Hemorrhage Volume drives Early Brain Injury and Outcome in Poor Grade Aneurysmal Subarachnoid Hemorrhage

Results from the POGASH Registry

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Supplemental digital content:

Supplemental Digital Content Study Variables: a detailed description of the entire variable list is provided

Studied variables were grouped according to the different phases of the clinical course of the disease.

In the "***Early Brain Injury***" phase we included variables referring to the first clinical phase lasting from the admission into the emergency department up to the neurointensive care admission after treatment. The included variables are as follows:

World Federation of Neurosurgeons grading scale WFNS (either IV or V) assessed either after neurological resuscitation when feasible or as the worst pre-treatment grading , presence or absence of cardiac arrest before treatment, presence or absence of loss of consciousness (only long-lasting episodes of loss of consciousness, i.e. lasting at least 60 minutes, were included for the present.study). Modified Fisher Grade (either 3 or 4). Presence or absence of intraventricular (IVH) or intracerebral (ICH) haemorrhage, presence or absence of acute subdural hematoma, presence or absence of global cerebral edema, presence or absence of acute hydrocephalus (defined according to temporal horns width and the ratio between frontal horns diameter and inner table diameter). Presence or absence of ultra-early vasospasm (UEV), detectable on both angioCT and digital subtraction angiography or on angioCT only in patients directly admitted to the operatory theater and not due to intrinsic arterial disease (e.g. atherosclerosis). Time in hours from symptoms' onset and external ventricular drain placement and aneurysmal treatment; time, when available, was directly derived from retrievable charts of the ambulance service of each participating center. Location (anterior VS posterior circulation of aneurysm and involved artery; posterior communicating artery aneurysms are considered as part of anterior circulation due to the PCom representing the embryological posterior or caudal division of internal carotid artery development). Largest diameter, in millimeters, of the culprit aneurysm. Type of aneurysm, differentiating saccular from dissecting aneurysms. Treatment (surgical or endovascular) and complications (further subdivided into ischemic and hemorrhagic ones). Presence or absence of rebleeding episode/s. The temporal relationship between external ventricular drain placement and the occurrence of rebleeding was scored (dichotomized into "before" or "after").

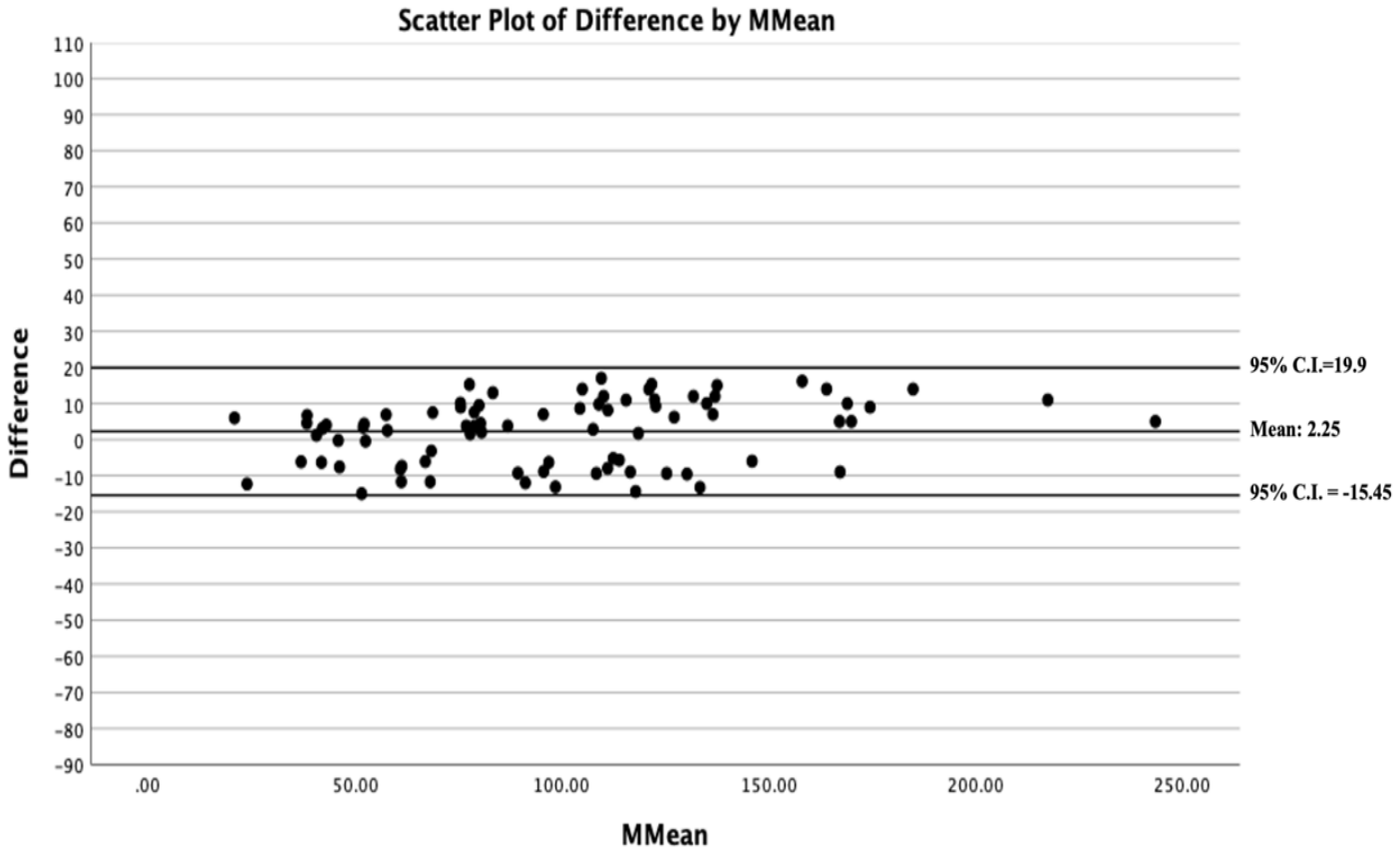
In the "***ICU phase"***, we included variables related to major details of treatment in the neurointensive care unit as well as logistic details. Length (in days) of permanence in Neurointensive Care Unit and of mechanical ventilation. Tracheostomy (yes or no). Use (yes or no) of decompressive craniectomy as a surgical way to treat intracranial hypertension. Decompressive craniectomy strategy was further defined as primary if occurring directly during surgical treatment of the culprit aneurysm or immediately after endovascular treatment but during the first 24hours since clinical onset, or secondary if used as an extreme measure to treat refractory intracranial hypertension. Craniectomy strategy was at the discretion of the

treating neurosurgical team. Vascular spasm detected (yes or no) by digital subtraction angiography. Numbers of angiographic treatment sessions related to it. Angiographic treatment dichotomized into pharmacological or mechanical (use of stentretrievers or balloon angioplasty). Detection of left ventricular dysfunction attributable to the intracranial bleeding.

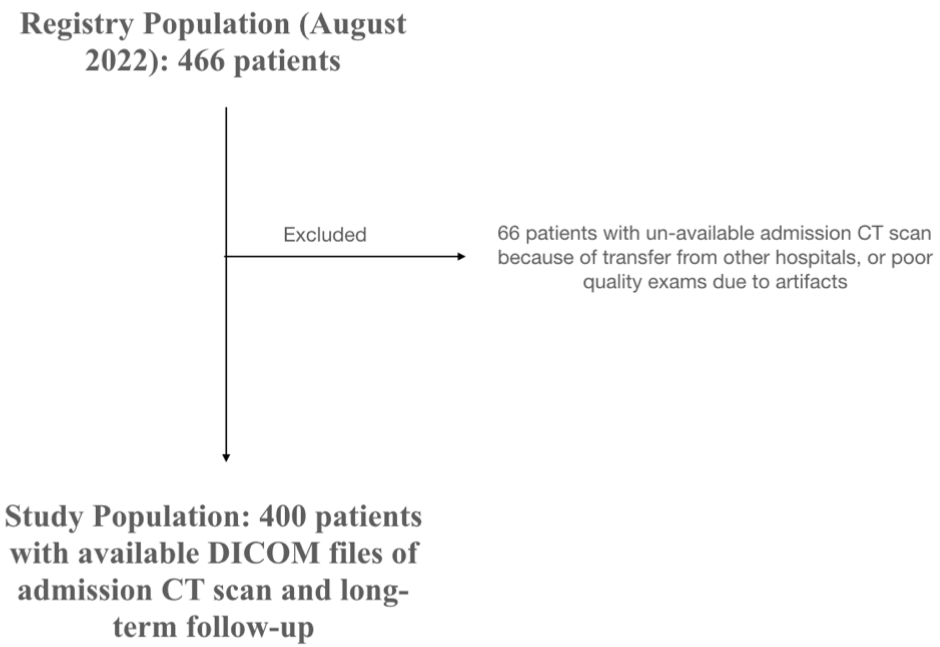
For each day of intensive care unit, presence or absence of at least one episode of intracranial hypertension (defined as $\geq$ 20mmHg lasting more than 5 minutes despite maximal therapy) and presence or absence of septic status were recorded.

In the "***Hospitalization and Follow-up"*** we evaluated variables related to the post-intensive care hospitalization and follow-up of. Presence or absence of delayed cerebral ischemia (defined according to the consensus led by Vergouwen MD et Al.), need for ventriculo-peritoneal shunt placement, modified Rankin scale at discharge and at last follow-up, death before discharge, length of follow-up (assessed in months). Cause of death (dichotomized into attributable to aSAH or not).

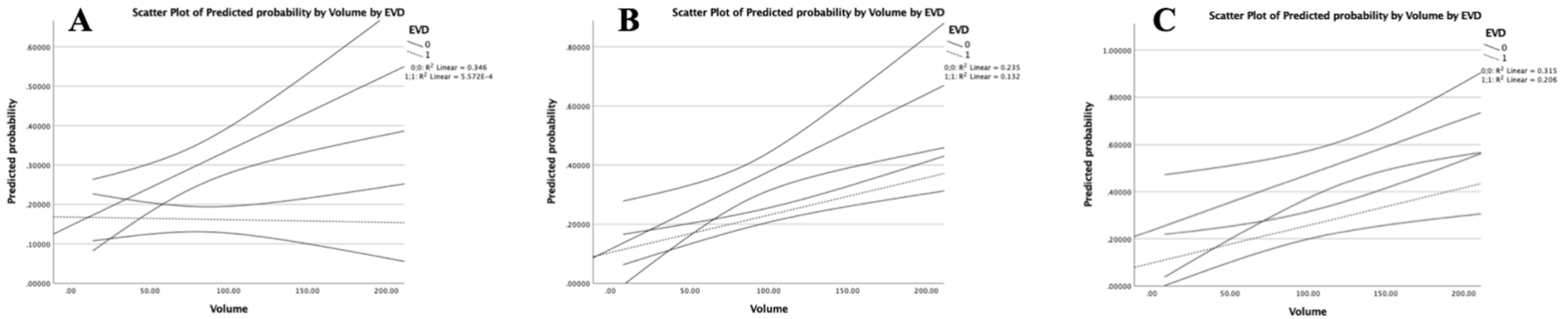
Supplementary Figure 1: Bland Altman Plot of 2 independent observers' calculations of GHV. Mean difference (2.25 mL) with relative upper and lower bound of 95% Confidence Intervals.



Supplemental Figure 2: study population flow-chart.


Registry Population (August 2022): 466 patients
Excluded
66 patients with un-available admission CT scan because of transfer from other hospitals, or poor quality exams due to artifacts
Study Population: 400 patients with available DICOM files of admission CT scan and long-term follow-up

Supplemental Figure 3: scatter plot showing multivariable analysis derived predicted probabilities of in-hospital mortality according to age, baseline GHV and presence/absence of EVD. Panel A: effect of GHV and EVD placement on in-hospital mortality probabilities for patients younger than 50 years old. Panel B: effect of GHV and EVD placement on in-hospital mortality probabilities for patients between 50 and 70 years old. Panel C: effect of GHV and EVD placement on in-hospital mortality probabilities for patients older than 70 years old.



Supplemental Table 1: baseline features, hospital course and follow-up of the studied population (no. 400 patients).

Baseline & Demographics	No. (%)
Age (median, IQR)	59 (50-68)
Sex (M/F)	256/144 (64/36)
Hypertension	189 (47.3)
Smoking	98 (24.5)
Prior Stroke	18 (4.5)
Early Brain Injury Phase	
WFNS 5	256 (64)
GHV (mL)	91 (59-128)
CardiacArrest	31 (7.8)
Loss of Consciousness	292 (73)

SEBES 0 1 2 3 4	 19 (4.8) 53 (13.3) 109 (27.3) 82 (20.5) 136 (34)
mFISHER 4	327 (81.8)
IVH	263 (65.8)
ICH	163 (40.8)
aSDH	53 (13.3)
Hydrocephalus	302 (75.5)
HyperacuteSpasm	41 (10.3)
TimeEVD (hrs)	4 (3-6)
TimeTreatment (hrs)	5 (3-8)
Aneurysm Location (posterior circulation)	65 (16.3)

Size (largest diameter, mm); median, IQR	7 (5-10)
Dissecting Aneurysm	32 (8)
Treatment Surgical Endovascular Abstention	 110 (27.5) 258 (64.5) 32 (8)
Rebleeding	70 (17.5)
NeuroICU	
Ventilation Length (days)	7 (2-17)
Tracheostomy	166 (41.5)
EVD	296 (74)
Decompressive Craniectomy Primary Secondary	96 (24) 42 (44) 54 (56)
Neurogenic Cardiomyopathy	20 (5)

Delayed Brain Injury Phase & Outcomes	
D.C.I.	81 (20.3)
V.P.S.	91 (22.8)
InHospitalMortality	123 (30.8)
mRS Discharge 0 1 2 3 4 5 6	5 (3-6) 10 (2.5) 38 (9.5) 39 (9.8) 50 (12.5) 41 (10.3) 98 (24.5) 123 (30.8)

mRS Follow-Up	4 (1-6)
0	55 (13.8)
1	57 (14.2)
2	43 (10.8)
3	30 (7.5)
4	29 (7.2)
5	46 (11.5)
6	140 (35)
Length Follow-Up (months)	13 (2-36)

WFNS: world federation of neurological surgeons grading scale; GHV: global intracranial hemorrhage volume; SEBES: severe early brain edema score; ICH: intracerebral hemorrhage; IVH: intraventricular hemorrhage; aSDH: acute subdural hematoma; EVD: external ventricular drain; DCI: delayed cerebral ischemia; VPS: ventriculo-peritoneal shunt.

Supplemental Table 2: results of multivariable analyses for independent predictors of SEBES grades 3-4 (as marker of Global Cerebral Edema), in-hospital mortality and long-term functional independence (mRS 0-2 VS 3-6).

Variable	**Independent predictors of GCE aOR, 95%C.I., p**	**Independent predictors of GCE aOR, 95% C.I., p** (hemorrhagic distributions: ICH/IVH/SAH)	**Independent predictors of in-hospital mortality aOR, 95% C.I., p**	**Independent predictors of in-hospital mortality aOR, 95% C.I., p** (hemorrhagic distributions: ICH/IVH/SAH)	**Independent predictors of long-term outcome (mRS 0-2 VS 3-6) aOR, 95% C.I., p**	**Independent predictors of long-term outcome (mRS 0-2 VS 3-6) aOR, 95% C.I., p** (hemorrhagic distributions: ICH/IVH/SAH)

Baseline & Demographics						
Age (median, IQR)	***.90 (.88-.93); < .001***	***.92 (.91-.95); <.001***	***1.02 (1.005-1.05); .014***	1.02 (1-1.4); .051	***.93 (.91-.96); <.001***	***.93 (.90-.95); <.001***
Hypertension	1.1 (.65-2.06); .60	.56 (.30-1.03); .06	.96 (.45-2.04); .92		N.I.	N.I.
Smoking	1.3 (.73-2.25); .4	1.3 (.71-2.3); .394	N.I.	N.I.	N.I.	N.I.
Prior stroke	.98 (.23-4.1); .98	.51 (.09-2.7); .43	N.I.	N.I.	N.I.	N.I.
Early Brain Injury						
WFNS 5	***1.9 (1.2-3.2); .009***	***2.15 (1.2-3.7); .006***	***3.7 (2.0-6.7); < .001***	***3.07 (1.6-5.9); <.001***	***.51 (.28-.93); .029***	.64 (.33-1.2); .17
GHV (for every mL) *- ICH Volume* *-IVH Volume* *-SAH Volume*	***1.007 (1.002-1.012); .007***	***- 1.02 (1.01-1.04); <.001*** - 1 (.99-1.02); .24 - 1 (.99-1.008); .31	***1.006 (1.001-1.01); .018***	- .99 (.98-1.01); .76 ***- 1.03 (1.01-1.05); <.001*** ***- 1 (1.01-1.02); .014***	***.992 (.98-.996); <.010***	***- .96 (.94-.98); .002*** ***- .95 (.92-.97); <.001*** ***- .99 (.98-1); .037***
Cardiac arrest	1.2 (.49-2.98); .67	1.8 (.6-5.4); .27	1.5 (.51-4.3); .453	2.5 (.9-7.1); .078	***.12 (.037-.41); <.001***	***.16 (.05-.52); .003***
Loss of consciousness	1.3 (.6-2.5); .50	1.9 (.88-4.4); .09	1.9 (.88-4.06); .102	2.4 (.89-6.7); .08	.85 (.38-1.9); .70	.83 (.41-1.7); .62
mFISHER 4	1.4 (.68-2.7); .36	2.3 (.9-3.0); .07	1.35 (.47-3.89); .57	1.9 (.65-5.6); .231	.75 (.25-2.3); .62	.44 (.18-1.08); .08
aSDH	1.9 (.97-4.1); .060	N.I.	N.I.	N.I.	N.I.	N.I.
Hydrocephalus	.84 (.48-1.5); .55	.70 (.34-1.5); .35	.78 (.42-1.44); .434	.56 (.27-1.17); .124	1.3 (.67-2.5); .42	1.7 (.83-3.5); .142
Acute Spasm	N.I.	N.I.	2.1 (.89-5.2); .09	1.4 (.42-4.8); .56	N.I.	N.I.
Rebleeding	N.I.	N.I.	***2.5 (1.3-4.5); .003***	***2.4 (1.3-4.58); .006***	***.42 (.20-.85); .017***	***.40 (.19-.859); .018***

Time-to-treatment (hrs)			.98 (.95-1.01); .319	.92 (.84-1.02); .08	.99 (.98-1.01); .76	1 (.98-1.01); .96
Aneurysm Location (anterior VS posterior circulation)	N.I.	N.I.	.49 (.20-1.19); .117	2.6 (.8-8.5); .109	.90 (.40-1.9); .79	.88 (.36-2.1); .77
Size (mm)	N.I.	N.I.	1.06 (.9-1.14); .054	1.05 (.97-1.1); .195	.95 (.89-1.01); .16	.99 (.92-1.07); .93
Saccular VS Dissecting	N.I.	N.I.	1.75 (.77-3.9); .18	1.5 (.39-5.8); .549	1.4 (.51-3.8); .50	.82 (.22-3.07); .77
Treatment & Clinical Course						
EVD	N.I.	***N.I.***	***.48 (.27-.85); .012***	***.41 (.21-.77); .006***	***3.4 (1.6-7.4); .002***	***2.2 (1.07-4.7); .032***
Craniectomy	N.I.	***N.I.***	***N.I.***	***N.I.***	***.18 (.08-.40); <.001***	***.016 .07-.36); <.001***
D.C.I.	N.I.		***N.I.***	***N.I.***	***.24 (.11-.51); <.001***	***.21 (.09-.47); <.001***

Supplemental Table 3: bivariate comparison between the study population (available admission CT for volumetric calculation of intracranial bleeding) and excluded population because of unavailable admission CT. Baseline, demographics and Early Brain Injury variables.

Baseline & Demographics	Study Population (400 pts)	Excluded Population (66 pts)	P
Age (median, IQR)	59 (50-68)	60 (51-71)	.505
Sex (M/F)	256/400	36/66	.122
Hypertension	189/400	31/66	.778
Smoking	98/400	21/66	.208
Prior Stroke	18/400	3/66	1.00
Early Brain Injury Phase			
WFNS 5	256/400	41/66	.540
CardiacArrest	31/400	7/66	.321
Loss of Consciousness	292/400	56/66	.017
mFISHER 4	327/400	25/66	.530

IVH	263/400	20/66	.583
ICH	163/400	13/66	.541
aSDH	53/400	4/66	1.00
Hydrocephalus	302/400	19/66	.650
AcuteSpasm	41/400	6/66	.589
TimeEVD (hrs)	4 (3-6)	5 (4-11)	.352
TimeTreatment (hrs)	5 (3-8)	7 (4-16)	.138
Aneurysm Location (posterior circulation)	65/400	6/66	.104
Size (largest diameter, mm); median, IQR	7 (5-10)	7 (5-11)	.299
Dissecting Aneurysm	32/400	4/66	1.00

Rebleeding	70/400	6/66	.146

WFNS: world federation of neurosurgeon grading scale; SEBES: severe early brain edema score; IVH: intraventricular hemorrhage; ICH: intracerebral hemorrhage; aSDH: acute subdural hematoma.

Supplemental Table 2: results of univariable and multivariable binary logistic regression analyses for factors independently associated with severe global cerebral edema (SEBES 3-4) on the admission CT scan. Population younger than 70 y.o. (no. 321 patients). Hydrocephalus has been forced into the multivariable analysis.

Predictors of SEBES grades 3-4 on the admission CT scan (population younger than 70 y.o., no. 319 patients)		
Baseline & Demographics	Odds Ratio, 95% C.I., p	Adjusted Odds Ratio, 95% C.I., p *
Age (median, IQR)	0.93 (0.90-0.96); <0.001	***0.91 (0.88-0.94); <0.001***
Sex (M/F)	0.65 (0.40-1.03); 0.06	***0.45 (0.26-0.8); 0.006***

Hypertension	0.77 (0.5-1.3); 0.29	N.I.
Smoking	1.4 (0.8-2.4); 0.22	N.I.
Prior Stroke	0.45 (0.12-1.7); 0.25	N.I.
Early Brain Injury		
WFNS 5/4	2.6 (1.6-4.13); <0.001	***1.9 (1.04-3.75); 0.036***
GHV (mL)	1.006 (1.001-1.01); 0.031	***1.01 (1.004-1.017); <0.001*** ***- ICH Volume 1.03 (1.02-1.05); <.001*** ***- IVH Volume N.I.*** ***- SAH Volume N.I.***
ICH Volume	1.02 (1.01-1.03); <.001	***1.03 (1.02-1.05); <.001***
IVH Volume	1.002 (.99-1.01); .70	***N.I.***
SAH Volume	1.0 (.99-1.004); .879	***N.I.***

CardiacArrest	1.6 (0.7-3.7); 0.27	N.I.
Loss of Consciousness	1.5 (0.9-2.7); 0.142	N.I.
mFISHER 4/3	1.6 (0.8-3.002); 0.120	N.I.
IVH	0.8 (0.5-1.3); 0.444	N.I.
ICH	1.7 (1.03-2.7); 0.038	1.3 (0.72-2.529); 0.34
aSDH	2.1 (1.002-4.5); 0.05	1.8 (0.72-4.7); 0.203
Hydrocephalus	0.91 (0.5-1.6); 0.76	0.88 (0.42-1.8); 0.73
HyperacuteSpasm	0.8 (0.4-1.6); 0.564	N.I.
Aneurysm Location Anterior/Posterior circulation	0.8 (0.4-1.4); 0.471	N.I.
Size (largest diameter; mm)	0.96 (0.91-1.003); 0.067	0.95 (0.89-1.002); 0.09

SaccularVSDissecting	0.96 (0.43-2.12); 0.923	N.I.

WFNS: world federation of neurosurgeon grading scale; GHV: global intracranial hemorrhage volume; IVH: intraventricular hemorrhage; ICH: intracerebral hemorrhage; aSDH: acute subdural hematoma.

*Hosmer-Lemeshow: 0.256.

Supplemental Table 3: results of univariable binary logistic regression analysis for for factors associated with severe global cerebral edema (SEBES 3-4) on the admission CT scan.

Baseline & Demographics	Odds Ratio, 95% C.I., p
Age (median, IQR)	0.92 (0.90-0.94); < 0.001
Sex (M/F)	0.83 (0.55-1.3); 0.387
Hypertension	0.62 (0.40-0.95); 0.031
Smoking	1.4 (0.88-2.3); 0.144
Prior Stroke	0.29 (0.10-0.85); 0.024
Early Brain Injury	
WFNS 5/4	2.3 (1.5-3.5); < 0.001
GHV (mL) - ICH V (mL) - IVH V (mL) - SAH V (mL)	1.005 (1.0-1.01); 0.031 - 1.02 (1.01-1.035) <.001 - 1.0 (.99-1.01); .69 - 1.0 (.99-1.004); .90

CardiacArrest	2.02 (.90-4.52); 0.086
Loss of Consciousness	2.08 (1.3-3.4); 0.003
mFISHER 4/3	1.45 (.83-2.5); 0.188
IVH	0.79 (0.52-1.2); 0.28
ICH	1.6 (1.05-2.3); 0.030
aSDH	2.28 (1.2-4.3); 0.011
Hydrocephalus	0.88 (0.54-1.4); 0.6
AcuteSpasm	1.08 (0.56-2.08); 0.81
Aneurysm Location Anterior/Posterior circulation	0.88 (0.51-1.5); 0.65
Size (largest diameter; mm)	0.98 (0.94-1.02); 0.4

SaccularVSDissecting	1.05 (0.50-2.2); 0.89

WFNS: world federation of neurological surgeons grading scale; GHV: global intracranial hemorrhage volume; IVH V: intraventricular haemorrhage volume; ICH V: intracerebral haemorrhage volume; SAH V: subarachnoid hemorrhage volume; aSDH: acute subdural hematoma. N.I.: not included.

Suplemental Table 4: results of univariable binary logistic regression analysis for independent predictors of in-hospital mortality.

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Baseline & Demographics	Odds Ratio, 95% C.I., p
Age	1.02 (1.0-1.04); <0.005
Sex (M/F)	1.3 (0.8-1.9); 0.267
Hypertension	0.7 (0.4-1.1); 0.15
Smoking	1.2 (0.7-2.03); 0.41
Prior Stroke	1.2 (0.44-3.3); 0.69
Early Brain Injury	
WFNS 5/4	3.6 (2.1-6.02); <0.001
GHV - ICH V - IVH V	1.009 (1.004-1.013); <0.001 - 1.00 (.99-1.01); .364

- SAH V	- 1.03 (1.02-1.04); <.001 - 1.006 (1.001-1.01); .011
CardiacArrest	2.6 (1.2-5.4); 0.012
Loss of Consciousness	2.7 (1.4-5.2); 0.002
mFISHER 4/3	2.4 (1.1-4.8); 0.019
IVH	1.9 (1.2-3.2); 0.006
ICH	1.4 (0.9-2.1); 0.147
aSDH	1.01 (0.5-1.9); 0.95
SEBES 3-4	1.18 (0.7-1.8); 0.44
Hydrocephalus	0.9 (0.5-1.5); 0.67
AcuteSpasm	1.7 (0.8-3.2); 0.13

Rebleeding	1.9 (1.1-3.3); 0.02
Time-to-EVD (hrs)	1.001 (0.98-1.017); 0.8
Time-to-Treatment (hrs)	0.97 (0.94-1.009); 0.149
Aneurysm Location Anterior/Posterior circulation	0.6 (0.31-1.13); 0.11
Size (largest diameter; mm)	1.07 (1.02-1.12); 0.004
SaccularVSDissecting	1.8 (0.8-3.8); .13
EVD	0.38 (0.24-0.62); <0.001
Craniectomy	0.89 (0.54-1.5); 0.682
D.C.I.	1.2 (0.7-2.08); 0.40

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WFNS: world federation of neurological surgeons grading scale; SEBES: severe early brain edema score; GHV: global intracranial hemorrhage volume; IVH V: intraventricular haemorrhage volume; ICH V: intracerebral haemorrhage volume; SAH V: subarachnoid hemorrhage volume; EVD: external ventricular drain; aSDH: acute subdural haemorrhage; DCI: delayed cerebral ischemia; mRS: modified Rankin scale. N.I.: not included.

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Supplemental Table 5: results of univariable binary logistic regression analysis for independent predictors of clinical outcome (long-term functional independence, mRS 0-2).

Baseline & Demographics	Odds Ratio, 95% C.I., p
Age	0.96 (0.94-0.98); <0.001
Sex (M/F)	1.05 (0.7-1.6); 0.798
Hypertension	1.3 (0.85-2.0); 0.21
Smoking	1.1 (0.71-1.9); 0.54

Prior Stroke	0.76 (0.27-2.0); 0.59
Early Brain Injury	
WFNS 5/4	0.34 (0.22-0.52); <0.001
GHV - ICH V - IVH V - SAH V	0.98 (0.98-0.99); <0.001 - .97 (.95-.98); <.001 - .96 (.94-.98); <.001 - .99 (.98-.99); .005
CardiacArrest	0.19 (0.07-0.57); 0.003
Loss of Consciousness	0.61 (0.38-0.99); 0.047
mFISHER 4/3	0.31 (0.17-0.56); <0.001
aSDH	0.85 (0.46-1.6); 0.6
SEBES 3-4	0.89 (0.6-1.3); 0.58

Hydrocephalus	1.3 (0.81-2.2); 0.26
AcuteSpasm	0.75 (0.38-1.5); 0.40
Rebleeding	0.53 (0.3-0.94); 0.03
Time-to-EVD (hrs)	0.99 (0.98-1.01); 0.86
Time-to-Treatment (hrs)	1.06 (0.99-1.1); 0.29
Aneurysm Location Anterior/Posterior circulation	1.3 (0.75-2.2); 0.37
Size (largest diameter; mm)	0.93 (0.88-0.98); 0.006
SaccularVSDissecting	0.88 (0.42-1.9); 0.75
EVD	1.8 (1.06-2.8); 0.028

Craniectomy	0.37 (0.21-0.63); <0.001
D.C.I.	0.48 (0.28-0.83); 0.008

WFNS: world federation of neurological surgeons grading scale; SEBES: severe early brain edema score; GHV: global intracranial hemorrhage volume; IVH V: intraventricular haemorrhage volume; ICH V: intracerebral haemorrhage volume; SAH V: subarachnoid hemorrhage volume; EVD: external ventricular drain; aSDH: acute subdural haemorrhage; DCI: delayed cerebral ischemia; mRS: modified Rankin scale. N.I.: not included.

Supplemental Table 6: crude numbers of patients according to age groups (<50, 50-70 and > 70 years old), GHV, SEBES grades, in-hospital mortality and long-term clinical outcome.

Age	***Severe SEBES no. (%)***	***No severe SEBES no (%)***	***In-Hospital Mortality in SEBES 3-4***	***mRS 0-2 in SEBES 3-4***
	GHV ml; median (IQR)	***GHV mL; median (IQR)***	***In- Hospital Mortality in SEBES 0-2***	***mRS 0-2 in SEBES 0-2***
< 50	76 (81.7)	17 (18.3)	23 (30.3)	37 (48.7)
	85 (48-113) mL	54 (32-107)	1 (5.9)	12 (70.6)
50-70	125 (55.1)	102 (44.9)	38 (30.4)	45 (36)

	97 (75-134)	87 (53-120)	22 (21.8)	48 (47.5)
> 70	17 (21.5)	68 (78.5)	9 (52.9)	0 (0)
	124 (99-172)	88 (51-136)	29 (46.8)	13 (21)

SEBES: severe early brain edema score; ICHV: intracranial hemorrhage volume.