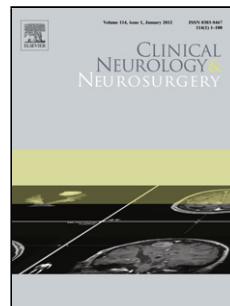


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ANEURYSMAL INTRACEREBRAL HEMATOMA: RISK FACTORS AND SURGICAL TREATMENT DECISIONS

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Highlights

- This article reports on aneurysmal intracerebral hematoma (ICH)
- A large retrospective cohort is analyzed regarding risk factors and impact of ICH
- Over 30 variables were tested
- Aneurysm location remained the main risk factor for occurrence and volume of an ICH
- The clinically relevant cutoff for additional surgical interventions was 17mL

Abstract

Objectives: Intracerebral hematoma (ICH) complicates the course of aneurysmal subarachnoid hemorrhage (SAH). To date, there are no unique guidelines for

management of aneurysmal ICH. The aim of this study was to identify risk factors for and impact of aneurysmal ICH with special attention on treatment decisions derived from ICH volume.

Patients and Methods: All patients admitted with aneurysmal SAH between 2003 and 2016 were eligible for this study. Various demographic, clinical and radiographic characteristics of patients were correlated with the occurrence and volume of ICH in univariate and multivariate manner. The associations between ICH volume and the need for surgical procedures and functional outcome were also analyzed.

Results: 991 patients were included into final analysis. ICH occurred in 301 (30.4%) cases. Location in the middle cerebral artery (MCA, $p<0.001$, aOR=7.04), WFNS grade 4-5 ($p<0.001$, aOR=4.43), rebleeding before therapy ($p=0.004$, aOR=2.45), intracranial pressure over 20 mmHg upon admission ($p=0.008$, aOR=1.60) and intraventricular bleeding ($p=0.008$, aOR=1.62) were independently associated with ICH presence. In turn, WFNS grade 4-5 ($p<0.001$) and MCA aneurysms ($p<0.001$) were the only independent predictors of ICH volume. According to the receiver operating characteristic curves, the clinically relevant cutoff for additional surgical interventions (decompression/hematoma evacuation) was 17 mL. ICH occurrence and ICH volume ≥ 17 mL independently predicted poor outcome at 6 months after SAH (defined as modified Rankin Scale>3).

Conclusion: Of over 30 tested variables, the location of the ruptured aneurysm in the MCA remains the major risk factor for occurrence and volume of ICH. Given the presence of brain swelling and other bleeding components of SAH, surgical intervention on aneurysmal ICH is indicated at lower volume values, than it is generally accepted for spontaneous ICH.

KEYWORDS:

Aneurysm, subarachnoid hemorrhage, intracerebral hematoma, decompressive craniectomy

Introduction

Intracerebral hematoma (ICH) due to rupture of intracranial aneurysm (IA) occur in 10 to 38% of cases with subarachnoid hemorrhage (SAH) [19,25,22,17,12,2,10,16]. It is commonly accepted that aneurysmal ICH complicates the natural course of disease and is connected to increased morbidity and mortality [19,25,22]. The mass effect caused by the hematoma might lead to a prolonged intracranial pressure (ICP) known as one of the possible contributors to early brain injury (EBI) [21]. IA of the anterior circulation especially located in the middle cerebral artery (MCA) [19,1,27,16] but also in the anterior cerebral artery (ACA) [25,1] have been identified as risk factors for ICH occurrence. Recent studies focused on identification of additional patient- and IA-related risk factors for aneurysmal ICH. Premorbid conditions like arterial hypertension, diabetes and smoking as well as administration of antiplatelet drugs prior to ictus have been correlated with ICH occurrence [12,10,27,16]. Alongside with IA location as acknowledged ICH predictor, size and morphology of ruptured IA have also been analyzed as potential risk factors, however with conflicting results [12,10,16]. It has been reported that SAH patients with an additional ICH are more likely to present with poor initial clinical condition [25,10,27,16] and develop rebleeding prior to treatment [25,16].

In contrast, there is less evidence on predictors and clinical impact of ICH size. In particular, there are no unique recommendations for SAH patients on treatment decisions derivable from the volume of ICH. Critical volume for aneurysmal ICH associated with poor outcome has been reported at 25 mL, however upon applying arbitrary cutoff values [22,15]. Larger IA size, location in the MCA and administration of aspirin prior to bleeding event have been mentioned as risk factors for larger ICH volume in one study [10].

The aim of this study was to elucidate independent risk factors for occurrence and especially volume of aneurysmal ICH in a large single center series. Furthermore, we aimed to investigate factors influencing the neurosurgical management of aneurysmal ICH, as well as associations with SAH outcome.

Material and methods

All patients admitted to our institution between January 2003 and June 2016 with an aneurysmal SAH were eligible for this study. Approval for this study was given by the institutional review board. Afterwards, it was registered in the German Trial Register (DRKS, Unique identifier: DRKS00008749).

SAH Treatment regime

Our institutional policy included early IA occlusion within 24 hours, when applicable. Decision about microsurgical or endovascular treatment was made upon interdisciplinary consensus. Patients with acute hydrocephalus were treated by diversion of cerebrospinal fluid using external ventricular or lumbar drainage. In cases of SAH with ICH, decision about surgical decompression and/or hematoma evacuation was made by neurosurgeon on duty based on individual judgment of space occupying effect of the bleeding and clinical condition of the patient.

Post treatment imaging by computed tomography (CT) of the head was performed during the first 24 hours after treatment. Further imaging was performed as necessary. Vasospasm prevention therapy included oral nimodipine for 21 days and daily transcranial Doppler ultrasonography for 14 days in all cases. If cases of symptomatic vasospasm, endovascular treatment was performed by intra-arterial nimodipine application and/or transluminal catheter angioplasty, if necessary.

Data management

Patients' charts were reviewed for demographic and clinical parameters. Imaging was reviewed for all radiographic parameters.

ICH was assessed as seen on initial CT scan. For recording of the volume, the formula $A \times B \times C / 2$ was used [11]. Presence of intraventricular hemorrhage (IVH) was documented. For assessment of IVH severity, the original Graeb score (oGS) was used [5]. The radiographic severity of SAH was assessed utilizing the original Fisher scale [3]. For analysis, the radiographic severity was dichotomized into low (Fisher scale 1 and 2) and high (Fisher scale 3 and 4) grades.

IA size, location and morphology were documented as seen on digital subtraction angiography (DSA). All IA that presented with daughter sac(s) (<50% of aneurysm size) or multiple lobes (>50 % of aneurysm size) were defined as irregular. For

statistical analysis aneurysms of the vertebral, basilar artery and posterior cerebral artery were amalgamated as “posterior circulation” (PC) aneurysms.

Initial clinical severity of SAH was assessed according to the world federation of neurological surgery grading system (WFNS) [24]. For statistical analysis, we dichotomized patients into good (WFNS 1-3) and poor grade (WFNS grade 4 and 5) cases.

Patient charts were reviewed for age, sex, preexisting morbidities (arterial hypertension, diabetes mellitus, smoking) and anticoagulation (vitamin k antagonists, antiplatelet therapy, new oral anticoagulants) prior to admission. Furthermore blood pressure levels (maximal and minimal values for the systolic and mean overall value for the mean arterial pressure) and ICP in case of placement of an EVD (dichotomized into increased ICP (over 20 mmHg) and not increased) at admission were documented.

All events with clinical deterioration before treatment of the IA in conjunction with new hemorrhage on CT scan were judged as rebleeding events. Rebleeding episodes on referring hospitals, during transport and at our institution were recorded.

All new hypodensities in post treatment imaging that were not connected to ICH or surgical approach were defined as de-novo cerebral infarction. New hypodensities visible on the first post-treatment CT scan, were defined as early infarcts. Accordingly, infarctions identified in the later follow-up imaging, were referred as delayed cerebral ischemia (DCI).

Need for shunt implantation due to persisting hydrocephalus was documented.

As functional endpoints, in-hospital mortality and poor outcome at 6 months after SAH (defined as modified Rankin scale (mRS) [26] > 3) were used.

Statistical analysis

Statistical analysis was performed using SPSS Version 22 for Mac (IBM Corp.). Continuous variables are given in mean +/- standard deviation (SD) if not indicated

differently. They were analyzed using the Student's t-test for normally distributed and the Mann-Whitney U test for non-normally distributed data. Correlations between two continuous variables were analyzed by Pearson correlation. Categorical variables were analyzed using the Chi-Square-Test; for samples smaller than 5, the Fisher-Exact-Test was used. P-values smaller than 0.05 were defined as significant. Factors predictive for occurrence of ICH in univariate analysis were included in final multivariate binary logistic regression analysis. Factors associated with ICH volume were included in final multivariate linear regression analysis. For ICH volume a cutoff was identified regarding the need for further surgical intervention using the receiver operating characteristic (ROC) curve analysis. Missing data were replaced using multiple imputations.

Results

A total of 994 SAH patients were treated during the 13.5 years surveillance period at our institution. In 3 cases, the occurrence of an ICH was not retrospectively evaluable due to incomplete imaging/documentation. Therefore 991 patients were included into final analysis. ICH occurred in 30.4% (n=301) of cases with a mean volume of $25.98 \text{ mL} \pm 32.06 \text{ mL}$. The following mean volumes of ICH were identified for different aneurysm locations: MCA - $44.68 \text{ mL} \pm 39.74 \text{ mL}$; ICA – $17.94 \text{ mL} \pm 23.87 \text{ mL}$; ACA – $13.89 \text{ mL} \pm 16.60 \text{ mL}$; PC $7.53 \text{ mL} \pm 7.60 \text{ mL}$ (Examples for different bleeding volumes are given in figure 1). The highest rate of ICH occurrence had IA located in the MCA (57.7%) followed by the ACA (35.7%), whereas the internal carotid artery (ICA; 15.5%) and the PC (8.2%) presented with lower rates (see also figure 2). The majority of the patients were females (n=663; 66.9%) and Caucasians (n=948; 95.7%). The mean age at presentation was $55 \text{ years} \pm 14 \text{ years}$. 306 (30.9%) patients presented in poor initial clinical conditions and 740 (86.1% after exclusion of 132 cases with not assessable Fisher grades) with a high radiographic severity of SAH. Over half of the patients were treated by coil embolization (n=577; 61.4%; after exclusion of 51 patients that received no treatment) and 683 (68.9%) needed cerebrospinal fluid drainage for acute hydrocephalus.

Predictors of ICH occurrence

Of the risk factors identified in univariate analysis (Table 1), IA location in the MCA ($p<0.001$, adjusted odds ratio (aOR) = 7.04, 95% confidence interval (95% CI) 4.84-10.24), poor WFNS grade ($p<0.001$, aOR=4.43, 95% CI 3.11-6.31), rebleeding before therapy ($p=0.004$, aOR=2.45, 95% CI 1.34-4.50), increased intracranial pressure over 20 mmHg upon admission ($p=0.008$, aOR=1.60, 95% CI 1.13-2.27) and presence of IVH ($p=0.008$, aOR=1.62, 95% CI 1.14-2.31) were independently associated with ICH. IA size failed to be an independent predictor ($p=0.990$). Furthermore, in univariate analysis for patients with IVH, the severity measured by oGS correlated with risk of ICH ($p<0.001$, 6.57 ± 3.48 vs. 4.16 ± 2.78). Premorbid conditions like arterial hypertension ($p=0.228$), diabetes mellitus ($p=0.532$), smoking ($p=0.934$) and anticoagulation prior to SAH event ($p=0.532$) did not influence the risk for ICH. Finally, blood pressure levels at admission were not associated with ICH presence on admission CT scan as well (Table 1).

Predictors of ICH volume

In univariate analysis, poor initial WFNS grade, location of the IA in the MCA ($p=0.007$ and $p<0.001$, respectively; see also Figure 3) and larger IA size ($p=0.024$) could be identified as predictive for larger ICH volume. In multivariate analysis, poor WFNS grade ($p<0.001$) and IA in the MCA ($p<0.001$) remained as the only independent predictors of ICH volume. IA sack size ($p=0.436$) and morphology ($p=0.422$), presence of IVH ($p=0.392$) and rebleeding before therapy ($p=0.227$) did not influence ICH volume. No correlation with ICH volume could be shown regarding premorbid conditions (arterial hypertension, diabetes and smoking; $p=0.216$, $p=0.335$ and $p=0.332$ respectively) as well as previous anticoagulation medication ($p=0.395$).

ICH and treatment decisions

Patients with an ICH were more likely to be treated by clipping ($p<0.001$, OR=4.166, 95% CI 3.10 - 5.60) and to need a decompressive craniectomy ($p<0.001$, OR=14.33, 95% CI 9.72 – 21.12). Both also correlate with higher ICH volumes in the ICH subgroup (Figure 4). 153 (50.8%) patients needed ICH evacuation. Necessity of ICH evacuation also correlated with higher ICH volume (Figure 4). Cutoffs for decision in

favor of decompression or hematoma evacuation were 17 mL as defined in ROC curve analysis (supplements figure E1 and E2).

For all aneurysm locations but ACA ($p=0.073$), presence of an additional ICH was associated with higher likelihood of treatment allocation in favor of microsurgical clipping: $p<0.001$ ($OR=8.13$, 95% CI 3.38 – 19.55) for MCA, $p=0.032$ ($OR=3.48$, 95% CI 1.14 – 10.64) for ICA, and $p=0.023$ ($OR=3.02$, 95% CI 1.12 – 8.16) for PC aneurysms).

ICH and complications

Occurrence of cerebral infarcts was more likely in patients with ICH ($p=0.001$, $OR=1.59$, 95% CI 1.21 – 2.11). Further analysis showed the association of ICH with early ($p<0.001$, $OR= 1.73$, 95% CI 1.30 – 2.31), but not with DCI ($p=0.168$, $OR=1.263$, 95% CI 0.91 – 1.76). However, risk of symptomatic vasospasm was also increased for ICH patients ($p=0.044$, $OR=1.39$, 95% CI 1.01 – 1.91). ICH patients also carried a higher risk to develop a persisting hydrocephalus requiring permanent shunting ($p=0.008$, $OR=1.53$, 95% CI 1.12 – 2.09).

ICH and outcome

ICH led to a higher in-hospital mortality ($p<0.001$, $OR=3.17$, 95% CI 2.39 – 4.20) and a higher risk of poor outcome at 6 month follow up ($p<0.001$, $OR= 2.16$, 95% CI 1.55 – 3.01). The impact on outcome was independent of poor initial clinical conditions, age, occurrence of de-novo infarcts and symptomatic vasospasms ($p<0.001$, $aOR=2.39$, 95% CI 1.65 – 3.48; table 2). In the sub-cohort of SAH patients with ICH, volume aneurysmal ICH ≥ 17 mL independently predicted the functional outcome (Table 2).

Discussion

The aim of this study was to identify risk factors and consequences of aneurysmal ICH, with special emphasis on critical ICH volumes necessitating surgical interventions. We performed a detailed analysis including a variety of SAH- related and unrelated potential risk factors. In our cohort, IA location in the MCA was the

only independent predictor of larger ICH volume among factors existent prior to SAH. Patients with larger hematomas presented in poorer initial clinical condition and were more likely to require additional neurosurgical interventions in terms of decompressive craniectomy or hematoma evacuation.

Risk factors for ICH occurrence

Increased risk for ICH in case of rupture of an MCA aneurysm has been described by many authors [19,7,1,12,10,27,16]. Also the ACA has been mentioned as location at risk [7,25,1,6]. One reason might be that both locations tend to have an IA dome trapped between cortex surfaces. IA located like this have been reported to be more likely to cause intraparenchymal hematoma [20]. Our data confirms higher risk for ICH with MCA and ACA aneurysms, whereas IA in the MCA was confirmed as independent predictor. Larger IA size has been connected with increased risk of IA rupture [8,14] as well as the occurrence of ICH in case of SAH [6,10,16]. Also in our cohort, ICH occurrence correlated with IA size. However, it failed to be an independent predictor. IA morphology so far has been only examined in smaller cohorts regarding the risk for ICH and has not been connected with the risk of ICH [25,12]. Our data confirm these results.

For spontaneous ICH, it is well known that it is connected to premorbid conditions that are known to have a long term impact on vessel wall integration like arterial hypertension, diabetes or smoking [9,18]. For aneurysmal ICH, most of the published data failed to prove a similar connection so far [16,12,27]. Only one author has connected premorbid arterial hypertension with ICH risk in SAH patients [10]. Also previous intake of anticoagulation did not effect ICH occurrence in our series as described before [10].

Risk factors for ICH volume

Patients with ICH are at risk for increased ICP. Increased ICP might be connected also to the volume of the hematoma itself. Location and size of the IA are factors that might contribute to the volume of the ICH [10]. Also pre-ictus intake of aspirin [10] has been connected to higher ICH volumes. In our cohort, only poor initial clinical

conditions and IA location in the MCA were independently connected with larger ICH volume. Interestingly, all tested premorbid conditions (mostly, components of metabolic syndrome) as well as previous anticoagulation therapy did not influence the volume of the ICH. These factors have all been connected to ICH volume in case of spontaneous ICH [13].

Clinical impact of ICH

Patients that present with an ICH due to IA rupture are more likely to be treated by clipping than by coiling, as well as requiring additional surgical interventions in terms of decompressive craniectomy and hematoma evacuation. However, presence of ICH from ruptured ACA aneurysms did not influence the treatment decision in favor of clipping for this location. This circumstance might issue from relatively smaller size of ICH from ACA aneurysms. Interestingly, cutoffs for decompressive craniectomy and hematoma evacuation were defined at 17 mL. This seems quite small compared with volumes defined in studies with spontaneous ICH [23]. The same volume independently predicted poor outcome for the ICH subgroup – again, this volume is smaller than those reported to be predictive in spontaneous ICH cases were volumes at least over 20 mL, in most cases over 30 mL [13].

Other authors have arbitrarily set the cutoff for clinical relevance of aneurysmal ICH at 25 mL. In addition, only MCA aneurysms were included in these studies [22,15]. IA in the MCA have been shown to have an increased risk for larger ICH volume in our and other series [10]. ICH occurrence was connected to many SAH associated complications including development of de-novo cerebral infarction regarding early infarcts, symptomatic vasospasm and chronic hydrocephalus. Moreover it is strongly associated with increased ICP and associated brain-shift. Prolonged increased ICP has been connected with EBI [21,4]. It might therefore be suggested that EBI is an important factor influencing the impact of ICH on outcome. ICH remains a strong contributor to mortality and morbidity in SAH patients [19,7,25,22,1,17,12,2,10,16]. Especially patients with larger hematomas are at increased risk of devastating outcome despite maximal therapy.

Limitations

As this is a retrospective study, there are typically drawbacks like lower rate of

complete data as well as lower accuracy compared with a prospective study design. This accounts especially for premorbid conditions and medications, which strongly depends on its correct and complete documentation in the patients' charts at admission. However, our data is congruent with most prior published studies regarding influence of these factors on ICH [16,12,27]. Nevertheless, we present a detailed evaluation of risk factors for ICH and were able to define cutoffs urging for further surgical therapy.

Conclusion

In this large single center study, we were able to show that ICH volume cutoffs necessitating additional surgical therapy are lower than accepted for spontaneous ICH. This also accounts for ICH volume impacting the outcome of SAH. Clinical impact of ICH is more likely to be conditioned by the consequences of early brain injury. Finally, location of the ruptured IA in the MCA remains the only major predictor for occurrence and volume of aneurysmal ICH.

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Conflict of Interest/Disclosure

MDO is a consultant for Brainlab AG.

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FIGURES LEGENDS

Figure 1.: Examples for ICH volumes (A/B: 10ml, C/D: 20ml, E/F: 30ml). Left side: CT-scans showing the axial plane with the largest axial volume. Right side: Showing a 3D (right/left inverted) reconstruction of the hemorrhage created with brainlab elements (Brainlab AG, Munich, Germany)

Abbreviations: CT – computed tomography; ICH – Intracerebral hematoma

Figure 2.: Showing the proportions of patients with concomitant aneurysmal ICH depending on the location of the ruptured aneurysm.

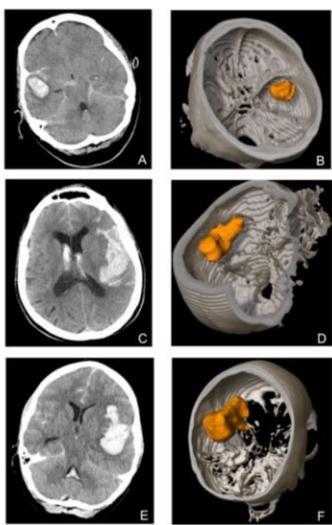
Abbreviations: ACA – Anterior cerebral artery; ICA – Internal carotid artery; ICH – Intracerebral hematoma; MCA – Middle cerebral artery; PC – Posterior circulation

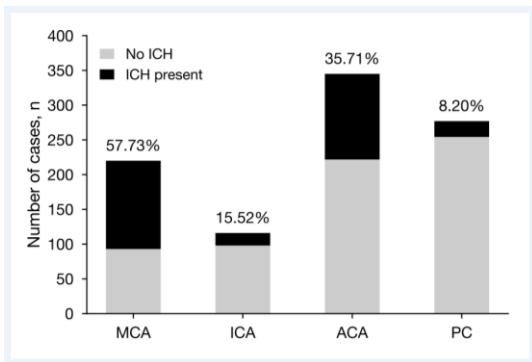
Figure 3.: Showing the differences in the volumes of aneurysmal ICH depending on the location of the ruptured aneurysm in the MCA (**A**) and initial clinical presentation (**B**). The median values for ICH volume (including quartiles/minimum/maximum) are given.

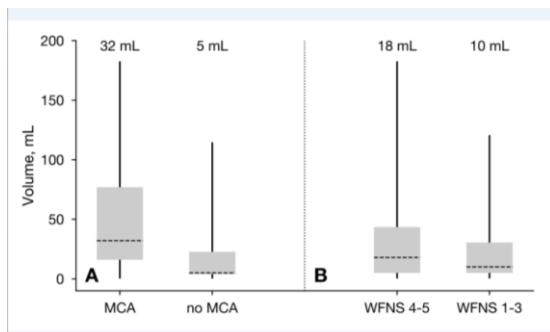
Abbreviations: MCA – Middle cerebral artery; WFNS – World Federation of Neurosurgical Societies

Figure 4.: Showing the differences in the volumes of aneurysmal ICH depending on the treatment conditions (**A**), need for additional decompressive surgery (**B**) and hematoma evacuation (**C**). The median values for ICH volume (including quartiles/minimum/maximum) are given.

Abbreviations: DC – Decompressive craniectomy; HE – Hematoma evacuation







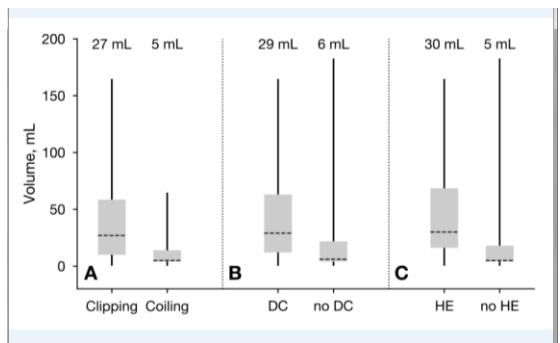


Table 1.: Univariate analysis of factors contributing to and influenced by aneurysmal ICH. Significant p-values are marked bold.

	ICH (n=301)	no ICH (n=690)	p	OR	95% CI
Parameter	%/Mean ± SD	%/Mean ± SD			
Age (years)	55±13	55±14	0.393		
Female sex	65.4%	67.5%	0.521	0.91	0.68 - 1.21
Anticoagulation prior to ictus *	18.2%	16.1%	0.538	1.16	0.72 - 1.88
Art. Hypertension †	54.8%	49.8%	0.228	1.22	0.88 - 1.69
Smoking ‡	23.4%	23.1%	0.934	1.02	0.69 - 1.49
Diabetes ‡	4.9%	6.1%	0.532	0.79	0.38 - 1.65
Sack size (mm)	8.01±4.47	7.06±4.81	0.006		
Morphology irregular (all) §	50.2%	46.6%	0.334	1.16	0.86 - 1.55
Morphology daughter sack §	20.8%	22.3%	0.637	0.92	0.64 - 1.31
WFNS 4-5	32.7%	30.1%	<0.001	4.78	3.57 - 6.39
Fisher 3-4	100%	78.7%	-		
Rebleeding before therapy II	11.1%	3.8%	<0.001	3.28	1.91 - 5.62
ICH volume (mL)	25.98±32.06				
IVH #	59.3%	40.4%	<0.001	2.14	1.62 - 2.83
IVH severity (oGs)	6.57±3.48	4.16±2.78	<0.001		
Treatment clipping ¶	62.7%	28.6%	<0.001	4.19	3.12 - 5.64
Acute hydrocephalus	70.8%	68.1%	0.407	1.11	0.84 - 1.52
Persisting hydrocephalus **	40.1%	30.5%	0.008	1.53	1.12 - 2.09
Decompressive craniectomy	47.5%	5.9%	<0.001	14.33	9.72 - 21.12
Symptomatic vasospasm	25.6%	19.9%	0.044	1.39	1.01 - 1.91
De-novo infarct ***	54.0%	42.5%	0.001	1.59	1.21 - 2.11
Early Infarct ***	41.5%	28.7%	<0.001	1.73	1.30 - 2.31
DCI ***	23.9%	19.9%	0.168	1.26	0.91 - 1.76
In hospital mortality	26.6%	14.3%	<0.001	2.16	1.55 - 3.01
Unfavorable outcome at 6 month****	61.3%	33.3%	<0.001	3.17	2.39 - 4.20
ICP > 20 mmHg at admission	49.1%	31.1%	<0.001	2.14	1.56 - 2.95
Bloodpressure syst max. (mmHg)	165±27	165±26	0.966		
Bloodpressure syst. min.(mmHg)	125±68	123±54	0.583		
MAP mean (mmHg)	90±16	91±15	0.619		
* Data missing for 428 patients					
† Data missing for 283 patients					
‡ Data missing for 293 patients					
§ Data missing for 80 patients					
II Data missing for 10 patients					
¶ 51 patients with no treatment					
# Data missing for 10 patients					
** Data missing for 152 patients					
*** Data missing for 37 patients					
**** Data available for 984 patients					

Table 2.: Multivariate analysis of factors contributing poor outcome for the whole cohort and the ICH subgroup (ICH volume over 17 ml analyzed as contributor).

Parameter	Whole cohort			ICH subgroup		
	p	aOR	95% CI	p	aOR	95% CI
Age (years)	<0.001	1.06	1.05 - 1.07	<0.001	1.06	1.03 - 1.09
WFNS 4-5	<0.001	4.48	3.17 - 6.34	0.009	2.39	1.25 - 4.59
ICH//ICH \geq 17 mL	<0.001	2.39	1.65 - 3.48	0.011	2.36	1.22 - 4.57
De-novo infarct	<0.001	8.98	6.30 - 12.79	<0.001	8.47	4.39 - 16.33
Symptomatic vasospasm	0.167	1.33	0.89 - 1.97	0.278	1.46	0.74 - 2.92

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