Aneurysm rebleeding before therapy: a predictable disaster?

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OBJECTIVE Current guidelines for subarachnoid hemorrhage (SAH) include early aneurysm treatment within 72 hours after ictus. However, aneurysm rebleeding remains a crucial complication of SAH. The aim of this study was to identify independent predictors allowing early stratification of SAH patients for rebleeding risk.

METHODS All patients admitted to the authors' institution with ruptured aneurysms during a 14-year period were eligible for this retrospective study. Demographic and radiographic parameters, aneurysm characteristics, medical history, and medications as well as baseline parameters at admission (blood pressure and laboratory parameters) were evaluated in univariate and multivariate analyses. A novel risk score was created using independent risk factors.

RESULTS Data from 984 cases could be included into the final analysis. Aneurysm rebleeding occurred in 58 cases (5.9%), and in 48 of these cases (82.8%) rerupture occurred within 24 hours after SAH. Of over 30 tested associations, preexisting arterial hypertension ($p = 0.02$; adjusted odds ratio [aOR] 2.56, 1 score point), aneurysm location at the basilar artery ($p = 0.001$, aOR 4.5, 2 score points), sac size ≥ 9 mm ($p = 0.04$, aOR 1.9, 1 score point), presence of intracerebral hemorrhage ($p = 0.001$, aOR 4.29, 2 score points), and acute hydrocephalus ($p < 0.001$, aOR 6.27, 3 score points) independently predicted aneurysm rebleeding. A score built upon these parameters (0–9 points) showed a good diagnostic accuracy ($p < 0.001$, area under the curve 0.780) for rebleeding prediction.

CONCLUSIONS Certain patient-, aneurysm-, and SAH-specific parameters can reliably predict aneurysm rerupture. A score developed according to these parameters might help to identify individuals that would profit from immediate aneurysm occlusion.

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KEYWORDS aneurysm; rebleeding; subarachnoid hemorrhage; vascular disorders

ANEURYSM rebleeding before therapy is the most relevant preventable cause of death after subarachnoid hemorrhage (SAH).⁶ Furthermore, it is one of the main causes of poor outcome in surviving patients.²⁸ Both the European Stroke Organization³⁰ and American Stroke Association¹¹ have recently issued guidelines recommending aneurysm occlusion in the first 72 hours after ictus (early treatment) as long it is feasible in light of the patient's condition.

Rebleeding rates are still reported to be between 7% and 21%.^{5,33} The first 24 hours after initial SAH has been

identified as a critical time with the highest rebleeding risk.^{19,21,22} Most of the North American and Western European neurovascular centers have introduced an ultra-early (< 24 hours after admission) aneurysm occlusion therapy as standard of care. However, patients who are at risk for early rebleeding might benefit from immediate aneurysm occlusion. Therefore, efforts have been made to identify possible predictors of rebleeding events, but many of these studies have relied on small cohorts and present conflicting results.^{4,8,16,18,19,25,26} Recent meta-analyses proposed aneurysm size, high systolic blood pressure, high clinical

ABBREVIATIONS aOR = adjusted odds ratio; CSF = cerebrospinal fluid; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; oGS = original Graeb Score; ROC = receiver operating characteristic; SAH = subarachnoid hemorrhage; WFNS = World Federation of Neurosurgical Societies.

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SAH severity, intraventricular/intracerebral bleeding, and placement of a cerebrospinal fluid (CSF) drainage system as well as aneurysm location as predictors of aneurysm rebleeding.^{5,7,31} Additionally, sentinel headache has been reported to be a strong predictor of rebleeding.⁴

The aim of this study was to identify independent risk factors for aneurysm rebleeding in a large institutional SAH cohort. In addition, we aimed to develop a risk score for better estimation of patient-specific rebleeding risk at admission.

Methods

All consecutive patients treated for aneurysmal SAH in our neurosurgical department between January 2003 and June 2016 were included in this retrospective analysis. This study has been approved by the institutional review board. All persons or their relatives gave their informed consent within a written treatment contract prior to their inclusion in the study.

Treatment Regime

According to our institutional policy, all SAH patients undergo aneurysm occlusion within 24 hours after admission. Decisions about microsurgical or endovascular treatment were based on interdisciplinary consensus. Acute hydrocephalus (defined as presentation with ventriculomegaly or intraventricular hemorrhage [IVH] and decreased level of consciousness that could not be attributed to other causes than hydrocephalus⁹) was treated by drainage of CSF via an external ventricular or lumbar drain. Space-occupying intracerebral hemorrhage (ICH) was treated by urgent surgical decompressive craniectomy and, if applicable, hematoma evacuation. Prior to aneurysm occlusion, a rigorous blood pressure regimen was applied to keep the systolic pressure at ≤ 150 mm Hg.

An early posttreatment CT scan of the head was performed in the first 24 hours after aneurysm occlusion in all cases. Further imaging was performed as necessary.

All patients were administered oral nimodipine for 21 days and underwent transcranial Doppler ultrasonography daily for 14 days. Symptomatic vasospasm was treated by intraarterial nimodipine application or transluminal catheter angioplasty, if necessary.

Data Management

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

All events involving clinical deterioration before treatment of the aneurysm in conjunction with new hemorrhage on CT were judged as rebleeding events. Rebleeding episodes in referring hospitals, during transport, and at our institution were recorded. Intraprocedural aneurysm rupture or index bleedings following a sentinel headache were not considered rebleeding in this report.

Clinical severity of SAH was assessed according to the World Federation of Neurosurgical Societies (WFNS) grading system.³² For statistical analysis, we dichotomized cases into good grade (WFNS grades I–III) and poor grade (WFNS grades IV and V). For assessment of

radiographic severity, the original Fisher scale¹⁵ was used. For analysis, the radiographic severity was dichotomized into low (Fisher grades 1 and 2) and high (Fisher grades 3 and 4) grades.

Patient charts were reviewed for age, sex, preexisting morbidities (arterial hypertension, diabetes mellitus, smoking), and anticoagulation treatment (vitamin K antagonists, antiplatelet therapy, new oral anticoagulants) prior to admission. Presence of preexisting comorbidities (diabetes mellitus and arterial hypertension) was judged upon the records in the institutional admission protocol, which contains data on past medical history (past illnesses, surgeries, medications, etc.). Furthermore, a wide range of vital and laboratory parameters at admission were also recorded, including blood pressure levels (maximum and minimum values for the systolic and mean overall value for the mean arterial pressure), body temperature (maximum values), and baseline laboratory test values for serum and CSF.

The timings of the bleeding event, hospital admission, and rebleeding event were also documented. Timing of the rebleeding event was stratified into 3 intervals: < 12 hours, 12–24 hours, and > 24 hours after the initial bleeding event or admission.

Along with the Fisher grade, the following radiographic parameters were also collected: presence of ICH; presence of IVH; size, location, and shape of the ruptured aneurysm; and the presence of multiple aneurysms. IVH severity was assessed using the original Graeb Score (oGS).¹⁷ All aneurysms that presented with daughter sac(s) ($< 50\%$ of aneurysm size) or multiple lobes ($> 50\%$ of aneurysm size) were defined as irregular.

Functional endpoints were in-hospital mortality and poor outcome at 6 months after SAH (defined as modified Rankin Scale³⁵ score > 2).

Statistical Analysis and Score Building

Statistical analysis was performed using SPSS 22 for Mac (IBM Corp.). Continuous variables are presented as mean $\pm$ standard deviation. They were analyzed using the Student t-test for normally distributed and the Mann-Whitney U-test for nonnormally distributed data. Categorical variables were analyzed using the chi-square test; for samples smaller than 5, the Fisher exact test was used. Statistical significance was set at $p < 0.05$. Factors predictive for occurrence of rebleeding in univariate analysis were included in final multivariate binary logistic regression analysis. For continuous variables, a cutoff was identified using the receiver operating characteristic (ROC) curve analysis prior to multivariate analysis. Multivariate analysis was conducted in 2 steps. First, parameters that were present before and those characterizing SAH event were analyzed separately. Then, parameters identified in both analyses were included to the final multivariate model. The results of this cumulative multivariate analysis were used to build a risk score. The adjusted odds ratios (aORs) of these variables were divided by the smallest coefficient and then rounded up to the nearest integer. We used the result to weight the value of each parameter. Finally, the total score value was calculated for each SAH individual in the cohort, depending on the presence of identified risk

FIG. 1. Rebleeding rate by aneurysm location. The incidence of aneurysms by location for the whole cohort was as follows: anterior cerebral artery (ACA), 374; posterior circulation (PC), 274 (non-basilar artery [BA], 190; BA, 84); middle cerebral artery (MCA), 219; and internal carotid artery (ICA), 117. * $p = 0.01$ regarding risk of rebleeding (vs all other locations).

factors for rebleeding. Missing data were replaced using multiple imputations. Diagnostic accuracy of the new score was tested using the ROC curve.

Results

A total of 994 patients were eligible for this study. Due to initial severe presentation of SAH, a judgment about rebleeding was not possible in 10 cases, and therefore 984 patients were included in final analysis. The majority of the patients were female (66.9%) and Caucasian (95.5%). The mean age at admission was 54.8 ± 13.6 . Rebleeding occurred in 58 cases (5.9%), and in 34 of these cases (58.6%) it occurred in the first 12 hours after ictus. In the remaining cases, 14 rebleeding events (24.1%) occurred during the next 12 hours post-SAH (i.e., 48 cases within 24 hours). Only 10 (17.2%) events occurred later in the clinical course. Thirty-two events (55.2%) occurred after admission at our institution, 17 (29.3%) during hospital transport, and 9 (15.5%) at a referring hospital. CSF drainage was required in 674 (68.4%) cases due to acute hydrocephalus. Patients presented in poor initial clinical condition in 41.0% of cases. Radiographic severity was high in 86.8% of cases. There was no significant difference in the timing of treatment for the patients with and without rebleeding ($p = 0.28$ for treatment < 8 hours after admission).

Parameters Present Prior to Admission

In univariate analysis, higher age at admission (58.9 vs 54.5 years, $p = 0.018$), previous use of anticoagulation medication ($p = 0.02$, OR 2.78, 95% CI 1.22–5.95), and premorbid arterial hypertension ($p = 0.01$, OR 2.47, 95% CI 1.21–5.06) were predictive for occurrence of rebleeding. Regarding the characteristics of the ruptured aneurysm, larger size (mean 8.94 vs 7.2 mm, $p = 0.005$) and location at the basilar artery ($p = 0.12$, OR 2.74, 95% CI 1.36–5.5; see also Fig. 1) increased the risk of rebleeding significantly. Aneurysm morphology (judged as irregu-

lar shape or presence of a daughter sac, $p = 0.88$ and $p > 0.99$, respectively) and presence of multiple aneurysms ($p = 0.32$) had no predictive value (see also Table 1). For further analysis, aneurysm size was dichotomized as < 9 mm versus ≥ 9 mm and age was dichotomized as < 57 vs ≥ 57 years (according to the ROC curves; Supplemental Fig. E1).

In multivariate analysis of parameters prior to SAH, we were able to identify premorbid arterial hypertension ($p = 0.03$, aOR 2.44, 95% CI 1.10–5.45), aneurysm location at the basilar artery ($p = 0.14$, aOR 2.5, 95% CI 1.2–3.75), and sac size ≥ 9 mm ($p = 0.02$, aOR 2.04, 95% CI 1.11–3.75) as independent predictors of aneurysm rebleeding (Table 2).

Clinical and Radiographic Features of SAH

Patients who initially presented in poor clinical condition had a significantly increased risk of aneurysm rebleeding ($p < 0.001$, OR 3.45, 95% CI 1.95–6.11). Higher Fisher grade (grades 3–4, $p = 0.006$, OR 8.76, 95% CI 1.2–64.02), presence of ICH ($p < 0.001$, OR 2.9, 95% CI 1.7–4.95) and higher IVH severity (mean oGS 6.45 vs 4.98, $p = 0.02$), and acute hydrocephalus ($p < 0.001$, OR 6.66, 95% CI 2.39–18.57; see also Table 1) were also associated with rebleeding risk. The clinically relevant cutoff for IVH severity was set at an oGS of 5 (with an oGS ≥ 5 considered to indicate severe IVH) (Supplemental Fig. E1).

In multivariate analysis of SAH characteristics, only presence of ICH ($p = 0.004$, aOR 2.42, 95% CI 1.33–4.38) and acute hydrocephalus ($p = 0.003$, aOR 5.05, 95% CI 1.73–14.79) independently predicted occurrence of rebleeding (Table 3).

Initial Management of SAH and Laboratory Tests

Systolic blood pressure ($p = 0.31$ for maximum and $p = 0.71$ for minimum), mean arterial pressure ($p = 0.89$), and maximum temperature ($p = 0.16$) at admission did not differ significantly between the 2 groups. A cutoff for maximum systolic blood pressure of 182 mm Hg (according to

TABLE 1. Univariate analysis of parameters predictive for aneurysm rebleeding before treatment

Parameter	Rebleeding	No Rebleeding	OR (95% CI)	p Value
No. of patients	58 (5.9%)	926 (94.1%)	—	—
Parameters present prior to SAH event				
Mean age, yrs	58.9 ± 13.58	54.5 ± 13.68	—	0.02
Sex: female	65.52%	66.95%	0.94 (0.54–1.64)	0.89
Race: Caucasian	98.28%	95.36%	2.78 (0.38–20.53)	0.51
Previous anticoagulation	33.3%	15.67%	2.69 (1.22–5.95)	0.02
Arterial hypertension	71.05%	49.85%	2.47 (1.21–5.06)	0.01
Smoker (previous or current)	25.71%	23.11%	1.15 (0.53–2.51)	0.69
Diabetes mellitus	11.43%	5.44%	2.24 (0.75–6.7)	0.13
Presence of multiple aneurysms	27.59%	34.67%	0.72 (0.4–1.3)	0.32
Aneurysm location (BA)	13.1%	8.01%	2.74 (1.36–5.5)	0.01
Mean aneurysm size, mm	8.94 ± 5.07	7.2 ± 4.64	—	0.005
Irregular shape	48.98%	47.64%	1.06 (0.59–1.88)	0.88
Daughter sac	22.45%	21.91%	1.03 (0.52–2.06)	>0.99
Clinical & radiographic features of SAH				
WFNS grade IV or V	68.97%	39.2%	3.45 (1.95–6.11)	<0.001
Fisher grade 3 or 4	98.18%	86.04%	8.76 (1.2–64.02)	0.006
Mean oGS (IVH severity)	6.45 ± 3.69	4.98 ± 3.21	—	0.02
ICH presence	53.45%	28.39%	2.9 (1.7–4.95)	<0.001
Acute hydrocephalus	93.1%	66.95%	6.66 (2.39–18.57)	<0.001
Initial management of SAH				
Mean max SBP, mm Hg	169.8 ± 27.4	164.8 ± 26	—	0.31
Max SBP >182 mm Hg	23.08%	17.89%	1.38 (0.7–2.69)	0.35
Mean min SBP, mm Hg	121.4 ± 18.04	123.9 ± 59.87	—	0.71
Mean arterial pressure, mm Hg	91.11 ± 14.24	90.69 ± 14.93	—	0.89
Mean max temperature, °C	36.99 ± 0.72	37.07 ± 1.62	—	0.16
Lab parameters at admission, mean values				
Serum WBC count, ×10 ³ /μl	12.64 ± 4.76	13.1 ± 4.82	—	0.48
Hemoglobin, g/dl	12.32 ± 1.83	12.68 ± 1.95	—	0.16
CRP in serum, mg/dl	1.5 ± 3.46	1.15 ± 2.51	—	0.68
IL-6 in CSF, pg/ml	1914 ± 2814	3878 ± 7043	—	0.37
Cells in CSF, /μl	949.2 ± 1063	1494 ± 4036	—	0.51
Troponin T in serum, ng/L	0.345 ± 1.03	1.78 ± 25.28	—	0.81
Myoglobin in serum, μl/L	79.25 ± 53.38	134.9 ± 232.3	—	0.93
Min pO ₂ in BGA, mm Hg	92.23 ± 21.51	91.4 ± 39.1	—	0.52
Max pCO ₂ in BGA, mm Hg	40.94 ± 7.4	39.56 ± 5.68	—	0.24

BA = basilar artery; BGA = blood gas analysis; CRP = C-reactive protein; IL-6 = interleukin 6; max = maximum; min = minimum; SBP = systolic blood pressure; WBC = white blood cell.

Boldface type indicates statistical significance.

the ROC curves; see Supplemental Fig. E1) also failed to show a significant difference between the 2 groups.

Finally, analysis of the baseline laboratory parameters at admission (serum, CSF, and blood gas tests) did not reveal any valuable laboratory biomarker for aneurysm rebleeding (Table 1).

Construction and Predictive Value of the Risk Score

All significant risk factors identified in the first-step multivariate analysis could be confirmed as independent rebleeding predictors in final multivariate analysis (Ta-

ble 4) and were therefore included in the risk score (0–9 points): premorbid arterial hypertension (1 point, aOR 2.56), aneurysm location at basilar artery (2 points, aOR 4.5), sac size ≥ 9 mm (1 point, aOR 1.9), presence of ICH (2 points, aOR 4.29), and acute hydrocephalus (3 points, aOR 6.27; see also Table 5).

The constructed score showed a good diagnostic accuracy for rebleeding prediction ($p < 0.001$, area under the curve 0.78; Supplemental Fig. E2). For patients with a score < 3, the relative risk of rebleeding was 0%. In SAH patients with a score ≥ 5, the relative risk of rebleeding

TABLE 2. Multivariate analysis of parameters predicting rebleeding that are present before SAH

Parameter	aOR	95% CI for aOR	p Value
Age ≥ 57 yrs	1.44	0.78–2.64	0.24
Previous anticoagulation	1.53	0.67–3.50	0.30
Arterial hypertension	2.44	1.10–5.45	0.03
Aneurysm location (BA)	2.50	1.20–5.19	0.01
Sac size ≥ 9 mm	2.04	1.11–3.75	0.02

Boldface type indicates statistical significance.

was 12.8%. None of the patients reached either of the 2 highest scores of 8 or 9 points. Of the patients with the highest scores within the tested SAH cohort (7 points), 22.2% developed rebleeding (vs 1.1% for the remaining SAH cohort, i.e., a 20-fold higher rebleeding risk).

Rebleeding and Outcome

The rate of in-hospital mortality among patients who suffered rebleeding was 53%, which was significantly higher than the rate for patients who had no rebleeding event (15%, $p < 0.001$, OR 6.45, 95% CI 3.73–11.13; Fig. 2). Also the incidence of poor outcome was twice as high among patients with rebleeding (84% vs 40%, $p < 0.001$, OR 7.99, 95% CI 3.86–16.52; Fig. 3).

Discussion

The aim of this study was to identify independent risk factors for aneurysm rebleeding prior to therapy. We were able to show that premorbid arterial hypertension, location of the aneurysm at the basilar artery, sac size ≥ 9 mm, presence of ICH, and acute hydrocephalus independently predicted aneurysm rebleeding. As shown in prior publications, rebleeding was strongly associated with poor outcome^{4,16,23,28,29} and mortality.^{4,6,16,19,29}

Parameters Present Prior to Admission

In this study, we evaluated the prognostic value of various potential rebleeding predictors that are known prior to SAH: demographic data, aneurysm characteristics, premorbid conditions, and prior medication. These parameters are of particular interest, since their clinical utility may also apply to patients with unruptured aneurysms. Therefore, these parameters might be used as additional

TABLE 3. Multivariate analysis of parameters predicting rebleeding that are present after initial SAH

Parameter	aOR	95% CI for aOR	p Value
WFNS grade IV or V	1.68	0.87–3.23	0.12
Fisher grade 3 or 4	1.28	0.27–6.23	0.75
IVH w/ oGS ≥ 5	1.42	0.76–2.65	0.27
ICH	2.42	1.33–4.38	0.004
Acute hydrocephalus	5.05	1.73–14.78	0.003

Boldface type indicates statistical significance.

TABLE 4. Multivariate analysis of all independent predictors of rebleeding among parameters present prior to and after SAH

Parameter	aOR	95% CI for aOR	p Value
Arterial hypertension	2.56	1.20–5.48	0.02
Aneurysm location (BA)	4.50	1.91–10.59	0.001
Sac size ≥ 9 mm	1.90	1.03–3.50	0.04
ICH	4.29	2.26–8.15	<0.001
Acute hydrocephalus	6.27	2.22–17.73	0.001

Boldface type indicates statistical significance.

arguments in favor of treatment of unruptured aneurysms that are prone to repetitive rupture.

Our findings were similar to those of most previous studies in not showing a correlation between the patients' age^{4,23,33} or sex^{4,23,26,33} and risk of rebleeding. But there are also conflicting reports stating that male patients have increased rebleeding risk.^{8,10}

The size of the ruptured aneurysm is the most discussed risk factor for rebleeding. The majority of authors used cutoffs of 10 mm.⁵ Despite some conflicting results,¹⁹ larger aneurysm size is generally accepted as a predictor of aneurysm rebleeding and this status has recently been confirmed by meta-analysis.^{5,31} We identified aneurysm size of ≥ 9 mm by ROC curve analysis as a cutoff for increased risk of rebleeding. The anterior communicating artery⁸ and the posterior circulation¹ have been reported as "locations at risk." The authors of a recent meta-analysis reported that aneurysm location in the posterior circulation was predictive for rebleeding, but there were large discrepancies in the pooled data.³¹ Our analysis indicates that specifically the basilar artery, rather than the "posterior circulation" as a whole, is the crucial location increasing rerupture risk. Conflicting with our results, one previous study has found the presence of multiple aneurysms to be predictive for rebleeding.⁴

Regarding aneurysm morphology, there are conflicting results stating that "bump-like" aneurysms are connected to higher rebleeding rates.^{2,3} Other authors state that irregularity¹ or blebs¹⁹ are not generally connected to rebleeding events. However, these reports date back to the time before introduction of 3D angiography^{13,14} and consist predominantly of small series. In our series, we could not draw any connection between aneurysm shape and rate of rebleeding events.

The impact of premorbid hypertension on rebleeding events has been the subject of controversy.^{12,24,33} Our find-

TABLE 5. Construction of the risk score

Parameter	aOR	Not Weight Adjusted	Weight Adjusted
Arterial hypertension	2.56	1.4	1
BA aneurysm	4.50	2.4	2
Sac size ≥ 9 mm	1.90	1	1
Presence of ICH	4.29	2.3	2
Acute hydrocephalus	6.27	3.3	3

FIG. 2. Risk of in-hospital mortality according to pretreatment rebleeding.

FIG. 3. Risk of poor outcome according to pretreatment rebleeding.

ings are consistent with those of De Marchis et al.,¹² who confirmed premorbid arterial hypertension as an independent risk factor for rebleeding. Smoking also has been reported to increase the risk of rebleeding²⁴ but failed to do so in our and other cohorts.⁴

In our cohort, the use of anticoagulants before SAH was significantly associated with rebleeding risk in univariate assessment, but it failed to show independent association in multivariate analysis. Our finding is consistent with results of prior analysis.³³

Clinical and Radiographic Features of SAH

Clinical severity of SAH has been identified by the majority of authors to be a risk factor for aneurysm rebleeding,^{10,19,22,24,33,34} and therefore it was also included in the risk factors identified in meta-analysis.³¹ There are conflicting results regarding the impact of radiographic severity of SAH on aneurysm rebleeding.^{4,8,22,33,37} Furthermore, IVH and ICH have been reported to predict rebleeding.^{10,16,26,37} In our analysis, only the presence of ICH was independently associated with risk of rebleeding.

Initiation of CSF drainage has been connected with aneurysm rebleeding in previous studies,^{7,33,34} and in our cohort also, patients with acute hydrocephalus had a significantly increased risk of rebleeding.

Initial Management of SAH

In our series, there was no difference regarding timing of treatment between the rebleeding and the no-rebleeding groups. It has been previously reported that patients with rebleeding events were admitted early after ictus.^{10,16} This might be an effect of the initial higher clinical severity of this group and therefore the more rapid diagnostic workup at external hospitals and/or direct transfer to a neurovascular center. Systolic blood pressure at admission or at transport has been reported to correlate with rebleeding risk.^{10,16,26,31} Like other authors,^{12,19,22} we found that systolic peaks did not increase rebleeding probability in our SAH cohort. This finding may be due to early and rigorous intravenous antihypertensive treatment at our center, limiting such peaks to short intervals without clinical impact.

Laboratory Parameters at Admission

Different parameters have been described as being (thrombin/antithrombin complex, enhancement of platelet sensitivity,¹⁶ high blood glucose levels,^{10,22} and high white blood cell count¹⁰) or not being (platelet count,^{10,26} PTT [partial thromboplastin time], and bleeding time²⁶) connected with aneurysm rupture risk.

None of the laboratory parameters that were tested in our cohort showed any significant correlation with increased rebleeding risk. This included inflammatory parameters in blood and CSF as well as classic cardiac markers. Overall, our data suggest that the role of laboratory parameters might be negligible with respect to the prediction of rebleeding risk.

Implementation of a Score and Clinical Consequences

Rebleeding was confirmed as a strong contributor to morbidity and mortality in our SAH cohort. Therefore, it is crucial to avoid this preventable occurrence. Many institutions changed from early (first 72 hours) to an ultra-early (first 24 hours) treatment due to the fact that most rebleeding occurs during the first 24 hours after the initial bleeding event.^{20–22,36} It has been suggested that patients would profit from a change in strategy regarding even earlier aneurysm repair.³³ Retrospective analysis of data from 2 different decades has shown that this change in strategy could lead to a significant reduction in rebleeding rates.²⁷ Other authors advocate that a 24-hour immediate aneurysm repair protocol would only affect a very small number of rebleeding events.²⁴ Given the fact that a 24-hour emergency treatment protocol might have certain drawbacks, such as uncommon hours of treatment and a need for a higher number of vascular/endovascular neurosurgeons on call, the solution is not necessarily to aim at this standard of care for all patients. One solution might be the early selection and immediate treatment of patients at high risk for rebleeding. In our institution, standard operating procedure for SAH patients includes aneurysm treatment within 24 hours. However, stable patients do not undergo overnight treatment and are instead treated the next day. The proposed score might be used for the triage of tim-

ing urgency in SAH patients. In particular, patients scoring ≥ 5 on the risk score should be considered for immediate treatment (regardless of time of day), whereas patients scoring < 3 can easily be treated according to a standard 24-hour protocol. Finally, SAH patients with scores ≥ 7 require special attention from neurosurgeons and neuro-radiologists, given the fact that this subgroup accounts for most of the cases with rebleeding in our cohort. Immediate treatment of ruptured aneurysms should be mandatory for patients with these scores.

Limitations

This retrospective study is burdened with the classic drawbacks of its design, including reduced accuracy and completeness of the recorded data, compared to a prospective cohort. In addition, we were unable to include sentinel headache into our analysis, and it has been reported to be a strong predictor of aneurysm rebleeding before therapy.⁴ Moreover, there was no external validation of the developed score. Nevertheless, we present a detailed evaluation of various factors contributing to aneurysm rebleeding as well as a new risk score for proper estimation of rebleeding risk.

Conclusions

In this large study, we were able to identify 5 parameters that independently predicted aneurysm rupture before treatment: premorbid arterial hypertension, location of the aneurysm at the basilar artery, sac size ≥ 9 mm, presence of ICH, and acute hydrocephalus. Furthermore, upon these parameters we developed a score that enables medical staff to determine, using easily accessible information, which patients are at increased risk for rebleeding events. Those patients might profit from rapid treatment with aneurysm occlusion therapy. Further validation of the risk score should be performed.

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Disclosures

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Conception and design: Darkwah Oppong. Acquisition of data: Darkwah Oppong, Gümüş, Jabbarli. Analysis and interpretation of data: Darkwah Oppong, Jabbarli. Drafting the article: Darkwah Oppong, Jabbarli. Critically revising the article: Gümüş, Pierscianek, Hertel, Kneist, Wrede, Barthel, Forsting, Sure, Jabbarli. Reviewed submitted version of manuscript: Sure, Jabbarli. Approved the final version of the manuscript on behalf of all authors: Darkwah Oppong. Statistical analysis: Darkwah Oppong, Jabbarli. Administrative/technical/material support: Sure. Study supervision: Jabbarli.

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