

# BRAIN COMMUNICATIONS

## The PRESSURE score to predict decompressive craniectomy after aneurysmal subarachnoid haemorrhage

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The prognosis of patients with aneurysmal subarachnoid haemorrhage requiring decompressive craniectomy is usually poor. Proper selection and early performing of decompressive craniectomy might improve the patients' outcome. We aimed at developing a risk score for prediction of decompressive craniectomy after aneurysmal subarachnoid haemorrhage. All consecutive aneurysmal subarachnoid haemorrhage cases treated at the University Hospital of Essen between January 2003 and June 2016 (test cohort) and the University Medical Center Freiburg between January 2005 and December 2012 (validation cohort) were eligible for this study. Various parameters collected within 72 h after aneurysmal subarachnoid haemorrhage were evaluated through univariate and multivariate analyses to predict separately primary (PrimDC) and secondary decompressive craniectomy (SecDC). The final analysis included 1376 patients. The constructed risk score included the following parameters: intracerebral ('Parenchymal') haemorrhage (1 point), 'Rapid' vasospasm on angiography (1 point), Early cerebral infarction (1 point), aneurysm Sac > 5 mm (1 point), clipping ('Surgery', 1 point), age Under 55 years (2 points), Hunt and Hess grade  $\geq 4$  ('Reduced consciousness', 1 point) and External ventricular drain (1 point). The PRESSURE score (0–9 points) showed high diagnostic accuracy for the prediction of PrimDC and SecDC in the test (area under the curve = 0.842/0.818) and validation cohorts (area under the curve = 0.903/0.823), respectively. 63.7% of the patients scoring  $\geq 6$  points required decompressive craniectomy (versus 12% for the PRESSURE < 6 points,  $P < 0.0001$ ). In the subgroup of the patients with the PRESSURE  $\geq 6$  points and absence of dilated/fixed pupils, PrimDC within 24 h after aneurysmal subarachnoid haemorrhage was independently associated with lower risk of unfavourable outcome (modified Rankin Scale > 3 at 6 months) than in individuals with later or no decompressive craniectomy ( $P < 0.0001$ ). Our risk score was successfully validated as reliable predictor of decompressive craniectomy after aneurysmal subarachnoid haemorrhage. The PRESSURE score might present a background for a prospective randomized clinical trial addressing the utility of early prophylactic decompressive craniectomy in aneurysmal subarachnoid haemorrhage.

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**Keywords:** subarachnoid haemorrhage; decompressive craniectomy; risk score; prediction; outcome

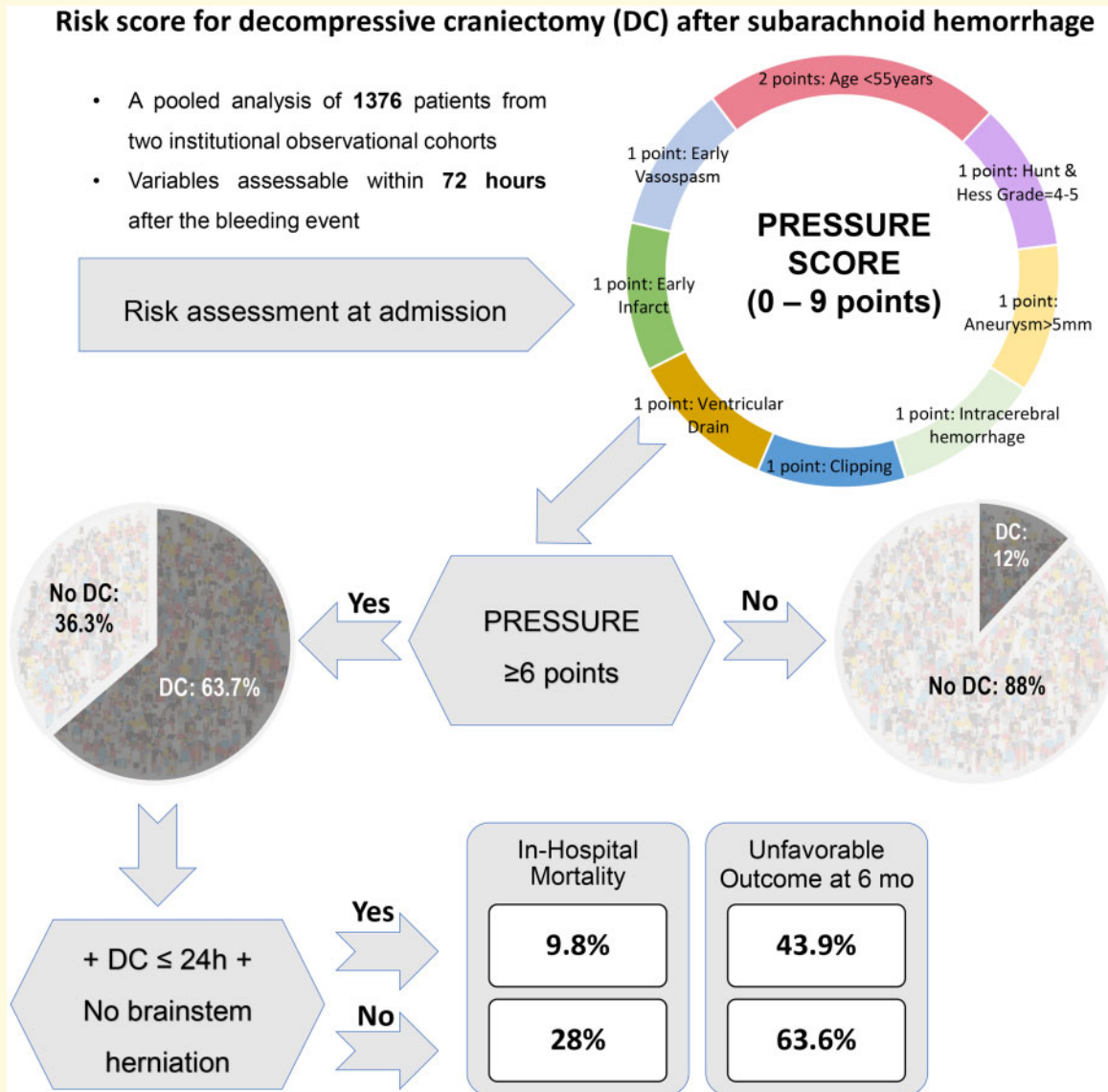
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**Abbreviations:** aOR = adjusted odds ratio; AUC = area under the curve; CT = computed tomography; DC = decompressive craniectomy; DSA = digital subtraction angiography; EVD = external ventricular drainage; ICH = intracerebral haematoma; IVH = intraventricular haemorrhage; PrimDC = primary decompressive craniectomy; SAH = (aneurysmal) subarachnoid haemorrhage; SD = standard deviation; SecDC = secondary decompressive craniectomy

### Graphical Abstract



## Introduction

Decompressive craniectomy (DC) is an effective neurosurgical treatment against intractable intracranial hypertension in different neurocritical conditions (Berge, 2007; Fung *et al.*, 2012; Hutchinson *et al.*, 2016; Hadjiathanasiou *et al.*, 2018; Koliass *et al.*, 2018; Peng *et al.*, 2019). However, a clinical benefit from DC has been proven so far only for space-occupying cerebral infarction (Vahedi *et al.*, 2007).

In patients with aneurysmal subarachnoid haemorrhage (SAH) presenting with severe onset or secondary

ischaemic and haemorrhagic complications, DC might also be required as a lifesaving option. There is still no guideline for DC after SAH, since the present evidence is limited to mostly small mono-centric retrospective series (Fisher and Ojemann, 1994; Smith *et al.*, 2002; D'Ambrosio *et al.*, 2005; Buschmann *et al.*, 2007; Park *et al.*, 2007; Schirmer *et al.*, 2007; Kang, 2008; Otani *et al.*, 2008; Guresir *et al.*, 2009a, b; Nagel *et al.*, 2009; Dorfer *et al.*, 2010; Otani *et al.*, 2011; Stuart *et al.*, 2011; Fung *et al.*, 2012; Tuzgen *et al.*, 2012; Hwang *et al.*, 2014; Mori, 2014; Uozumi *et al.*, 2014; Jussen *et al.*, 2015; Jabbarli *et al.*, 2017). Accordingly,

indications to DC in SAH patients are still based on case-by-case decisions.

Across the previous SAH reports, DC cases can be simply dichotomized into primary (PrimDC) and secondary (SecDC) DC, depending on the time when DC was initiated (primary at admission or secondary in case of intractable intracranial hypertension). In a recent meta-analysis (Alotaibi *et al.*, 2017), a better outcome of SAH patients after PrimDC, as compared to SecDC, was reported. In addition, a clinical benefit of an early PrimDC (performed within 24 h after SAH) over later DC cases was shown in a large retrospective series (Jabbarli *et al.*, 2017). Similar results were also demonstrated after ischaemic stroke, where early DC within 24 h or before clinical signs of herniation improved overall mortality and functional outcomes (Dasenbrock *et al.*, 2017; Shah *et al.*, 2019).

In view of the above-mentioned data, early selection and timing of DC might improve the outcome of SAH patients requiring DC. An appropriate risk score, which could reliably estimate the risk of DC throughout the acute phase of SAH, might be helpful for early selection of DC candidates. Therefore, we aimed at development and validation of a novel risk score for early identification of individuals who undergo DC after SAH, using two large institutional SAH cohorts. A special attention was paid on high accuracy of the score for prediction of both PrimDC and SecDC, as separate indication subgroups.

## Materials and methods

### Patient population

This retrospective analysis is based on two observational institutional SAH cohorts containing consecutive cases with aneurysmal SAH treated at the university hospitals of Essen (between January 2003 and June 2016) and Freiburg (between January 2005 and December 2012). Both observational studies were approved by the local Institutional Ethics Committees (Ethik-Kommission, Albert-Ludwigs-Universität Freiburg, Registration number: 446/13 and Ethik-Kommission, Medizinische Fakultät der Universität Duisburg-Essen, Registration number: 15-6331-BO) and registered in the German clinical trial register (DRKS, Unique identifiers: DRKS00005486 and DRKS00008749).

SAH patients were included from the databases if they were admitted and treated by means of endovascular coiling or microsurgical clipping within 72 h after the bleeding event. The cases without aneurysm treatment, with DC surgery before SAH and later admission/treatment were excluded from the final analysis.

### SAH management

Initial admission and treatment of SAH patients were performed in the neurosurgical intensive care units of the

centres. Ruptured aneurysms were commonly identified by digital subtraction angiography (DSA) with further treatment allocation to either coiling or clipping. In both centres, treatment of a ruptured aneurysm was performed within 24 h after admission. In SAH cases with clinical signs of brainstem herniation (fixed/dilated pupils) at admission and space-occupying intracerebral haematoma (ICH) on computed tomography (CT) scan, the diagnostic phase was limited to CT angiography with subsequent immediate surgical treatment of the patients. In these cases, diagnostic DSA was performed after the aneurysm treatment. Acute hydrocephalus was treated with an external ventricular drainage (EVD) allowing continuous monitoring of intracranial pressure. Conservative management of cerebral vasospasm included oral nimodipine and maintenance of normovolemia. Endovascular vasospasm treatment was initiated in cases of refractory cerebral vasospasm. SAH patients developing chronic hydrocephalus underwent ventriculo-peritoneal shunt placement. Along with a native CT scan at admission, SAH patients underwent additional CT scans: within 24 h after aneurysm treatment, prior to SecDC and/or shunt placement, as well as in cases of any clinical deterioration. There were no relevant changes in the management protocols for SAH over the reported years in the centres.

### DC after SAH

In both centres, patients underwent PrimDC based on clinical (poor neurological condition) and radiological presentation (ICH and brain oedema on the initial CT scan) at admission, as well as intraoperative presence of brain swelling. The actual decision to perform PrimDC was up to the neurosurgeons on duty. The majority of the PrimDC cases (175/185, 94.6%) were selected for aneurysm clipping with simultaneous DC. In the remaining 10 cases, PrimDC was performed immediately after aneurysm coiling.

The patients were selected for SecDC in case of persistent intracranial pressure raise  $>20$  mmHg despite maximal conservative treatment (continuous cerebrospinal fluid drainage via EVD, deep sedation, osmotic diuresis, maintenance of normothermia and mild hyperventilation with goal PaCO<sub>2</sub> of 35 mmHg). In accordance to general recommendations for DC surgery (Carney *et al.*, 2017), the size of the bone flap for DC had a minimum diameter of 12 cm.

### Data management

The goal of this study was the development and validation of a novel risk score for *early prediction* of individuals who undergo PrimDC or SecDC after SAH. As potential score components, various demographic, clinical, radiographic and laboratory variables, which were *present within 72 h after SAH*, were collected (the full list of the tested parameters is shown in Table 1).

**Table 1** Univariate analysis of the predictors of PrimDC and SecDC in the test cohort

Parameter	Prim DC versus No DC		SecDC versus NO DC	
	Mean ( $\pm$ SD) or OR (95% CI)	P-value	Mean ( $\pm$ SD) or OR (95% CI)	P-value
Age, years	52.9 ( $\pm$ 12.6) versus 52.9 ( $\pm$ 12.6)	<b>0.0379</b>	49.7 ( $\pm$ 10.1) versus 52.9 ( $\pm$ 12.6)	<b>0.0008</b>
Sex (female)	1.11 (0.77–1.6)	0.5820	1.56 (0.94–2.6)	0.1054
Prior anticoagulation	0.81 (0.41–1.6)	0.6244	0.67 (0.23–1.98)	0.6272
Arterial hypertension	1.2 (0.82–1.75)	0.3841	1.59 (0.91–2.78)	0.1143
Smoking (history)	0.88 (0.53–1.46)	0.7058	1.0 (0.51–2.13)	0.8565
Diabetes mellitus	0.84 (0.34–2.09)	0.8265	0.34 (0.04–2.53)	0.5018
Hunt and Hess scale (IV–V)	4.54 (3.15–6.54)	<b>&lt;0.0001</b>	2.46 (1.48–4.08)	<b>0.0007</b>
Dilated/fixed pupils	6.08 (3.67–10.06)	<b>&lt;0.0001</b>	1.46 (0.55–3.89)	0.3995
Fisher scale (III–IV)	30.77 (4.24–223.0)	<b>&lt;0.0001</b>	2.17 (0.85–5.58)	0.1322
Aneurysm (anterior circulation)	5.74 (3.29–10.02)	<b>&lt;0.0001</b>	2.83 (1.45–5.51)	<b>0.0016</b>
Aneurysm size, mm	8.7 ( $\pm$ 4.8) versus 6.7 ( $\pm$ 4.2)	<b>&lt;0.0001</b>	8.1 ( $\pm$ 5.1) versus 6.7 ( $\pm$ 4.2)	<b>0.0118</b>
Treatment modality (clipping)	68.14 (32.66 - 142.2)	<b>&lt;0.0001</b>	2.05 (1.21–3.46)	<b>0.0110</b>
Acute hydrocephalus	0.88 (0.61–1.27)	0.5096	3.67 (1.64–8.18)	<b>0.0005</b>
Presence of IVH	1.17 (0.83–1.64)	0.3865	1.48 (0.89–2.46)	0.1553
Severity of IVH (Graeb score)	2.89 ( $\pm$ 3.8) versus 2.17 ( $\pm$ 3.1)	0.1207	2.58 ( $\pm$ 3.3) versus 2.17 ( $\pm$ 3.1)	0.1771
Presence of ICH	20.07 (13.01–30.95)	<b>&lt;0.0001</b>	3.88 (2.29–6.56)	<b>&lt;0.0001</b>
ICH volume, ml	38.86 ( $\pm$ 35.2) versus 13.9 ( $\pm$ 16.8)	<b>&lt;0.0001</b>	13.4 ( $\pm$ 16) versus 13.9 ( $\pm$ 16.8)	0.6165
Rebleeding	3.88 (1.91–7.85)	<b>0.0004</b>	2.79 (0.99–7.87)	0.0595
Early angiographic vasospasm	2.76 (1.62–4.69)	<b>0.0004</b>	3.51 (1.91–6.45)	<b>0.0001</b>
Early Infarction	2.97 (2.07–4.25)	<b>&lt;0.0001</b>	4.22 (2.5–7.11)	<b>&lt;0.0001</b>
WBC, $\times 10^9/l$	14.02 ( $\pm$ 4.5) versus 13 ( $\pm$ 4.7)	<b>0.0068</b>	14.7 ( $\pm$ 4.7) versus 13 ( $\pm$ 4.7)	<b>0.0052</b>
Haemoglobin, $\times 10^1 g/l$	12.4 ( $\pm$ 2) versus 12.7 ( $\pm$ 1.9)	0.1099	12.9 ( $\pm$ 1.9) versus 12.7 ( $\pm$ 1.9)	0.6074
CRP, $\times 10^{-3} g/l$	0.7 ( $\pm$ 1.6) versus 1.0 ( $\pm$ 1.9)	0.1504	1.0 ( $\pm$ 2.1) versus 1.0 ( $\pm$ 1.9)	0.5202
CSF Interleukin-6, $\times 10^{-6} g/l$	4.16 ( $\pm$ 6.14) versus 3.4 ( $\pm$ 6.51)	0.7950	4.39 ( $\pm$ 7.3) versus 3.4 ( $\pm$ 6.51)	0.9597
CSF cells, $\times 10^6/l$	2705 ( $\pm$ 7204) versus 1229 ( $\pm$ 2963)	0.5562	1380 ( $\pm$ 1853) versus 1229 ( $\pm$ 2963)	0.3275
Troponin-I, $10^{-9} g/l$	0.6 ( $\pm$ 2) versus 2.5 ( $\pm$ 31.7)	0.2435	0.5 ( $\pm$ 1) versus 2.5 ( $\pm$ 31.7)	0.9254
Maximal systolic BP, mmHg	161.6 ( $\pm$ 22.6) versus 165.4 ( $\pm$ 25.8)	0.0513	168.2 ( $\pm$ 24.7) versus 165.4 ( $\pm$ 25.8)	0.2476
Minimal systolic BP, mmHg	125.5 ( $\pm$ 88.6) versus 124.1 ( $\pm$ 57.4)	0.2574	122.9 ( $\pm$ 24.2) versus 124.1 ( $\pm$ 57.4)	0.9612
Mean MAP, mmHg	89.3 ( $\pm$ 14.8) versus 90.5 ( $\pm$ 14.6)	0.1131	93.1 ( $\pm$ 15.3) versus 90.5 ( $\pm$ 14.6)	0.2552
Maximal body temperature, $^{\circ}C$	37.2 ( $\pm$ 0.9) versus 37 ( $\pm$ 1.9)	0.5385	37.2 ( $\pm$ 0.9) versus 37 ( $\pm$ 1.9)	0.3009

For laboratory parameters, the first value at admission was considered. P-values set in boldface indicate statistical significance.

SD = standard deviation; OR = odds ratio; CI = confidence interval; WBC = white blood cells; CRP = C-reactive protein; CSF = cerebrospinal fluid; BP = blood pressure; MAP = mean arterial pressure.

Clinical condition at admission was graded according to Hunt and Hess (1968), wherein the presence of dilated/fixed pupils was additionally documented as a clinical sign of brainstem herniation (Fung et al., 2016). The cases with pupillary dysfunction related to local compression syndrome from aneurysm were not considered as brainstem herniation signs. Location and the size (maximal diameter) of the ruptured aneurysms were recorded from the DSA reports. In addition, the presence of an unequivocal narrowing of the arterial vessel lumen on the admission DSA suspicious for cerebral vasospasm was also recorded. The severity of SAH on the initial CT scans was assessed according to the original Fisher scale (Fisher et al., 1980). Further radiographic evaluation included the measurement of the severity of intraventricular haemorrhage (IVH) using the original Graeb score (Graeb et al., 1982), and the volume of aneurysmal ICH by the AxBxC/2-formula (Kothari et al., 1996). In both centres, all CT scans were reviewed by the first author (R.J.) blinded at that time for any clinical information. Occurrence of cerebral infarction within 72 h after SAH was defined as early infarction. Hypodensities resulting from ICH, EVD or

surgical approach were not considered as infarcts. Medical comorbidities (arterial hypertension, smoking history, diabetes mellitus and prior anticoagulation) were documented according to the electronic health records. The *functional endpoints* of the study were in-hospital mortality and unfavourable outcome at 6 months after SAH defined as a modified Rankin Scale  $>3$  (van Swieten et al., 1988). According to the standard operating procedures of both units, the follow-up evaluations of the patients were performed in the appropriate outpatient clinics on a routine basis.

## Statistical analysis

Data of the patients from the university Hospital of Essen were used for the creation of the risk score ('test cohort'), whereas the external validation of the score was performed on the SAH cohort from Freiburg ('validation cohort'). After the creation and validation of the score, further analyses regarding the associations between DC and SAH outcome were performed in the pooled data of both cohorts.

### Score creation

Prior to eventual inclusion to the risk score, all recorded 'admission' variables were subsequently tested through univariate and multivariate analysis for the associations with PrimDC and SecDC separately. Univariate assessments were performed using the Student's *t*-test for normally distributed and the Mann–Whitney *U* test for non-normally distributed continuous data, as well as the Fisher exact or chi-square tests for categorical variables. Significant parameters were considered for further multivariate analysis, where all included variables were converted to dichotomous variables to make them eligible as score components. Initial clinical condition (Hunt and Hess) was as assessed as good (I–III) and poor (IV–V) grades, and the Fisher scale as low (I–II) and high (III–IV) grades. The remaining continuous variables (age, aneurysm size, ICH volume, white blood cells count) were dichotomized according to the cut-off estimation in the receiver operating characteristic curve and the appropriate area under the curve (AUC) values.

Thereafter, independent predictors of PrimDC and SecDC in the test cohort were identified using multivariate binary logistic regression analysis. The significant parameters from both analyses were then included as final score components. The appropriate adjusted odds ratios (aOR) were divided by the smallest coefficient and then rounded to the nearest whole number.

### Score validation

Based upon the presence of the components of the new score, a total point value was calculated for each SAH patient from the final analysis. For both cohorts separately, the association between the risk score and PrimDC/SecDC was tested using the receiver operating characteristic curves, bivariate and multivariate analyses. In addition, the Hosmer–Lemeshow test for goodness of fit for logistic regression models and the bootstrapping method were also applied during the score validation.

### Association of DC with SAH outcome

Using univariate and multivariate analyses, the relationship between DC and outcome endpoints was evaluated in the pooled data from both cohorts. Therefore, the whole cohort was analysed in different subgroups depending on: (i) indication to DC (PrimDC, SecDC or no DC); (ii) timing of DC measured in days since the bleeding event; (iii) risk score values (low- and high-risk groups); and (iv) clinical manifestation (presence of brainstem herniation at admission).

Statistical analyses were performed with the help of PRISM (version 5.0, GraphPad Software Inc., San Diego, CA, USA) and SPSS (version 21, SPSS Inc., IBM, Chicago, IL, USA). Variables were expressed as mean  $\pm$  standard deviation (SD) or percentage of patients, as appropriate. Differences with a  $P < 0.05$  were regarded as statistically significant. Missing data were replaced using multiple imputation.

### Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Results

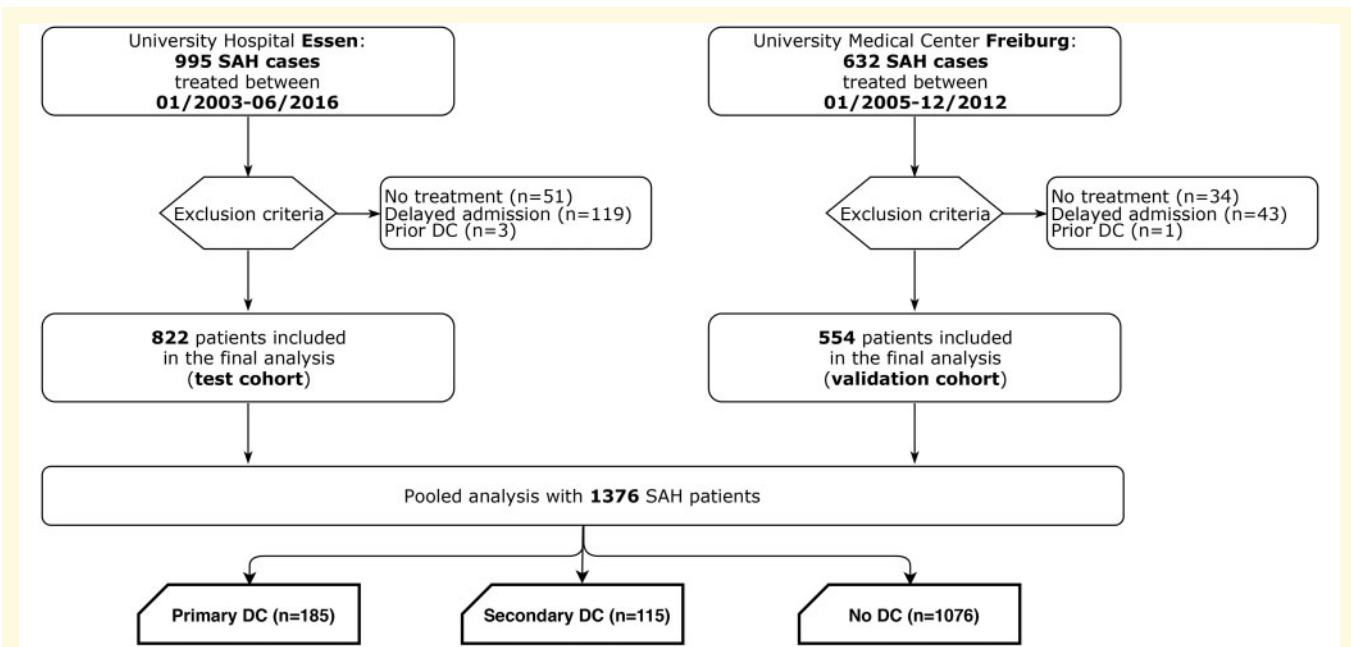
Data of 1627 SAH patients were available in the observational cohorts of both centres. Of them, 1376 individuals (822 and 554 in the test and validation cohorts, respectively) were eligible for this study (Fig. 1). There was no difference with regards to basic demographic, radiographic and clinical characteristics of the analysed cohorts (see Supplementary Table 1). According to the inclusion criteria, all SAH patients in the final analysis were treated within 72 h after the bleeding event. There was no association between the timing of aneurysm treatment and the rates of early CT infarctions ( $P = 0.633/P = 0.354$ ) and DC ( $P = 0.941/P = 0.293$  in the test and validation cohorts, respectively). However, the test cohort was characterized by a significantly higher proportion of patients undergoing PrimDC after SAH (21% versus 2.2% in the validation cohort,  $P < 0.0001$ ). In turn, there was no difference in the proportion of patients with SecDC between the cohorts (8.3% versus 8.5%,  $P = 0.9210$ ).

### Risk score construction

In the test cohort, 30 parameters at admission were correlated with the PrimDC and SecDC (Table 1). Accordingly, 13 and 10 significant variables were included in the multivariate analysis of PrimDC and SecDC predictors, respectively (see Supplementary Table 2). Based on both multivariate analyses, the following parameters were included to the new risk score for DC after SAH: *presence of ICH, early vasospasm on DSA, early CT infarction, aneurysm sac size  $\geq 5$  mm, microsurgical clipping, and younger age ( $\leq 55$  years old), poor initial clinical condition (Hunt and Hess grades IV–V) and the need for EVD*. According to the aOR values, all score components except age (2 points) were weighted with 1 point. Based on the included risk factors, the new score was named PRESSURE (Table 2).

### Risk score validation

In the receiver operating characteristic curves, the new risk score showed high diagnostic accuracy for the prediction of PrimDC and SecDC in the test (AUC = 0.842/0.818) and validation (AUC = 0.903/0.823) cohorts, respectively (hereinafter). There was a strong association between the PRESSURE score and DC in both cohorts ( $P < 0.0001/P < 0.0001$ , Fig. 2). Multivariate analysis confirmed independent association between the risk score and the PrimDC [aOR = 3.15 per point increase (95% confidence interval [CI]: 2.43–4.08),



**Figure 1** Flow-chart demonstrating the selection process of SAH patients eligible for this study in both cohorts.

**Table 2** Components, weights and acronym explanation of the PRESSURE score

Component	Weights	Acronym explanation
Presence of ICH	1	Parenchymal bleeding
Early DSA Vasospasm	1	Rapid Vasospasm
Early CT infarction	1	Early Infarct
Aneurysm size >5 mm	1	Size of aneurysm > 5 mm
Clipping	1	Surgery of aneurysm
Age <55 years	2	Under 55 years
Hunt and Hess IV – V	1	Reduced consciousness
Need for EVD	1	External ventricular drain

$P < 0.0001$ /aOR = 2.07 per point increase (95% CI: 1.12–3.81),  $P = 0.02$ ] and SecDC [aOR = 2.56 per point increase (95% CI: 1.93–3.39),  $P < 0.0001$ /aOR = 1.9 per point increase (95% CI: 1.42–2.55),  $P < 0.0001$ ] in the analysed cohorts. According to the Hosmer–Lemeshow test ( $P = 0.972$ / $P = 0.531$ ), there was no evidence for poor calibration of the PRESSURE score. The bootstrapping method confirmed the robustness of the score against possible variability in both cohorts.

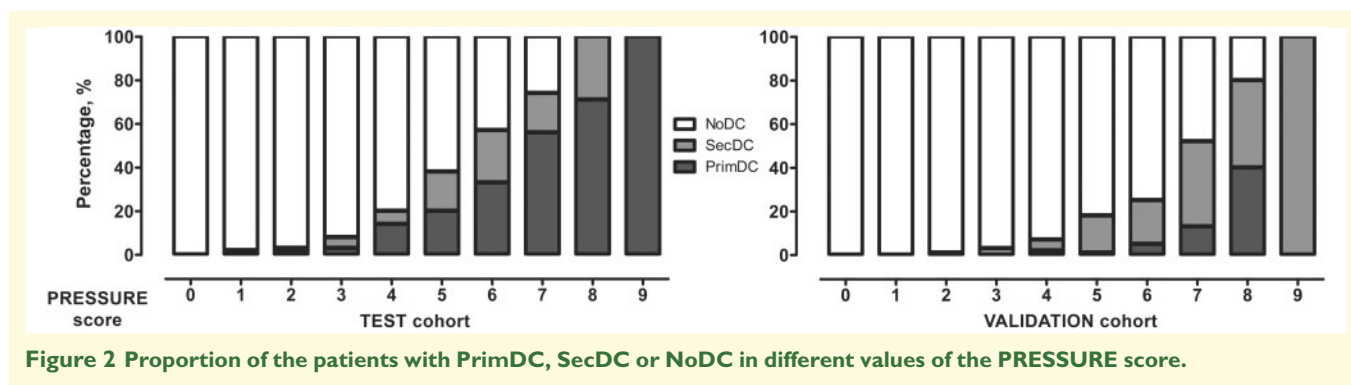
In the pooled data analysis, 63.7% of the patients scoring  $\geq 6$  points required DC, as compared with 12% among the cases with the PRESSURE value  $< 6$  points, OR = 12.87 (95% CI: 9.3–17.80),  $P < 0.0001$ . The difference in the DC rates at the PRESSURE cut-off of 6 points remained significant, when comparing in the test [OR = 15.14 (95% CI: 9.93–23.08),  $P < 0.0001$ ] and validation [OR = 11.16 (95% CI: 6.13–20.3),  $P < 0.0001$ ] cohorts separately. Accordingly, SAH patients scoring PRESSURE  $\geq 6$  points were regarded as individuals at ‘high risk for DC’.

Finally, the PRESSURE score showed independent association with the functional study endpoints in both cohorts: aOR = 1.55 (95% CI: 1.27–1.89),  $P < 0.0001$ /aOR = 1.47 (95% CI: 1.17–1.85),  $P = 0.001$  for in-hospital mortality and aOR = 1.7 (95% CI: 1.44–2.0),  $P < 0.0001$ /aOR = 1.57 (95% CI: 1.3–1.9),  $P < 0.0001$  for unfavourable outcome.

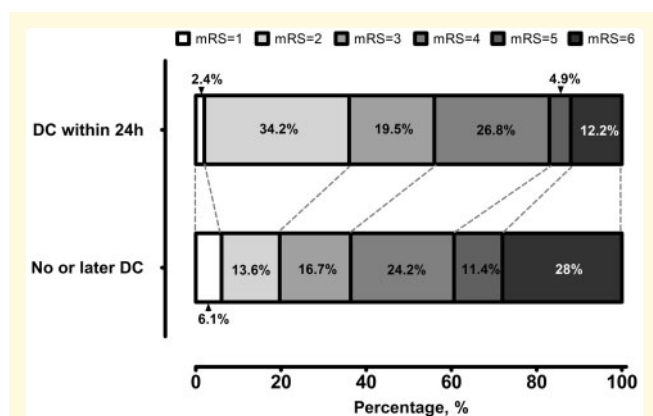
## DC and SAH outcome

In the whole cohort, the individuals selected for DC showed poorer outcome, than SAH patients without DC: (i) 26.5% (PrimDC) versus 42.1% (SecDC) versus 10.7% (NoDC) for in-hospital mortality ( $P < 0.0001$  for PrimDC versus no DC/ $P < 0.0001$  for SecDC versus no DC); (ii) 64.9% versus 78.3% versus 33.3% for unfavourable outcome ( $P < 0.0001$ / $P < 0.0001$ , respectively). In turn, SAH patients with PrimDC were at lower risk for in-hospital mortality ( $P = 0.0074$ ) and unfavourable outcome ( $P = 0.0142$ ), than the counterparts with SecDC. The multivariate analysis showed independent association between the timing of DC and functional outcome ( $P = 0.003$ ).

After restricting the analysis to the SAH patients at ‘high risk for DC’ (PRESSURE  $\geq 6$  points), but without dilated/fixed pupils at admission ( $n = 173$ ), we compared the outcome of SAH patients who underwent early PrimDC (performed within 24 h after SAH) with the remaining patients (i.e. *with later or no DC*). Herein, patients with early PrimDC showed lower risk of unfavourable outcome [OR = 0.45 (95% CI: 0.22–0.91),  $P = 0.0297$ ] and in-hospital mortality [OR = 0.28 (95% CI: 0.09–0.83),  $P = 0.0197$ , see Fig. 3 with full modified



**Figure 2** Proportion of the patients with PrimDC, SecDC or NoDC in different values of the PRESSURE score.



**Figure 3** Outcome of SAH individuals with PRESSURE  $\geq 6$  points. Functional outcome at 6 months after SAH in the subgroup of patients with  $\geq 6$  points on the PRESSURE score ('high risk for DC') and without fixed/dilated pupils at admission. The analysis is based on the pooled data from both cohorts.

Rankin Scale values at 6 months post-SAH of the patients in this subgroup]. Independent association between early PrimDC and the study endpoints could be confirmed in the multivariate analysis adjusted for demographic and clinical characteristics of the patients, treating centre and the PRESSURE score value ( $P < 0.0001/P = 0.018$  for unfavourable outcome and in-hospital mortality, respectively, see [Supplementary Table 3](#)).

## Discussion

In this pooled analysis of 1376 patients from two institutional observational SAH cohorts, we developed a new risk score for the prediction of DC after SAH. Despite significantly different rates of DC in the analysed cohorts, the PRESSURE score successfully underwent internal and external validation, showed a high diagnostic accuracy and robustness in prediction of both DC events: PrimDC and SecDC. The presented score might become a useful tool for early selection of individuals who are highly likely to require DC during SAH.

## DC after SAH: the current evidence

There are several retrospective institutional series reporting on indications to and outcome after DC in SAH patients (Fisher and Ojemann, 1994; Smith *et al.*, 2002; D'Ambrosio *et al.*, 2005; Buschmann *et al.*, 2007; Park *et al.*, 2007; Schirmer *et al.*, 2007; Kang, 2008; Otani *et al.*, 2008; Guresir *et al.*, 2009a, b; Nagel *et al.*, 2009; Dorfer *et al.*, 2010; Otani *et al.*, 2011; Stuart *et al.*, 2011; Fung *et al.*, 2012; Tuzgen *et al.*, 2012; Hwang *et al.*, 2014; Mori, 2014; Uozumi *et al.*, 2014; Jussen *et al.*, 2015; Jabbarli *et al.*, 2017). Due to negative selection bias, individuals necessitating DC after SAH are characterized with higher morbidity and mortality rates, than SAH patients without DC. In fact, DC remains mostly an ultima ratio against intractable intracranial hypertension, which is basically the consequence of severe early brain injury and secondary ischaemic complications after SAH. At the same time, these causal processes evoking DC are also acknowledged as strong outcome predictors of SAH (Jabbarli *et al.*, 2015a, b). As noted in a recent meta-analysis on DC in SAH (Alotaibi *et al.*, 2017), due to the lack of robust control groups, the effect of DC on functional outcomes versus that of other interventions for refractory intracranial hypertension is still unknown. As to the proper DC management in SAH patients, several studies highlighted the essential role of early DC for favourable outcome (Smith *et al.*, 2002; Schirmer *et al.*, 2007; Otani *et al.*, 2008; Jussen *et al.*, 2015; Jabbarli *et al.*, 2017). This conclusion is in line with a general consensus from stroke and traumatic brain injury trials, which pointed to the utmost importance of DC timing (Dasenbrock *et al.*, 2017; Shackelford *et al.*, 2018; Shah *et al.*, 2019).

## Clinical value of DC after SAH: a scope for prophylactic use with the PRESSURE score?

So far, indication for and timing of DC after SAH are based on individual decisions of treating neurosurgeons.

In this study, we developed and validated the novel risk score for prediction of necessity for DC after aneurysm rupture. Based on the risk factors assessable at admission, the PRESSURE score facilitates reliable and early selection of DC candidates after SAH. Since the individuals with SecDC showed the lowest chances for favourable outcome, early decompression of these patients at admission might improve the treatment results.

And even more, early DC might be a reasonable option *not only for* SAH individuals requiring SecDC. In a subgroup analysis of SAH patients who were at 'high risk for DC' ( $\geq 6$  points on the PRESSURE score), a positive effect of early DC on the functional outcome after SAH was shown. In particular, the significant difference in favour of early PrimDC (as against later DC or no DC at all) was observed only after the restriction of the analysis to the cases without brainstem herniation and without prolonged utilization of conservative intracranial pressure treatment (i.e. for DCs performed within 24 h after SAH). This finding is of eminent importance, since the clinical utility of DC is currently limited to the cases with medically refractory intracranial hypertension and/or clinical deterioration (Nirula et al., 2014). Because of rather disappointing functional outcome of SAH individuals undergoing DC, many authors expressed criticism regarding the clinical value of DC after SAH (D'Ambrosio et al., 2005; Buschmann et al., 2007; Kang, 2008; Dorfer et al., 2010). As noted above, this is due to negative selection bias of SAH individuals undergoing DC. Therefore, a PRESSURE score-based rethinking of indications to DC after SAH towards a more preventive ('prophylactic') use might bring new insight to the clinical value of DC after SAH. At the same time, certain risks of DC-related complications (like rebleeding or infection) as well as the need for reoperation for cranioplasty should be accounted when considering the initiation of DC. Nevertheless, our findings might provide a basis for a prospective randomized clinical trial evaluating the value of a prophylactic early DC in SAH individuals.

## Study limitations

The major limitation of the study is related to the retrospective nature of the presented analysis. The absence of strictly defined study protocols for DC after SAH in both institutions might limit the generalizability of the study results. Particularly, indications to PrimDC strongly depended on individual decisions of neurosurgeons on duty. Overall, the constructed score, at least partially, incorporates the selection bias accompanying DC indications in everyday practice, since there are no guidelines for DC after SAH based on certain measurable criteria. This circumstance may especially refer to the association between the treatment modality (clipping) and DC. On the other hand, objective intraoperative findings (like the presence of brain swelling or intraoperative complications) might also contribute to the decision to perform

DC. In summary, the selection of the score components was based on strict statistical evaluation, and the parameters included to the PRESSURE are in line with common predictors of DC reported previously for SAH patients (Fisher and Ojemann, 1994; Smith et al., 2002; D'Ambrosio et al., 2005; Buschmann et al., 2007; Park et al., 2007; Schirmer et al., 2007; Kang, 2008; Otani et al., 2008; Guresir et al., 2009a, b; Nagel et al., 2009; Dorfer et al., 2010; Otani et al., 2011; Stuart et al., 2011; Fung et al., 2012; Tuzgen et al., 2012; Hwang et al., 2014; Mori, 2014; Uozumi et al., 2014; Jussen et al., 2015; Jabbarli et al., 2017).

Although the inclusion of eight parameters makes the score somewhat complex, all components of the PRESSURE score are easily assessable. The included Hunt and Hess scale was reported to be inferior to the World Federation of Neurological Surgeons (WFNS) scale (Teasdale et al., 1988) with regards to outcome prediction. However, the Hunt and Hess scale is still widely accepted and a recent publication did not show any advantage of the WFNS over the Hunt and Hess scale (Dengler et al., 2018). Finally, due to a limited number of levels, the modified Rankin Scale used for outcome assessment may be less responsive to changes in neurological and functional condition of the patients than some other stroke scales (Broderick et al., 2017).

## Conclusion

Timing of DC seems to be of paramount importance for functional outcome of SAH patients requiring decompressive surgery. The presented score has been successfully validated as a reliable predictor of DC in two separate SAH cohorts and allows early selection of patients at admission. The PRESSURE score might present a background for prospective randomized clinical trial addressing the utility of the early prophylactic DC for SAH patients.

## Supplementary material

Supplementary material is available at *Brain Communications* online.

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## Competing interests

The authors report no competing interests.



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