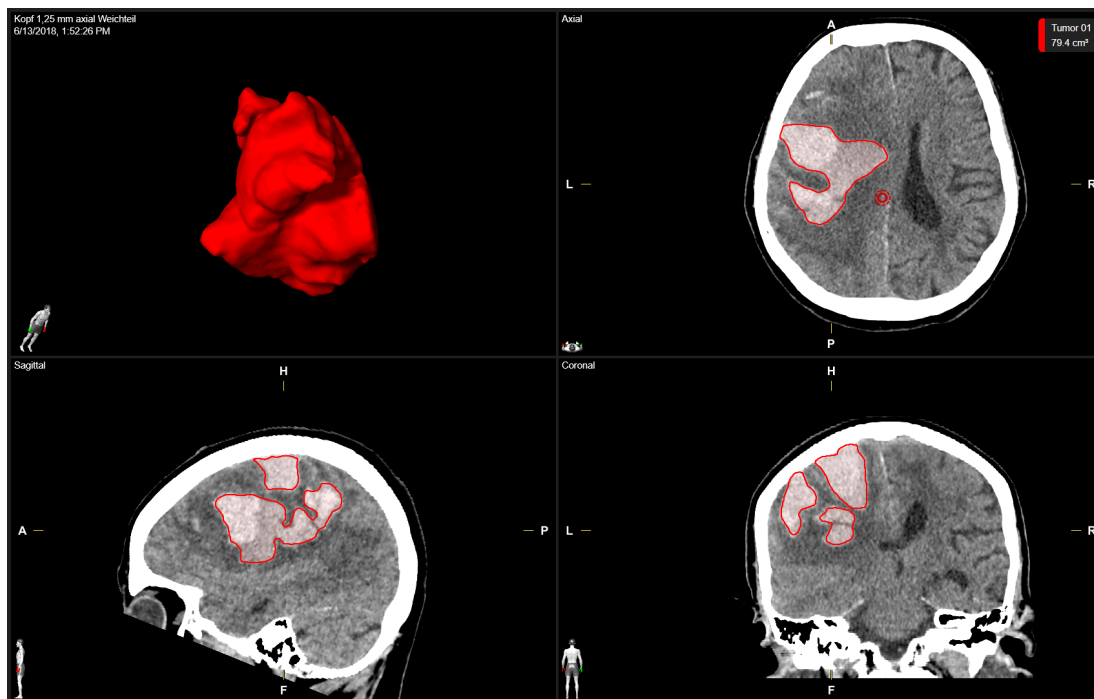


Figure 1: CT scan of the preoperative segmentation of a supratentorial hematoma in the right frontal and parietal lobes in the transverse (upper right), sagittal (lower left), and coronal (lower right) planes for 3D reconstruction and automatic calculation of the hematoma volume using iPlan cranial image guidance software.

grade ≤ 3 and > 3 distinguishes patients that are able to ambulate independently (mRS ≤ 3) from those that require assistance for ambulation (mRS > 3). The cutoff between an mRS grade ≤ 2 and > 2 is typically considered as a threshold to distinguish between favorable (≤ 2) and unfavorable (> 2) outcome. Mortality is defined as an mRS grade 6. In a meta-analysis the mRS grade was found to have a good interobserver and test-retest reliability, rendering it a suitable instrument to compare pre- and post-stroke conditions³⁵. In the present study, the mRS grade was determined by telephone interview with the patient or caregiver according to our institutional practice.

2.5 Preparation of Data and Statistical Analysis

Although not completely applicable to our retrospective design, we adapted the CONSORT-guidelines³⁶ to include a graphical representation describing patient inclusion (Fig. 2).

All data were assumed to be non-normally distributed and described as median, interquartile range (IQR) and number of subjects for whom information was not available (NA). For direct comparisons between groups regarding continuous variables bootstrapped 95% confidence intervals (95%-CI) of the median for estimation of significant differences were calculated³⁷. In the case of non-overlapping CIs of numerical data, subsequent statistical testing was done using Student's t-test after assuring the homogeneity of variances by Levene's test, while for ordinal variables the Wilcoxon signed-rank test was applied. If CIs for differences of proportions did not include 0, they were compared formally using Fisher's exact test. Correlation between a continuous and dichotomous variable was calculated using point-biserial correlation. All statistical tests were performed with an α of 5% as the cutoff value for statistical significance.

Statistical analysis was performed using R version 4.2.2 Patched (2022-11-10 r83330)³⁸, with the packages DescTools, dplyr, ggplot2, grid, gridExtra, gtable, kableExtra, lattice, latticeExtra, magrittr, plyr, rmarkdown, and tidyverse.

3 Results

3.1 Patient Characteristics

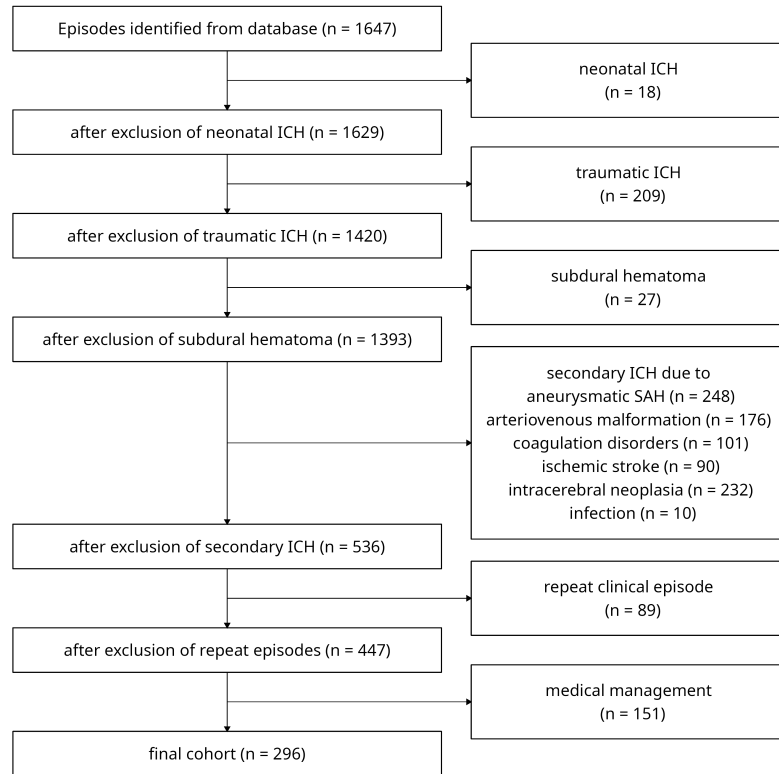


Figure 2: CONSORT-diagram of the study

Using the filtering criteria described above and summarized in Table 2 we identified a total number of 1,647 clinical episodes (observations) between January 2008 and December 2018. Of these, 227 were excluded due to ICH in neonates with perinatal intracerebral hemorrhage or due to traumatic ICH etiology. Another 27 episodes were excluded due to a leading diagnosis of subdural hematoma. Of the remaining 1,393 observations, 857 were secondary hemorrhages due to aneurysmatic subarachnoid hemorrhage (248), cerebral arteriovenous malformations (176), coagulation disorders from either preexisting disease, e.g., hematological malignancy, HELLP-syndrome, or therapeutic intervention, e.g., systemic lysis, extracorporeal circulation (101), and preex-

isting ischemic- (90), neoplastic- (232), or infectious lesions (10). Of the remaining 536 observations, 89 were excluded because they were linked to a prior intervention, such as cranioplasty after decompressive craniectomy. Of the remaining 447 observations, 151 were excluded due to medical management alone, resulting in a final sample of $n = 296$ [165 male, 131 female, median age 69 years (IQR 57 – 75), see Fig. 2 and Tab. 3].

3.2 Anticoagulation and Antiplatelet Therapy

Out of 296 patients that underwent microsurgical evacuation of spontaneous ICH, 86 patients (29%) received anticoagulation and 194 (66%) did not. In 16 patients (5%) information on prior anticoagulation was unavailable. nOAC patients tended to be younger (median: 66.5 years, IQR 55 – 74) than the patients receiving either VKAs (median: 71 years, IQR 64.5 – 77) or NOACs (median: 79 years, IQR 75 – 84). As the main medical co-morbidity requiring OAC, 67% and 94% of patients receiving VKA or NOAC suffered from AF, respectively.

27 patients (9%) received both OAC and APT, while 58 patients (20%) received only APT. Further information regarding prior pharmacotherapy is presented in Table 4.

3.3 ICH Characteristics

The hematoma localization was supratentorial in 207 patients (70%) and infratentorial in 81 patients (27%). In 8 patients (3%), no imaging was available. The median preoperative hematoma volume in patients with supratentorial hematoma localization was 62.1 ml (IQR 43.2 – 81.0) and did not differ between male and female patients (male: median 63.2 ml, 95%-CI 52.1 – 69.2; female: median 58.9 ml, 95%-CI 50.6 – 66.2, see Fig. 3). Higher preoperative supratentorial hematoma volumes were noted in patients who received OAC (OAC: median 77.1 ml, 95%-CI 70.0 – 89.7; nOAC: median 58.8 ml,

Table 3: Demographic and baseline characteristics of patients

Age		
years (median, range)	69	(2-87)
Sex		
male	165	(56%)
female	131	(44%)
Preexisting medical conditions		
hypertension	192	(65%, NA = 5)
coronary artery disease	37	(12%, NA = 6)
atrial fibrillation	64	(22%, NA = 5)
DVT	11	(4%, NA = 5)
PAD	14	(5%, NA = 9)
Premorbid mRS grade		
mRS 0	17	(6%)
mRS 1	128	(43%)
mRS 2	24	(8%)
mRS 3	14	(5%)
mRS 4	24	(8%)
mRS 5	5	(2%)
mRS not done	84	(28%)
GCS score at admission		
GCS 3 - 8	83	(28%)
GCS 9 - 12	74	(25%)
GCS 13 - 15	105	(35%)
GCS not done	34	(11%)
Hematoma		
Basal ganglia	83	(28%)
Basal ganglia and hemispheres	111	(38%)
Hemispheres	13	(4%)
Cerebellum	78	(26%)
Cerebellum and brain stem	2	(1%)
Brain stem	1	(0%)
No imaging available	8	(3%)
Sys. BP at admission		
mmHg (median, range)	176	(60-290, NA = 133)

Table 4: Medication of patients

Antihypertensive drugs		
RAAS-inhibitor mono	27	(9%)
beta-blocker mono	10	(3%)
calcium channel blocker mono	4	(1%)
diuretic mono	5	(2%)
combination therapy	83	(28%)
no antihypertensive drugs	106	(36%)
no available information	61	(21%)
Lipid-lowering therapy		
lipid-lowering drugs	50	(17%)
no lipid-lowering drugs	206	(70%)
no available information	40	(14%)
Anticoagulation		
Coumarin	60	(20%)
median INR (IQR, range)	2.4	(1.5 - 3.1, 1.1 - 7.4, NA = 33)
NOAC	16	(5%)
Rivaroxaban	9	(3%)
Apixaban	5	(2%)
Edoxaban	2	(1%)
Heparin	10	(3%)
No anticoagulation	194	(66%)
Anticoagulation unknown	16	(5%)
Platelet inhibition		
ASS mono	75	(25%)
P2Y12 receptor antagonists mono	4	(1%)
Dual inhibition	7	(2%)
No inhibition	194	(66%)
Platelet inhibition unknown	16	(5%)

95%-CI 54.2 – 63.7, $p = 0.006$). There was no apparent difference in supratentorial hematoma volume between VKA and NOAC patients (VKA: median 76.1 ml, 95%-CI 68.4 – 91.5; NOAC: median 81.2 ml, 95%-CI 47.6 – 122.4). Similarly, APT additional to OAC did not lead to an increased hematoma volume in supratentorial ICH (OAC and APT: median 80.1 ml, 95%-CI 68.1 – 108.6; OAC without APT: median 63.2 ml, 95%-CI 45.9 – 72.4, $p = 0.2$, formal statistical testing performed as an exception because of the seemingly large difference between medians and only a small overlap of 95%-CIs). Comparison of nOAC patients with or without APT also did not reveal any apparent differences in supratentorial hematoma volume (APT: median 63.2 ml, 95%-CI 45.9 – 72.4; no APT: median 56.0 ml, 95%-CI 48.9 – 60.1). Despite differences in overall hematoma volume, no difference was noted in the degree of preoperative midline shift between OAC and nOAC groups (OAC: median 7.4 mm, 95%-CI 6.5 – 9.7; nOAC: median 6.1 mm, 95%-CI 5.3 – 6.6), see Figure 3. Also, no difference in hematoma volume was noted between OAC and nOAC groups in patients with infratentorial hematoma localization (OAC: median 19.7 ml, 95%-CI 15.4 – 23.6; nOAC: median 19.4 ml, 95%-CI 16.5 – 24.0). The same was true for the comparison between OAC with or without additional APT (OAC and APT: median 16.9 ml, 95%-CI -8.3 – 18.9; OAC without APT: median 20.0 ml, 95%-CI 16.9 – 28.2) as well as the comparison of nOAC patients with or without APT (APT: median 20.0 ml, 95%-CI 16.9 – 28.2; no APT: median 19.1 ml, 95%-CI 15.9 – 23.5).

3.4 Treatment

3.4.1 Preoperative Reversal of Anticoagulation

Patients on VKAs received PCC (PCC, 32 / 60, 53%), FFPs (FFP, 2 / 60, 3%), or both (15 / 60, 25%). In patients with VKAs that did not receive preoperative hemostatic

Supratentorial hematoma characteristics

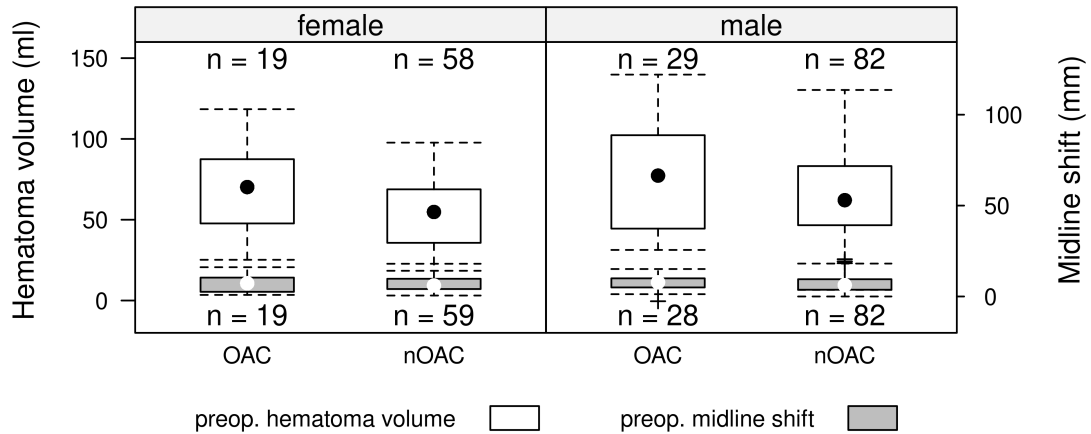


Figure 3: Dependence of supratentorial hematoma volume and midline shift on OAC and sex. As detailed in 3.3, higher preoperative hematoma volume is associated with oral anticoagulation but not with patient sex whereas midline shift is independent of either. Boxplots show median (dot), IQR (boxes) and extremes (whiskers) of preoperative supratentorial hematoma volume (upper row) and midline shift (lower row). Differences in subject numbers are due to missing information in single cases.

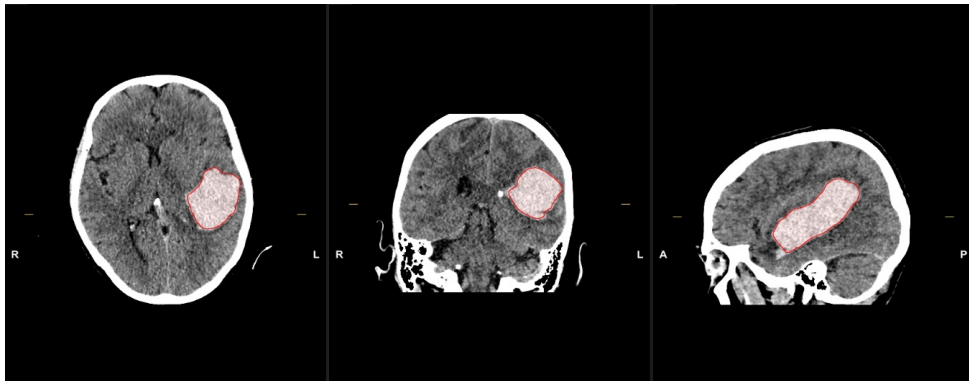
treatment (11 / 60, 18%) a maximum INR on admission of 1.3 (median: 1.1, IQR: 1.1 – 1.2) was noted. Overall, hemostatic treatment resulted in a drop in median INR from 2.4 (IQR 1.5 – 3.1, NA = 33) on admission to 1.2 (IQR 1.1 – 1.6, NA = 16) preoperatively. In 6 patients, neither admission nor preoperative INR was recorded. In patients with NOACs, hemostatic treatment was attempted in 15 / 16 (94%) patients, either with PCC alone (12 / 16, 75%), or in combination with FFPs (3 / 16, 19%).

3.4.2 Hematoma Evacuation Efficacy

Examples of supratentorial hematoma evacuation efficacy are shown in Figures 4 and 5 for homogenous and diffuse ICH, respectively.

Compared to the preoperative hematoma volumes described in 3.3, the median post-operative hematoma volume in patients with supratentorial ICH was 6.8 ml (IQR 2.9 –

A



B

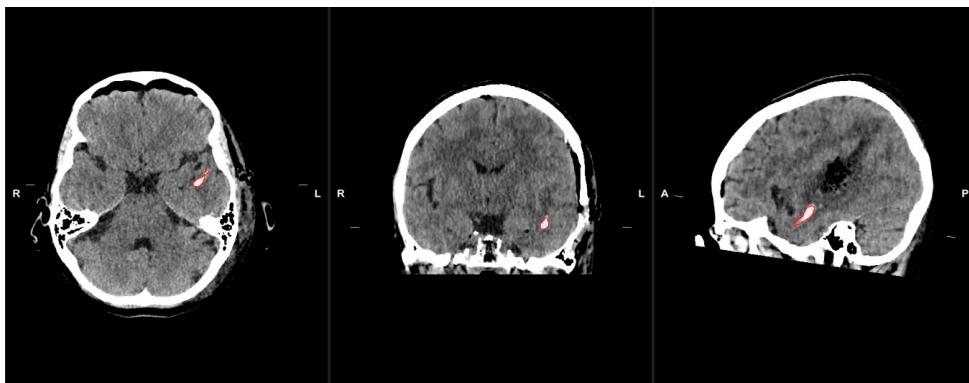
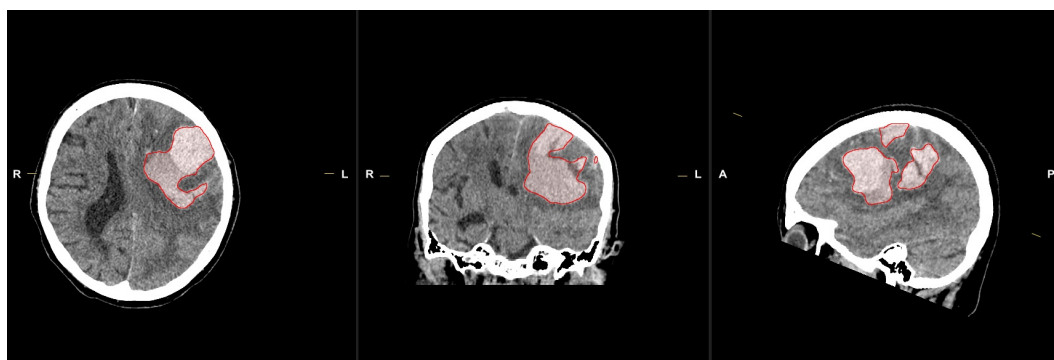


Figure 4: Efficacy of neurosurgical hematoma evacuation shown by comparison of preoperative (A) to postoperative (B) images in a case of homogenous ICH distribution. From left to right, the images depict transverse, coronal and sagittal CT images through the main axis of the hematoma. Hematoma segmentation, as described in the methods section (2.3.3), is illustrated by the area outlined and shaded in red. In the postoperative images, near complete removal can be noted.

19.8) and 2.5 ml (IQR 1.2 – 7.3) in patients with infratentorial ICH, corresponding to relative reductions of 87% (IQR 68 – 94) and 85% (IQR 68 – 93) from pre- to postoperatively in supra- and infratentorial ICH, respectively. There was no difference in postoperative hematoma volume between OAC and nOAC patients in either supratentorial (OAC: median 10.3 ml, 95%-CI -0.5 – 14.7, nOAC: median 6.4 ml, 95%-CI 3.7 – 7.8) or infratentorial ICH (OAC: median 2.8 ml, 95%-CI -2.4 – 4.2, nOAC: median 2.2 ml, 95%-CI 0.7 – 3.1) or between patients receiving VKA or NOACs (supratentorial VKA: median 7.8 ml, 95%-CI -2.0 – 10.6, supratentorial NOAC: median 19.1 ml, 95%-CI -11.1 – 32.9), see also Table 5; (infratentorial VKA: median 7.8 ml, 95%-CI -2.0 – 6.7, infratentorial NOAC: median 1.9 ml, 95%-CI -36.1 – 2.6) .

A



B

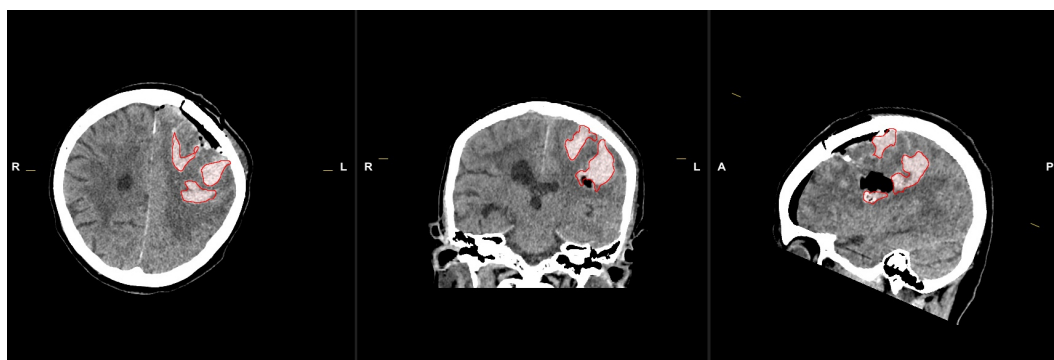


Figure 5: Efficacy of neurosurgical hematoma evacuation shown by comparison of preoperative (A) to postoperative (B) images in a case of diffuse ICH distribution. From left to right, the images depict transverse, coronal, and sagittal CT images through the main axis of the hematoma. Hematoma segmentation, as described in the methods section (2.3.3), is illustrated by the area outlined and shaded in red.

Table 5: Treatment results in patients with supratentorial hematoma

no anticoagulation		
preoperative hematoma volume (median, IQR)	58.8 ml	(42.9 – 77.1)
postoperative hematoma volume (median, IQR)	6.4 ml	(2.9 – 17.6)
relative reduction of hematoma volume (median, IQR)	87.6%	(69.6 – 94.0)
VKAs		
preoperative hematoma volume (median, IQR)	76.1 ml	(44.5 – 92.1)
postoperative hematoma volume (median, IQR)	7.8 ml	(2.3 – 26.6)
relative reduction of hematoma volume (median, IQR)	89.4%	(63.1 – 95.2)
NOACs		
preoperative hematoma volume (median, IQR)	81.2 ml	(40.1 – 92.0)
postoperative hematoma volume (median, IQR)	19.1 ml	(5.3 – 47.0)
relative reduction of hematoma volume (median, IQR)	70.9%	(52.0 – 90.9)

3.4.3 Hematoma Evacuation Efficacy in the Context of MISTIE III

For an additional perspective, in a next step we retrospectively applied the inclusion criterion of the minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III) trial regarding the required preoperative hematoma volume of ≥ 30 ml to our cohort and identified 176 / 207 patients (85%) with supratentorial ICH that matched the criterion. The aim of the original protocol to reduce hematoma volume to ≤ 15 ml²⁴ was reached in 111 / 176 (63%) patients. The revised surgical performance criterion (reduction of hematoma volume to ≤ 15 ml or $\leq 30\%$ of preoperative size)²⁶ was achieved in 129 / 176 (73%) of patients. Regarding prior anticoagulation, there was no difference in the proportions of patients in whom the revised surgical performance criteria were reached (OAC: 33 / 50, 66%; non-OAC: 110 / 143, 77%, 95%-CI -0.13 – 0.07).

3.5 Clinical Outcome

3.5.1 Overall Mortality

During the initial hospitalization period, 70 / 294 patients (24%) died. In 2 patients, no information on initial mortality was available. During the following 12 months, the death of an additional 28 patients was noted. In 79 patients, information on clinical outcome was not available. Thus, the overall mortality at one year was determined with 98 / 217 patients (45%).

Mortality rates according to hematoma localization were 51 / 206 (25%, NA = 1) initially and 70 / 156 (45%, NA = 51) after one year for supratentorial ICH, and 18 / 81 (22%, NA = 0) initially and 28 / 57 (49%, NA = 24) after one year for infratentorial ICH.

Mortality rates according to the use of OAC were 25 / 76 (33%, NA = 2) initially and 35 / 59 (59%, NA = 17) after one year for OAC-related ICH, and 37 / 192 (19%, NA = 0, 95%-CI 0.01 – 0.30, p = 0.02) initially and 54 / 141 (38%, NA = 53, 95%-CI 0.04 – 0.31, p = 0.008) after one year for non-OAC-related ICH.

In patients with supratentorial hematoma localization, mortality during the initial hospitalization was significantly lower if the hematoma volume was successfully reduced to ≤ 15 ml or $< 30\%$ of the preoperative volume [low residual volume: 22 / 128 (17%); high residual volume: 24 / 47 (51%), NA = 31, 95%-CI -0.52 – -0.17, p < 0.0001]. This beneficial performance-related effect on mortality remained notable at one year [low residual volume: 36 / 97 (37%); high residual volume: 28 / 37 (76%, NA = 22, 95%-CI -0.47 – -0.15, p < 0.0001)]. In contrast to surgical performance, the use of OAC did not affect survival: In patients with supratentorial hematoma localization, initial mortality rates were 17 / 50 for OAC-related ICH (34%) and 30 / 142 for non-OAC-related ICH (21%, NA = 0, 95%-CI -0.03 – 0.30). After one year, mortality rates were 23 / 39 for

Surgical efficacy and early survival

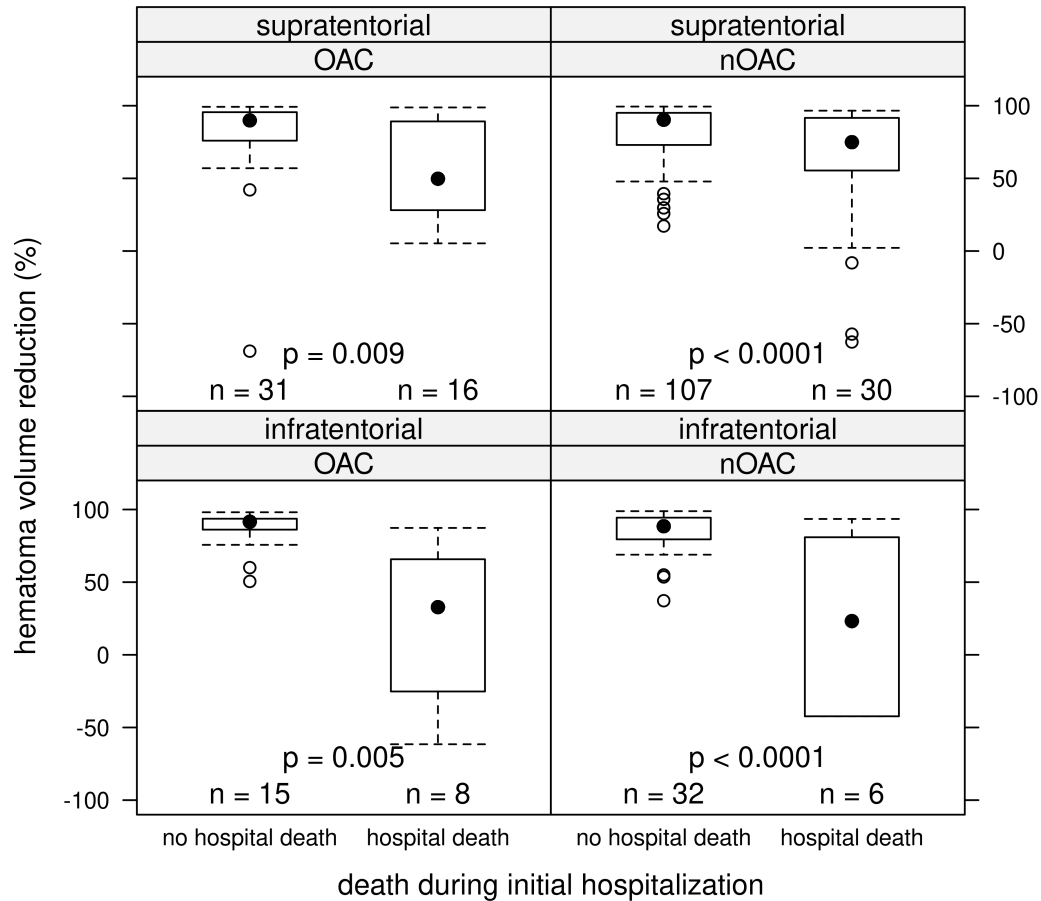


Figure 6: Death during initial hospitalization as a function of percentage of hematoma volume reduction (negative percentages indicating increased hematoma volume post-operatively) and stratified according to ICH localization (supra- vs. infratentorial) and oral anticoagulation (OAC vs. nOAC). Black circles indicate medians, boxes IQRs, whiskers extremes, and white circles outliers removed more than 1.5 x IQR from the lower quartile. Infratentorial ICH: OAC patients $r_{pb} = -3.13$, 95%-CI -0.79 - -0.20, $p = 0.005$, nOAC patients $r_{pb} = -4.40$, 95%-CI -0.77 - -0.34, $p < 0.0001$; supratentorial ICH: OAC patients $r_{pb} = -2.72$, 95%-CI -0.60 - -0.10, $p = 0.009$, nOAC patients $r_{pb} = -4.29$, 95%-CI -0.49 - -0.19, $p < 0.0001$.

OAC-related ICH (59%) and 42 / 107 for non-OAC-related ICH (39%, NA = 46, 95%-CI -0.003 – 0.32).

In 61 patients with infratentorial hematoma, localization information on mortality was available. Here, initial mortality correlated inversely with the percentage of hematoma volume reduction ($r_{pb} = -0.58$, 95%-CI -0.73 – -0.39, $p < 0.0001$, see Fig. 6), indicating a beneficial, performance-related effect of hematoma evacuation on survival, similar to patients with supratentorial ICH. Likewise, this performance-related effect remained notable at one year after ICH ($n = 45$, $r_{pb} = -0.35$, 95%-CI -0.58 – -0.06, $p = 0.02$). In contrast to surgical performance and also similarly to supratentorial localization, prior OAC did not relevantly affect survival: In patients with infratentorial hematoma localization, initial mortality rates were 8 / 25 for OAC-related ICH (32%) and 7 / 45 for non-OAC-related ICH (16%, NA = 0, 95%-CI -0.10 – 0.55). After one year, mortality rates were 12 / 20 for OAC-related ICH (60%) and 12 / 30 for non-OAC-related ICH (40%, NA = 20, 95%-CI -0.12 – 0.50).

3.5.2 Patient Performance as Assessed by mRS

We were able to obtain an mRS grade at twelve months in 114 patients after supratentorial ICH (NA = 93). Within the subgroup of patients with low and high residual hematoma volume according to the updated MISTIE III definition²⁶, no difference was detected between nOAC and OAC patients [low hematoma volume: nOAC ($n = 60$, median mRS: 4, IQR 3 – 5) vs. OAC ($n = 19$, median mRS: 4, IQR 4 – 6); high hematoma volume: nOAC ($n = 15$, median mRS: 6, IQR 4 – 6) vs. OAC ($n = 6$, median mRS: 6, IQR 5 – 6), NA for both comparisons = 14, see Fig. 7]. Likewise, no difference in outcome was detected between nOAC and OAC patients if low and high hematoma volumes were grouped [nOAC ($n = 88$, median mRS: 4, IQR 3 – 6) vs. OAC ($n = 26$, median mRS: 5, IQR 4 – 6)]. However, a significant difference was noted between

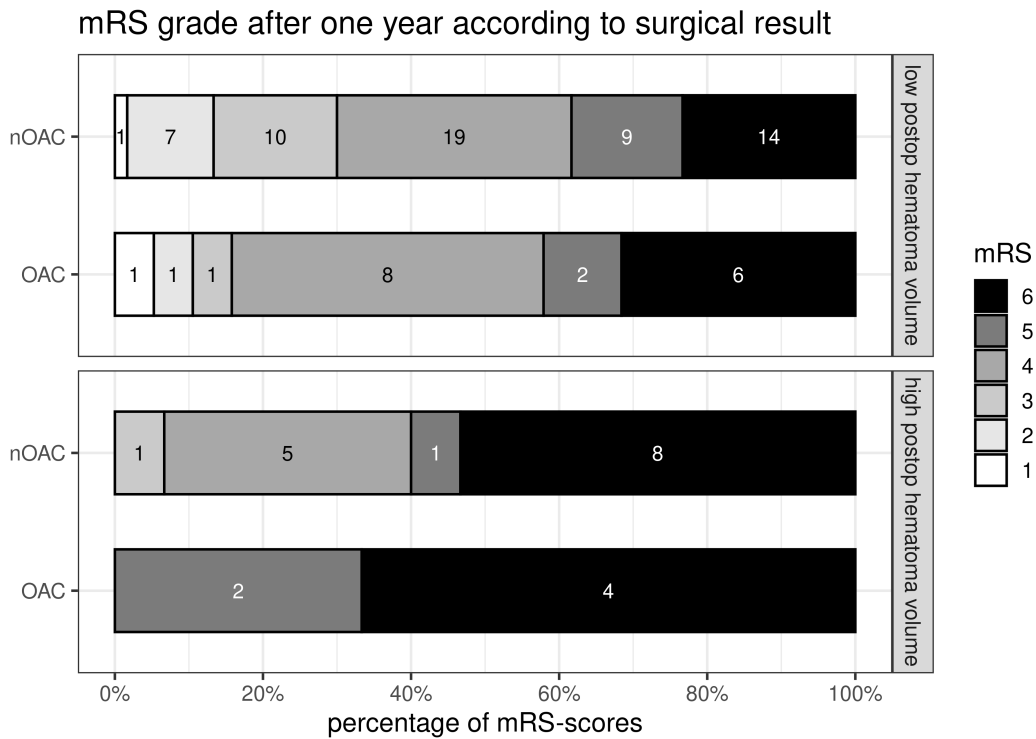


Figure 7: Functional outcome at 12 months in patients with supratentorial ICH stratified according to the prior use of anticoagulation (OAC) or no anticoagulation (nOAC) and low (upper panel) or high residual hematoma volume (lower panel) according to the MISTIE III criteria. The bar length represents the relative frequency of mRS-scores in each group and the numbers within the bars show the absolute numbers of patients in each category.

patients with low and high hematoma volume regardless of prior anticoagulation [low hematoma volume (n = 79, median mRS: 4, IQR 3 – 6) vs. high hematoma volume (n = 21, median mRS: 6, IQR 4 – 6), NA = 14, p = 0.002)], indicating worse outcome in patients with high residual hematoma volume compared to those with low residual volume. While this difference was no longer statistically significant after excluding deaths [low hematoma volume (n = 59, median mRS: 4, IQR 3 – 4) vs. high hematoma volume (n = 9, median mRS: 4, IQR 4 – 5), NA = 13, p = 0.1)], the distribution of the mRS grades of surviving patients at twelve months as shown in Figure 8 suggests that a sizeable proportion of patients profit from a good surgical result with regard to their functional outcome.

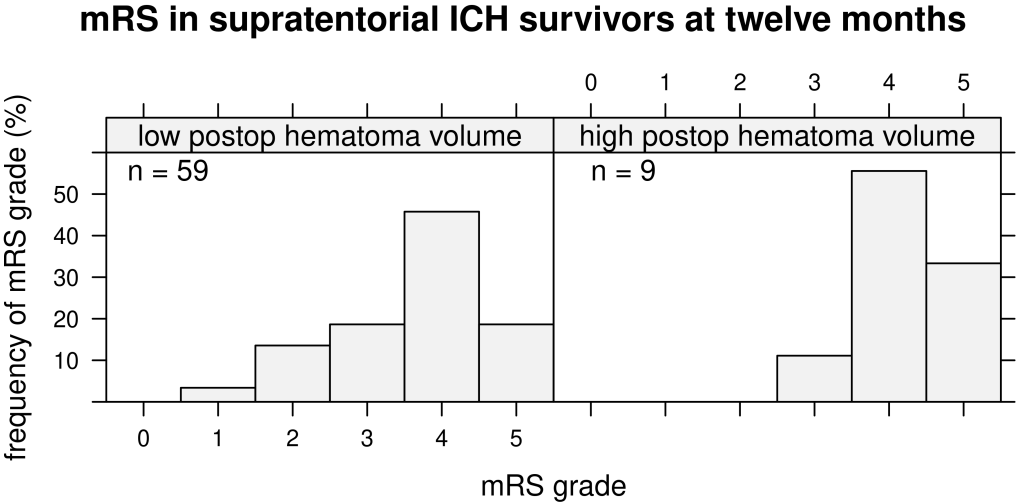


Figure 8: Distribution of mRS grade at 12 months in surviving patients with supratentorial ICH stratified according low (left panel) or high residual hematoma volume (right panel) according to the MISTIE III criteria.

We were able to obtain mRS grades after one year in 45 patients (NA = 36) with infratentorial hematoma localization. As in supratentorial hematoma, no difference in outcome was detected between nOAC and OAC patients [nOAC (n = 27, median mRS: 4, IQR 4 – 6) vs. OAC (n = 13, median mRS: 4, IQR 3 – 6), NA = 5]. Due to the small

number of patients in each group, we binned mRS grades into favourable (0 – 2) and unfavourable (3 – 5) outcomes and performed a biserial correlation with the surgical efficacy, which was not statistically significant ($n = 25$, $r_{pb} = -0.16$, 95%-CI $-0.52 - 0.25$, $p = 0.4$).

4 Discussion

4.1 Patient Characteristics

The demographic characteristics in the cohort that we identified appeared comparable to the patient characteristics in previously published RCTs on surgical ICH evacuation: Regarding sex, the male to female ratio was 1.3:1 in our cohort, similar to STICH I (1.3:1)²⁰, STICH II (1.3:1)²¹, and the OAC-ICH cohort (1.3:1)¹⁵, whereas MISTIE III reported a higher proportion of men (1.8:1)²⁴. Regarding age, the median age of our patients (69 years) was slightly higher than in STICH I (62 years)²⁰, STICH II (65 years)²¹, and MISTIE III (62 years)²⁴. Consistent with the previous observation of an older age of patients receiving OACs compared to patients without prior OAC medication¹⁵, patients in our cohort that received either VKAs (71 years) or NOACs (79 years) trended towards being older than patients without anticoagulation (66.5 years). Furthermore, the percentage of patients that received OACs in our cohort (29%) was within the range expected to be encountered in a large academic hospital setting³⁹, albeit higher than the reported 7%, 19%, and 10% in the neurosurgically treated arms of STICH I, STICH II, and MISTIE III, respectively^{20,21,24}. Possibly, this slightly older median age together with the higher percentage of patients that received OAC prior to the hemorrhage can be explained by the fact that the patients in our retrospective analysis did not meet the strict inclusion and exclusion criteria regarding age and anticoagulation as patients in the previously mentioned RCTs did. Furthermore, this effect could also be due to the fact that only patients that underwent surgery and also patients with infratentorial hemorrhage were included. On the other hand, we believe that our findings represent the clinical characteristics of the patient population that is considered for microsurgical ICH evacuation in an unmasked and generalizable fashion, because a detailed patient selection based on demographics was not performed. The higher median age that we

noted in NOAC compared to VKA patients may represent a phasing phenomenon during the still ongoing transition from VKA to NOAC prescription as first-line OAC, so that comparisons between these two groups have to be interpreted with caution. In addition to the older age in our cohort, the numerous cardiovascular medical comorbidities as listed in Table 3 might have resulted in a less favourable risk profile compared to the STICH^{20,21} and MISTIE III populations²⁴, as two thirds of our patients with prior VKAs and almost all patients with NOACs received OAC for prevention of embolic complications due to AF, and a high prevalence of patients with CAD on APT was noted. Although the prevalence of CAD is difficult to compare, the fact that (1) the previous history of CAD in our cohort was twice as high as the percentage of patients with prior myocardial infarction reported in the RCTs, along with (2) the lower percentage of patients that received APT in the STICH^{20,21} and MISTIE III²⁴ trials, at least to some degree suggests that our cohort may have suffered a higher cardiovascular risk before the ICH event.

4.2 Perioperative Anticoagulation Management

As outlined in the discussion on the limitations of the present work (please see 4.4), the suggested beneficial effect of hemostatic management on postoperative hematoma (re)expansion in patients receiving VKAs²⁷ could not be assessed due to lack of a control group. According to the internal standard operating procedure in our hospital, all ICH patients with an INR >1.3 were treated with either PCC, FFPs, or both, which appears to be in line with current recommendations¹⁸ and effectively improved the median, preoperative INR from initially 2.4 to 1.2. Similarly, an attempt was made to antagonize NOACs according to the guidelines pertinent before the availability of andexanet alfa in almost all NOAC patients¹⁸. However, information on the effectiveness of NOAC antagonization in the present study is likely hampered because the number of NOAC

patients in our cohort is small and routine plasmatic coagulation parameters, such as INR, are not suited to capture the anticoagulatory effect of NOACs. Furthermore, data on the last NOAC intake and anti-FXa activity as well as thrombin time on admission and before surgery were not routinely recorded. For dabigatran especially, elimination occurs predominantly by renal excretion (80%), and the risk of severe bleeding increases with impaired renal function, as anticoagulant activity is linearly correlated to its plasma concentration⁴⁰. Therefore, upcoming studies with more sizeable groups of NOAC patients beside routinely assessing quantitative information on patients' renal function should focus more on a wider spectrum of coagulation parameters such as calibrated anti-FXa-activity for FXa-i or thrombin time for direct thrombin (factor II) inhibitors. The appropriate hemostaseological management of NOAC patients regarding diagnostics and therapy is currently under constant change and the revision of guidelines is often outpaced by new developments⁴¹.

4.3 Hematoma Characteristics

4.3.1 Supratentorial Hematoma Characteristics

The preoperative supratentorial hematoma volumes in patients selected for surgery in the present study (62 ml, IQR 43 – 81) appeared larger than those reported in the neurosurgically treated groups of STICH I (40 ml, IQR 24 – 63)²⁰, STICH II (38 ml, IQR 24 – 54)²¹, and MISTIE III (43 ml, IQR 30 – 55)²⁴. This appears to be in line with recent findings suggesting that the benefits of surgery compared to medical management may be more pronounced at or above a hematoma volume of 30 – 40 ml⁴². Although no clear recommendations for an upper hematoma volume limit exists, currently, most would consider 80 – 90 ml to be reasonable, given that above such a volume, patients most likely present with a severely reduced GCS score below 8, which is reported to

be an indicator for medical instead of surgical management^{22,42,43}.

Consistent with the literature, patients with supratentorial ICH receiving either VKAs⁴⁴ or NOACs⁴⁵ had significantly larger preoperative hematoma volumes, whereas there was no difference noted in preoperative hematoma volumes between the two types of OAC. As mentioned above, the latter needs to be interpreted with caution because the number of patients in our NOAC cohort was very low compared to the number of patients receiving VKAs. Interestingly, however, preoperative OAC in patients undergoing surgery for ICH evacuation did not translate into worse outcome as suggested by a previous study on medical management of spontaneous ICH²⁸. This represents a main finding of our study and suggests that anticoagulation should not be regarded as an exclusion criterion for surgical ICH evacuation *per se* if perioperative management and correction of impaired anticoagulation is readily available.

4.3.2 Supratentorial Hematoma Evacuation Efficacy and Minimally Invasive Approach

While there is still much to be explored concerning the pathophysiology of brain injury due to ICH, the main rationales for neurosurgical hematoma evacuation are to reduce the primary mass effect of the hematoma and limit the risk of secondary neurological injury in the wake of hematoma degradation, such as inflammation, microthrombosis, excitotoxicity, spreading depolarization and perihematomal edema, among others. In addition, injury of the vulnerable perihematomal tissue by surgical intervention needs to be considered as a potential source of secondary damage that may negatively affect the outcome. Consequently, an increased interest has recently occurred regarding the development of less or minimally invasive approaches, as conventional early as well as delayed interventions have failed to improve outcomes^{20,21,46}. For this reason, we compared the results of our cohort with those of the recently published RCT on mini-

mally invasive supratentorial hematoma evacuation, MISTIE III⁴⁷. Although the main findings of this trial were negative, a subgroup analysis of patients with successful hematoma reduction below ≤ 15 ml or $\leq 30\%$ of the initial volume showed that in these cases, surgery did in fact lead to an improved outcome²⁶. Most importantly, the fact that only 60% of all patients included in the surgical arm of MISTIE III achieved this threshold, together with the fact that patients in the present study similarly experienced less favorable outcome in cases of high residual hematoma volume, highlights the relevance of achieving high evacuation rates when performing any type of surgery for supratentorial ICH evacuation. It is most likely that the low surgical evacuation performance in more than a third of the surgical MISTIE III cohort was one of the main reasons for the negative outcome of this well-designed RCT and consequently, other minimally invasive techniques still remain under investigation⁴⁸⁻⁵¹.

4.3.3 Infratentorial Hematoma Characteristics

In 27% of our patients the hematoma localization was infratentorial, which is higher than the reported 4.6% for the combined cohorts of INTERACT 1 and 2⁵², the 13.6% that were the result of a meta-analysis of four trials⁵³, or the 13% that were reported in a recent observational study⁵⁴. Again, a direct comparison to our study needs to be performed with caution, since our cohort only included patients that were treated surgically. Given the relative scarcity of patients being treated surgically in comprehensive stroke centers⁵⁵, our cohort was likely oversampled regarding patients with infratentorial ICH compared to cohorts that include both surgically and medically treated patients. Nevertheless, the small percentage (4%) of patients with brainstem as opposed to cerebellar hemorrhage in our study also mirrors the reluctance to surgically evacuate an infratentorial ICH with primary brainstem involvement^{52,54}. Regarding the hematoma volume, the median infratentorial hematoma volume that

we noted (20.0 ml) was considerably larger than the median infratentorial hematoma volume reported in the medically managed INTERACT trials (5.1 ml for cerebellar ICH localization and 1.6 ml for brain stem hemorrhage)⁵². This is likely explained by the fact that INTERACT only recruited patients that did not require surgical intervention, in which case hematoma volumes would be expected to be smaller than in a surgically treated cohort with infratentorial ICH, such as ours. Confirmation for this assumption was delivered by a recent meta-analysis showing that in cerebellar ICH, the median hematoma volume was 30 ml in the surgically treated patients vs. 4.7 ml in the medically treated patients⁵³. As 96% of our patients with infratentorial ICH had a cerebellar localization of hemorrhage, these data seem pertinent to our patient cohort. On the other hand, the percentage of patients with an infratentorial hematoma volume above 30 ml in our study (17%) was comparable to the percentage (20%) that was recently reported for the subgroup of cerebellar ICH in a prospective observational study of patients presenting with spontaneous ICH regardless of ensuing treatment⁵⁴ and to a certain degree this suggests a generalizability of our findings.

Since the evacuation rate of the hematoma volume in our cohort of infratentorial ICH patients was predictive of in-hospital- as well as one-year survival, whereas prior OAC was not and prospective data on the outcome of surgery for spontaneous infratentorial ICH is still lacking, future studies could focus on investigating the effect of surgery in the form of prospectively organized registries or cluster-based randomised trials, with comprehensive stroke centers randomized as clusters in order to limit contamination effects seen in RCTs due to biased inclusion through varying standard operating procedures and department policies on the management of this limited and complex patient cohort.

4.4 Limitations

The main limitation of the present study is the retrospective design with a lack of control groups regarding patients that did not receive hemostatic treatment (see 4.2) as well as patients that received non-surgical treatment. However, since surgical versus non-surgical management of ICH has already been reported in a number of RCTs, in the present study we deliberately focused on surgical aspects of hematoma evacuation in the context of OAC because despite the negative results reported in RCTs, surgery remains an accepted treatment option for carefully selected ICH patients and so far, information on the clinical course in the context of OAC with appropriate perioperative hemostatic management is still lacking.

Regarding our study design, comparability among retrospective single-center studies and to RCTs is naturally hampered by non-standardized patient identification and selection bias. In the present study, an example for this is that we also included patients with infratentorial ICH, despite known differences in patient selection criteria compared to supratentorial ICH. However, the decision for surgical versus non-surgical management also remains a matter of debate in patients with infratentorial spontaneous ICH⁵³, where the risk factors and hemostatic management considerations are the same as in supratentorial ICH. In order to increase the generalizability of our findings and minimize selection bias, we therefore systematically identified all patients with supra- and infratentorial spontaneous ICH according to the pertinent diagnostic ICD and therapeutic OPS codes recorded in the hospital information system. The reliability of such administrative datasets tends to be high and finalized administrative datasets most closely represent the existing clinical practice within an institution; however, their clinical validity regarding individual cases or particular subgroups is less clear⁵⁶, despite the fact that they represent the oldest form of systematic quality control in

the medical profession⁵⁷. Thus, the inhomogeneous distribution of confounders in single-center cohort studies is one of the main reasons why RCTs are considered the gold standard of study designs.

In addition to anticoagulation, one of the most highly relevant factors of ICH management is perioperative blood pressure management. The fact that this was not assessed in our analysis remains a clear limitation. On the other hand, blood pressure management in spontaneous ICH was also beyond the scope and purpose of our present study and remains a separate matter of debate, considering that recent meta-analyses showed no benefit regarding clinical outcome, despite modest beneficial effects on hematoma expansion after intensive blood pressure management in non-surgically treated patients⁵⁸⁻⁶⁰.

Another limitation is the variability of the mRS grade as the selected outcome parameter, because although the clinical outcome of “death” is unequivocal, the mRS grades 0 – 5 remain prone to a certain degree of subjectivity, albeit with good interobserver and test-retest reliability³⁵. Also, by design the mRS grade does not capture a detailed neurological status and is unable to represent neuropsychological outcome, quality of life, or limitations in daily living and activities, which are becoming increasingly important considering the often severe neuropsychological deficits and socioeconomic limitations that patients suffer after ischemic or hemorrhagic stroke. Post-stroke depression is present in up to a third of patients⁶¹, and anxiety in 22% according to a recent controlled prospective cohort study, often combined with posttraumatic stress disorder⁶². Other common neurological sequelae are apathy⁶³ and fatigue⁶⁴. While being important research fields with probably large impacts for the affected patients, all of these require elaborate clinical instruments to differentiate post-stroke from idiopathic psychiatric illness, whereas the mRS score is practical, simple and well estab-

lished by now, and also permits a dichotomous categorization of favorable (mRS grade 0 – 2) versus unfavorable (mRS grade 3 – 5) outcome. Of course, the answer to the question of what constitutes a favorable outcome differs between individual patients, caregivers and treating physicians. Most importantly, this requires a continuing debate and individual consideration in order to best counsel patients, particularly during the decision-making process towards the option of performing a potentially lifesaving procedure that will likely result in at least some degree of moderate disability.

While some studies suggest an additional detrimental effect of having APT in addition to OAC, we found no indication for this in our cohort when looking at hematoma volume in both supra- and infratentorial ICH (see 3.3), possibly due to the small number of patients receiving both OAC and APT ($n = 27$), and therefore did not analyze these patients as a separate subgroup but included them in the OAC group. The same was true for the comparison of nOAC patients with or without APT, that were analyzed as one group, accordingly.

Lastly, we performed a post-hoc exclusion of a small, inhomogeneous subgroup of patients ($n = 10$) with severe cardiovascular risk factors and continuous heparin monotherapy due to congenital cardiac malformations and cardiac assist devices for prevention of acute heart failure, because this group was considered too small for any reasonable analysis (see Tab. 4).

4.5 Conclusion

The present study mirrors the everyday experience of microsurgical ICH evacuation performed in one of the largest university hospitals in Europe. By analyzing an observation period of eleven years, the following key findings were identified: First, hematoma evacuation performance seems to affect early and late survival for

spontaneous ICH, which falls in line with the central findings of the recently published MISTIE III trial regarding a beneficial effect on mortality and functional outcome in cases of high surgical hematoma volume evacuation. Second, the use of anticoagulation did not relevantly affect the evacuation efficacy in our cohort, which appears to be at least partially due to hemostatic countermeasures initiated before surgery. Importantly, this underlines that the implementation of preoperative hemostasiologic management strategies can help to ensure effective microsurgical hematoma evacuation. Furthermore, the use of NOACs did not appear to negatively affect ICH evacuation efficacy, which is relevant because antidotes against NOACs were not readily available and the subgroup of patients receiving NOACs as OAC is expected to increase due to the aging demographic development, which will likely result in a higher number of patients with comorbidities requiring routine anticoagulation.

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Eidesstattliche Erklärung

„Ich, Julia Helene Raff, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Predictors of outcome in neurosurgically treated patients with spontaneous intracerebral hemorrhage (Einflussfaktoren auf das klinische Ergebnis von neurochirurgisch behandelten Patienten mit spontaner intracerebraler Blutung) selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.org) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§ 156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

04.04.2023
Datum

Unterschrift

Julia Helene Raff hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Hecht N, Czabanka M, Kendlbacher P, Raff JH, Bohner G, Vajkoczy P. Intraoperative CT and cone-beam CT imaging for minimally invasive evacuation of spontaneous intracerebral hemorrhage. Acta Neurochir (Wien). 2020;162(12):3167-3177. doi:10.1007/s00701-020-04284-y

Beitrag im Einzelnen: Der von der Doktorandin erstellte und aufbereiteten Datensatz war Grundlage der Publikation dahingehend,

- dass die in der Publikation beschriebenen Patienten von der Doktorandin in der im Kapitel Methoden beschriebenen Weise identifiziert wurden,
- die klinischen Daten der Patienten (unter anderem Tabelle 1 der Publikation) von der Doktorandin erhoben wurden und
- die Auswertungen der prä- und postoperativen CTs der Kohorte durch die Doktorandin in derselben Weise erfolgt wie für die in dieser Dissertation beschriebenen Kohorte (Ergebnisse siehe unter anderem Tabelle 2 der Publikation).

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Unterschrift des Doktoranden/der Doktorandin

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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Bescheinigung

Hiermit bescheinige ich, dass Frau *Julia Helene Raff* innerhalb der Service Unit Biometrie des Instituts für Biometrie und klinische Epidemiologie (iBikE) bei mir eine statistische Beratung zu einem Promotionsvorhaben wahrgenommen hat. Folgende Beratungstermine wurden wahrgenommen:

- Termin 1: 25.01.2022

Folgende wesentliche Ratschläge hinsichtlich einer sinnvollen Auswertung und Interpretation der Daten wurden während der Beratung erteilt:

- Darstellung der Daten mit Box- oder Violinplots
- Möglichkeit der Auswertung: Spearman Korrelation
- Andere Möglichkeit: Dichotomisieren der Modified Ranking Scale, auswerten mittels Logistischer Regression

Diese Bescheinigung garantiert nicht die richtige Umsetzung der in der Beratung gemachten Vorschläge, die korrekte Durchführung der empfohlenen statistischen Verfahren und die richtige Darstellung und Interpretation der Ergebnisse. Die Verantwortung hierfür obliegt allein dem Promovierenden. Das Institut für Biometrie und klinische Epidemiologie übernimmt hierfür keine Haftung.

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Name des Beraters/der Beraterin:

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