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Assessment and validation of proposed classification tools & multimodal outcome assessment after surgery for cavernous brainstem malformations.

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Assessment and validation of proposed classification tools for brainstem cavernous malformations

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Assessment and validation of proposed classification tools for brainstem cavernous malformations

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OBJECTIVE Treatment indications for patients with brainstem cavernous malformations (BSCMs) remain difficult and controversial. Some authors have tried to establish classification tools to identify eligible candidates for surgery. Authors of this study aimed to validate the performance and replicability of two proposed BSCM grading systems, the Lawton-Garcia (LG) and the Dammann-Sure (DS) systems.

METHODS For this cross-sectional study, a database was screened for patients with BSCM treated surgically between 2003 and 2019 in the authors' department. Complete clinical records, preoperative contrast-enhanced MRI, and a postoperative follow-up ≥ 6 months were mandatory for study inclusion. The modified Rankin Scale (mRS) score was determined to quantify neurological function and outcome. Three observers independently determined the LG and the DS score for each patient.

RESULTS A total of 67 patients met selection criteria. Univariate and multivariate analyses identified multiple bleedings ($p = 0.02$, OR 5.59), lesion diameter (> 20 mm, $p = 0.007$, OR 5.43), and patient age (> 50 years, $p = 0.019$, OR 4.26) as predictors of an unfavorable postoperative functional outcome. Both the LG (AUC = 0.72, $p = 0.01$) and the DS (AUC = 0.78, $p < 0.01$) scores were robust tools to estimate patient outcome. Subgroup analyses confirmed this observation for both grading systems (LG: $p = 0.005$, OR 6; DS: $p = 0.026$, OR 4.5), but the combined use of the two scales enhanced the test performance significantly ($p = 0.001$, OR 22.5).

CONCLUSIONS Currently available classification systems are appropriate tools to estimate the neurological outcome after BSCM surgery. Future studies are needed to design an advanced scoring system, incorporating items from the LG and the DS score systems.

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KEYWORDS brainstem CCM; cerebral cavernous malformation; CCM surgery; Dammann-Sure grading system; Lawton-Garcia grading system; vascular disorders

Cerebral cavernous malformations (CCMs) are abnormal low-flow vascular sinusoidal endothelial cell caverns within the central nervous system[1] and are considered the second most common type of neurovascular malformation.[2] They occur in either sporadic or familial form.[3] Oftentimes, CCMs are diagnosed incidentally and tend to have a benign natural history, usually requiring only clinical and radiological follow-up.[4,5] However, a considerable number of CCMs become symptomatic with new-onset headache, cavernoma-related epilepsy, or focal neurological deficits, mainly because of their tendency to cause hemorrhage.[5] Such events have been defined as "symptomatic hemorrhages."[6] Depending on the severity of clinical symptoms, lesion localization, history of symptomatic bleeding, and lesion size, surgical removal of the CCM may be indicated.[7–9] Notably, 20%–35% of CCMs are located within the brainstem.[5,10,11] Brainstem cavernous malformations (BSCMs) represent a unique subgroup of CCMs, as they can cause considerable functional impairment due to an increased risk of symptomatic hemorrhage[3,12] compared to that with otherwise localized CCMs.[5,13] Although technically challenging and associ-

ABBREVIATIONS AUC = area under the curve; BSCB = brainstem cavernoma bleeding; BSCM = brainstem cavernous malformation; CCM = cerebral cavernous malformation; DS = Dammann-Sure; DVA = developmental venous anomaly; LG = Lawton-Garcia; mRS = modified Rankin Scale; ROC = receiver operating characteristic.

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ated with significant perioperative morbidity,[11] surgical treatment of BSCM is a well-established procedure.[11,14–16] Because of the complex brainstem anatomy, treatment decisions for patients with BSCM remain difficult and controversial.[9] Only a few authors have tried to establish CCM grading systems to enable the identification of good candidates for surgery and to predict their individual outcomes. Up to now, three different grading systems have been proposed, one of them established by our own group.[17–19] Two of these scales are specifically applicable to BSCM, that is, the Lawton-Garcia (LG) grading system and the Dammann-Sure (DS) classification.

In order to include such grading systems into the clinical routine, repetitive validation is necessary but has not been sufficiently performed yet. Therefore, with this study, we aimed to validate the performance of these two available BSCM grading systems using a single center cohort of patients. In addition, we evaluated the interobserver agreement of the scales to test their clinical applicability. Finally, we examined whether a combination of the two grading systems would provide increased predictive performance.

Methods

Data Collection

The study was conducted at our tertiary care hospital in accordance with all guidelines set forth by the approving institutional review board. We performed a cross-sectional study of all patients admitted to our department from January 1, 2003, until June 30, 2019, who fulfilled the inclusion criteria listed below. Clinical data, preoperative multiplanar contrast-enhanced MRI, and functional outcome with pre- and postoperative modified Rankin Scale (mRS) scores were obtained for each patient. The LG and DS scores (see below) were calculated for each patient. The study was conducted according to the Declaration of Helsinki, and local ethics approval was obtained. Informed consent was obtained from all participants. The study was performed according to the STROBE protocol.

Inclusion Criteria and Exclusion Criteria

Patients aged ≥ 18 years with BSCM surgically treated at our center were included. All patients needed to have a minimum of 6 months of postoperative follow-up. Patients without a complete clinical assessment or missing imaging data were excluded from the study.

Grading Systems

The LG scale is based on clinical and MRI-derived items, that is, lesion size, lesion crossing of the axial midpoint, presence of a developmental venous anomaly (DVA), patient age, and hemorrhage timing.[18] Each item can be assigned points from 0 to 2, depending on the item, and the final score is the sum of the points for all the items. The total points range from 0 to 7. A favorable outcome (mRS score ≤ 2) is indicated by low grades (LG grades 0–III) and an unfavorable outcome (mRS > 2) by high grades (LG grades IV–VII).

The DS scale is based only on MRI-derived items.[19] The classification system was initially established to rate the difficulty of surgical dissection of a CCM in eloquent areas. It was validated with postoperative diffusion-weighted MRI, a surgical questionnaire, and functional outcome. Defining features are the presence of macrocaverns, lesion shape, form of hemosiderin deposits, and contrast enhancement, whereas associated features are a DVA, a macro-hemorrhage, perifocal edema, and a multi-aged macro-hemorrhage. The combination or quality of items applies to one type, and the typing ranges from 1 to 3. In cases of acute hemorrhage, the suffix “a” is additionally applied; otherwise, the suffix “b” is used. Favorable resection is indicated by low types (types 1a/b and 2a/b), and difficult resection is indicated by high types (types 3a/b).

Imaging Analysis

Imaging data were independently analyzed by three investigators (A.N.S., M.D.O., P.D.), including score determination for each patient. In cases of total disagreement, the most experienced investigator (P.D.) decided. Interrater agreement was indexed using Fleiss’ kappa statistic. Kappa represents the strength of agreement above the level of chance according to the following rating:[20] 0.2–0.4, slight to fair; 0.41–0.6, moderate; 0.61–0.8, substantial; > 0.8, excellent.

Statistical Analysis

We used SPSS 22 (IBM Corp.) for all statistical analyses. Univariate analyses were performed to determine predictors of postoperative clinical outcome. For dichotomized variables, the chi-square test (sample size > 5) or Fisher exact test (sample size ≤ 5) was used. Continuous variables were tested with the Student t-test (normally distributed data) or Mann-Whitney U-test (nonnormally distributed data). Data distribution was determined with the Kolmogorov-Smirnov test. Multivariate analyses were performed with a binary regression model and were based on an a priori hypothesis that predictors of unfavorable outcomes were analogous to those found in the LG grading system,[18] including patient age, presence of a DVA, chronic hemorrhage, lesion size, and lesion crossing the brainstem midpoint. As stated in the literature,[18] favorable surgical outcomes (mRS score ≤ 2) versus unfavorable ones (mRS score > 2) were considered at the last clinical evaluation adjusted for the follow-up observation time of a minimum of 6 months. To evaluate the prognostic performance of the different grading systems, the receiver operating characteristic (ROC) metric was used, quantified by the area under the curve (AUC), with values close to 1 indicating a perfect score and values close to 0.5 reflecting a nonrelevant score. A more detailed classification was applied according to the following rating:[21] 0.7–0.8, acceptable; 0.8–0.9, excellent; > 0.9, outstanding. A univariate analysis of patient subpopulations according to both LG and DS system scores was performed with the dependent outcome variable favorable (mRS ≤ 2) versus unfavorable (mRS > 2) at the last clinical evaluation. Scores in each grading system were dichotomized as stated in each of the systems. A p value < 0.05 was defined as statistically significant.

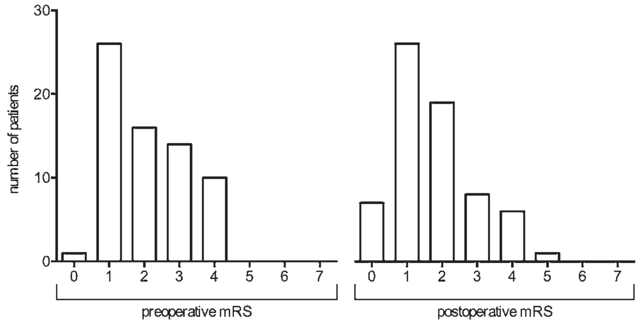

FIG. 1. Distribution of mRS scores preoperatively on admission and postoperatively at the final follow-up.

Results

Patient Demographics and Outcomes

Eighty-nine potentially eligible patients were identified. In 19 patients, the clinical data set was incomplete, and 4 patients were lost to follow-up. Therefore, 22 patients were excluded from the study and 67 patients were considered for analysis. The mean age was 40.6 ± 12.7 years, and 41 individuals (61.2%) were female. A total of 20 patients (30.0%) had a DVA associated with the BSCM, and 33 (49.3%) of the lesions crossed the axial midline. Thirty-two patients (47.8%) suffered an acute hemorrhage, 18 (26.9%) revealed subacute hemorrhage, and 17 (25.4%) had chronic hemorrhage, according to the definition of Garcia and colleagues.[18] Almost half of all the patients (47.8%) experienced more than one bleeding. The BSCMs were rather heterogeneously distributed within the brainstem. The most common location was the pons, accounting for 25 cases (37.3%), followed by the mesencephalon in 14 cases (20.9%). The mean diameter of the brainstem cavernoma bleeding (BSCB) was 18.5 ± 7.7 mm. On admission, 43 patients (64.2%) were in good clinical condition (mRS score ≤ 2). A favorable outcome after cavernoma resection was observed in 52 patients (77.6%), and the majority of patients (79.1%) revealed improved or unchanged scores. On the contrary, an unfavorable outcome (mRS score > 2) was found in 15 patients (22.4%), 8 (11.9%) whose condition had worsened compared to their preoperative baseline (Fig. 1 and Table 1).

Predictors of Postoperative Outcome

Univariate analysis identified preoperative multiple bleedings (OR 5.59, 95% CI 1.39–22.44, p = 0.02) as the only statistically significant predictor of an unfavorable postoperative outcome. Midline crossing (OR 2.18, 95% CI 0.64–7.37, p = 0.24) and the presence of a DVA (OR 1.41, 95% CI 0.41–4.9, p = 0.74) showed no statistically significant influence on outcome (Table 1). Multivariate analysis identified a maximum BSCB diameter > 20 mm (OR 5.43, 95% CI 1.58–18.69, p = 0.007) and patient age > 50 years (OR 4.26, 95% CI 1.27–14.33, p = 0.019) as independent predictors of an unfavorable postoperative outcome, whereas midline crossing (OR 3.21, 95% CI 0.9–11.4, p = 0.07), DVA (OR 0.82, 95% CI 0.23–2.96, p = 0.76), and chronic hemorrhage (> 8 weeks; OR 1.67, 95% CI 0.48–5.83, p = 0.42) were not independent predictors (Table 2).

Performance of Proposed BSCM Grading Systems

We performed an ROC analysis with AUC metrics and demonstrated that the LG grade (AUC = 0.72, 95% CI 0.56–0.88, p = 0.01) and the DS score (AUC = 0.78, 95% CI 0.64–0.9, p < 0.01; AUC = 0.74, 95% CI 0.62–0.87, p < 0.01) significantly correlated with postoperative outcome. The predictive value of each score was considered as substantial (AUC 0.8–0.7; Fig. 2 and Table 3). Subsequent analysis revealed that 75% of all patients with a favorable postoperative outcome were correctly classified in both grading systems (LG grades 0–III, DS types 1–2). An unfavorable outcome (LG grades IV–VII, DS type 3) was correctly predicted in 66.7% and 60% of patients, respectively (Table 4). Both the LG (OR 6, 95% CI 1.73–20.81, p = 0.005) and the DS (OR 4.5, 95% CI 1.34–15.07, p = 0.026) grading systems were strong predictors of the postoperative functional outcome. The combined use of the two scales enhanced the predictive performance (OR 22.5, 95% CI 3.33–152, p = 0.001).

Interobserver Variability

Independent investigators determined the individual scores for a total of 71 patients (A.N.S., M.D.O., P.D.). Evaluation revealed an interobserver disagreement in 25.4% (DS system) and 8.5% (LG system) of all cases. According to Fleiss' kappa statistic, the DS grading system had substantial interobserver agreement (κ = 0.7), whereas the LG grading system revealed excellent agreement (κ = 0.92; Supplemental Fig. 1).

Discussion

Validation of Proposed Grading Systems

Patient selection is mandatory for risk stratification and to identify eligible candidates for BSCM surgery. This selection can be performed by determining a wide variety of clinical and anatomical variables. Although they have limits in terms of sensitivity and specificity, grading systems can be helpful tools for neurosurgeons on which to base their clinical decisions, that is, using not only personal experience but also objective algorithms.

Currently, three grading systems for CCM are available.[17–19] While two studies have focused on CCM in general, Garcia and colleagues have established a grading system specifically for BSCM.[18] The first study, published in 2011, classifies the majority of BSCMs as high-risk grade 3 lesions with an almost 50% chance of long-term disability after surgery.[17] The grading system of Dammann and colleagues differentiates three types of CCM (DS types 1–3) according to the preoperative MRI data, measuring variables such as size of the caverns, lesion shape, and deposits of hemosiderin.[19] Moreover, the three-tiered classification system is extended to a more detailed grading system with six subgroups of CCM through the implementation of the item lesion-associated hemorrhage (DS types 1a–3b). Depending on the DS type, the difficulty of resection varies. The LG grading system was proposed in 2015 and combines clinical and imaging data to guide

TABLE 1. Univariate analysis of predictors of an unfavorable functional postoperative outcome

Variable	mRS Score Same or Improved	mRS Score Worse	p Value	OR	95% CI
No. of patients	53 (79.1%)	14 (20.9%)			
Mean age in yrs	40.3 ± 13.1	41.5 ± 11.6	0.76*	NA	NA
Female sex	32 (60.4%)	9 (64.3%)	>0.99†	1.18	0.35–4.12
Lesion location			0.71†	NA	NA
Medullary	6 (11.3%)	0 (0%)			
Pontomedullary	9 (17.0%)	2 (14.3%)			
Pontine	19 (35.8%)	6 (42.9%)			
Pontomesencephalic	9 (17.0%)	2 (14.3%)			
Mesencephalic	10 (18.9%)	4 (28.6%)			
Lesion side			0.9†	NA	NA
Lt	26 (49.1%)	6 (42.9%)			
Rt	24 (45.3%)	7 (50%)			
Medial	3 (5.7%)	1 (7.1%)			
Mean max BSCB diameter in mm	18.3 ± 8.3	19 ± 5.6	0.55*	NA	NA
DVA	15 (28.3%)	5 (35.7%)	0.74†	1.41	0.41–4.9
Midline crossing	24 (45.3%)	9 (64.3%)	0.24†	2.18	0.64–7.37
Preop multiple bleedings	21 (39.6%)	11 (78.6%)	**0.02†**	5.59	1.39–22.44
Age of hemorrhage			0.93†	NA	NA
Acute	26 (49.1%)	6 (42.9%)			
Subacute	14 (26.4%)	4 (28.6%)			
Chronic	13 (24.5%)	4 (28.6%)			
mRS score preop			0.1†	NA	NA
0	1 (1.9%)	0 (0%)			
1	20 (37.7%)	6 (42.9%)			
2	14 (26.4%)	2 (14.3%)			
3	8 (15.1%)	6 (42.9%)			
4	10 (18.9%)	0 (0%)			
5	0 (0%)	0 (0%)			
6	0 (0%)	0 (0%)			
mRS score postop			**<0.001†**	NA	NA
0	7 (13.2%)	0 (0%)			
1	26 (49.1%)	0 (0%)			
2	13 (24.5%)	6 (42.9%)			
3	6 (11.3%)	2 (14.3%)			
4	1 (1.9%)	5 (35.7%)			
5	0 (0%)	1 (7.1%)			
6	0 (0%)	0 (0%)			

NA = not applicable.
Univariate analysis of demographic, clinical, and anatomical factors for association with functional postoperative outcome (changes in mRS score between admission and final follow-up). All patients with a final follow-up ≥ 6 months after surgery were included. Values expressed as the mean ± standard error or as number (%), unless indicated otherwise. Boldface type indicates statistical significance.
* Student's t-test or Mann-Whitney U-test.
† Chi-square test or Fisher exact test.

surgical decision-making and to predict the postoperative functional outcome.[18] This score takes into account five variables, such as lesion size, crossing of the axial midpoint, presence of an associated DVA, age of the patient, and time of hemorrhage, to build an eight-tiered classification system.

Up to now, only one study has investigated the performance of one proposed grading system.[22] According to the authors of that study, there is a sufficient correlation not only between the LG grading scale and postoperative functional outcome, but also between the LG grading system and postoperative quality of life. Our study confirms that both grading systems are statistically significant predictors of postoperative outcome (Table 3 and Fig. 2). Since imaging data are mandatory for both classification tools, the determination of variables may differentiate between different raters. Thus, to ensure reliability, we additionally investigated the interobserver accuracy and found excellent agreement for the LG grade (Supplemental Fig. 1). This can be explained by the fact that the variables used for the LG tool, such as patient age, lesion size, or presence of DVA, are clear-cut variables that are easy to obtain. The

TABLE 2. Multivariate analysis of predictors of an unfavorable functional postoperative outcome

Variable	p Value	OR	95% CI
Maximum BSCB diameter >20 mm	**0.007**	5.43	1.58–18.69
Midline crossing	0.071	3.21	0.9–11.4
DVA	0.76	0.82	0.23–2.96
Age >50 yrs	**0.019**	4.26	1.27–14.33
Chronic hemorrhage (>8 wks)	0.424	1.67	0.48–5.83

Multivariate binary logistic regression model with the dependent outcome variable as favorable (mRS ≤ 2) versus unfavorable (mRS > 2) outcome at the last clinical evaluation. All patients with a last follow-up of ≥ 6 months were included. Boldface type indicates statistical significance.

DS score only includes MRI-based items and thus determines more subjective variables, such as lesion shape. These variables are more prone to interpretation, resulting in a lower interobserver agreement rate. However, our data revealed substantial agreement for the DS tool, making the score also applicable to clinical use.

Predictors of Postoperative Outcome

As stated above, the LG grading system takes five variables into account. When assessed individually, none of these variables was a significant predictor of postoperative outcome. Interestingly, multiple bleedings, which is not considered in this scale, was the only significant predictor of outcome in our analysis. Notably, this variable is elaborated on in the paper by Dammann and colleagues, who showed that evidence of several bleeding events on MRI correlated with a more difficult surgical dissection of the BSCM because "multiage bleeding" gives the lesion different consistencies.[19]

In our multivariate analysis, we investigated all items of the LG grading system. In our patient population, a BSCB diameter > 20 mm and an age > 50 years were independent predictors of an unfavorable postoperative outcome (Table 2). A young age is associated with a stronger resistance to surgery, improved recovery from surgery, and less comorbidity, making it an obvious predictor of a favorable outcome. The same applies to lesion size, since large lesions can involve more eloquent brainstem areas, making the resection more difficult.

Even though both grading systems consider chronic hemorrhage as a predictor of a favorable outcome, this item was not an independent predictor in our multivariate analysis. The same applied to DVA and axial midline crossing. Both study cohorts (from Garcia et al.[18] and Dammann et al.[19]) reveal a limited number of patients, which could be one explanation for the discrepancy observed here.

Combined Use of Proposed Grading Systems

In our study, we demonstrated that both classification systems are reliable tools to predict postoperative functional outcome (Table 4). While the LG grade includes clinical and radiological data, the DS type is mainly focused on imaging data, which raises the question of whether the combined use of the two scores might enhance the predictive performance. Notably, we found that the combination of the two grading scales is a stronger predictor for postoperative outcome, with an OR of 22.5, compared to 6 (LG alone) and 4.5 (DS alone). This is a new finding and requires further investigation in future BSCM studies.

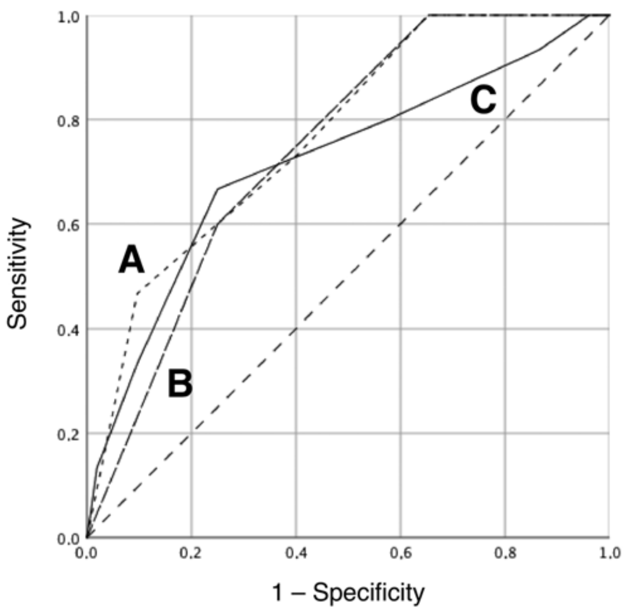

FIG. 2. ROC analysis to illustrate the test performance of available BSCM grading systems. DS score with subtypes for acute hemorrhage (A), DS score without subtypes for acute hemorrhage (B), and LG grade (C).

External Validity

Compared to those in meta-analyses of BSCM trials, our cohort seems representative in terms of patient characteristics and postoperative outcome.[11,23] This observation increases the external validity of our reported results.

Study Limitations

CCM is a rare vascular disease, accounting for 10%–15% of all intracranial vascular malformations.[2] Since only 35% of these lesions are localized in the brainstem[10] and only a small percentage of these lesions undergo surgical removal, single-center trials with large sample sizes remain difficult. Additionally, as BSCM is a rather rare

TABLE 3. Performance of proposed BSCM grading systems

Scale	AUC	p Value	95% CI
LG (grade 0–VII)	0.72	**0.01**	0.56–0.88
DS (type 1a–3b)	0.78	**<0.01**	0.64–0.9
DS (type 1–3)	0.74	**<0.01**	0.62–0.87

ROC analysis with AUC metrics to determine the test performance of available BSCM grading systems. Functional postoperative outcome (mRS ≤ 2 vs mRS > 2) at the last clinical evaluation was the dependent variable. All patients with a last follow-up ≥ 6 months were included. An AUC > 0.7 is considered as an acceptable test performance. The p values represent the asymptotic significance. Boldface type indicates statistical significance.

TABLE 4. Functional postoperative outcome according to proposed BSCM grading systems

Variable	mRS ≤2	mRS >2	p Value	OR	95% CI
No. of patients	52 (77.6%)	15 (22.4%)			
LG grade			**0.005***	6	1.73–20.81
0–III	39 (75%)	5 (33.3%)			
IV–VII	13 (25%)	10 (66.7%)			
DS type			**0.026***	4.5	1.34–15.07
1a/b, 2a/b	39 (75%)	6 (40%)			
3a/b	13 (25%)	9 (60%)			
Combination†			**0.001***	22.5	3.33–152
LG grade 0–III & DS types 1a/b & 2a/b	30 (88.2%)	2 (25%)			
LG grades IV–VII & DS type 3a/b	4 (11.8%)	6 (75%)			

Univariate analysis of patient subpopulations according to their test performance. The dependent outcome variable is favorable (mRS ≤ 2) versus unfavorable (mRS > 2) at the last clinical evaluation. All patients with a last follow-up of ≥ 6 months were included. Boldface type indicates statistical significance.

* Chi-square test or Fisher exact test.

† Individuals not fitting into this classification system were excluded from analysis.

vascular disease with few cases, our results are mainly representative of experienced, high-volume centers. Moreover, our data were in part obtained retrospectively, which can lead to well-known information and selection biases. Since the data set in this study is limited to surgically treated patients, our results do not provide guidance on conservatively treated BSCM. In a former study, a total of 21 patients from our current cohort has already been used to establish the DS score. This might bias the data of our current investigation. Nevertheless, our study contributes novel data and proposes the combined use of existing classification systems. Prospective multicenter trials are needed to validate our assumption and to examine new predictors of patient outcome.

Conclusions

The LG and the DS classification tools are appropriate for estimating the neurological outcome after BSCM surgery. This study confirms the predictive accuracy of both grading systems and gives evidence supporting their combined use.

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Author Contributions

Conception and design: Dammann. Acquisition of data: Santos, Forsting. Analysis and interpretation of data: Rauschenbach, Darkwah Oppong, Dammann. Drafting the article: Santos, Rauschenbach. Critically revising the article: Santos, Rauschenbach, Darkwah Oppong, Chen, Herten, Sure, Dammann. Reviewed submitted version of manuscript: Santos. Statistical analysis: Rauschenbach, Dammann. Administrative/technical/material support: Rauschenbach, Darkwah Oppong, Sure, Dammann. Study supervision: Sure, Dammann.

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Multimodal outcome assessment after surgery for brainstem cavernous malformations

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OBJECTIVE The object of this study was to assess outcome after surgery for brainstem cavernous malformations (BSCMs) using functional, health-related quality of life (HRQOL), and psychological surveys to analyze the interrelation of these measurements, and to compare HRQOL and anxiety and depression scores with those in a healthy population.

METHODS The authors performed a cross-sectional outcome study of all patients surgically treated for BSCM in their department between January 1, 2003, and December 31, 2019. They assessed functional outcome via the modified Rankin Scale (mRS), health-related quality of life (HRQOL) via the SF-36 and 9-item Life Satisfaction Questionnaire (LISAT-9), cranial nerve and brainstem function using a questionnaire, symptom-based psychological outcome via the Hospital Anxiety and Depression Scale (HADS), and timepoint of a return to previous employment. They analyzed the correlation between absolute (mRS score ≤ 2) and relative (postoperative deterioration in initial mRS score) outcome endpoints and the interrelation of the outcome measures and performed a comparison of HRQOL and HADS scores with findings in a healthy population.

RESULTS Seventy-four patients were eligible for inclusion in the study. HRQOL was impaired after surgery for BSCM compared to that in a healthy population. This impairment was substantial in patients with an unfavorable functional outcome (mRS > 2) but was also present in those with a favorable outcome (mRS ≤ 2) in selected domains. Psychological impairment was negligible in patients with a favorable outcome and grave in those with an unfavorable outcome. LISAT-9 results revealed that brainstem and cranial nerve symptoms reduce satisfaction mainly in self-care abilities for both unfavorable and favorable outcome patients. Among the brainstem and cranial nerve symptoms, balance impairment showed the most significant impact on HRQOL. Absolute outcome endpoints were superior to relative outcome endpoints in reflecting impairment in HRQOL after surgery.

CONCLUSIONS The study data can improve patient counseling and decision-making in BSCM treatment and may function as a benchmark. The authors report outcomes after BSCM surgery in high detail, emphasizing the specific impact of cranial nerve and brainstem symptoms on HRQOL. When reporting BSCM surgery outcome, absolute outcome endpoints should be applied.

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KEYWORDS brainstem cavernous malformation; surgery; health-related quality of life; functional outcome; CCM; cerebral cavernous malformation; cavernous angioma; HRQOL; vascular disorders

Cerebral cavernous malformations (CCMs) are prone to intracerebral hemorrhage.[1,2] And while hemorrhages from CCMs are oftentimes mild and can even remain unrecognized by the patient,[3–5] symptomatic hemorrhages (term defined in reporting standards)[6] occur with an overall annual risk of 2%–6%[7] and can cause seizures or focal neurological deficits.[7,8] Especially when located in the brainstem, hemorrhage from CCM is more often symptomatic and causes more severe disability than that due to supratentorial CCM.[1,8–11] Brainstem CM (BSCM) has been found in roughly 30% of the cases in larger series.[1] The 5-year risk of a recurrent hemorrhage

ABBREVIATIONS AUC = area under the curve; BSCM = brainstem cavernous malformation; CCM = cerebral cavernous malformation; HADS = Hospital Anxiety and Depression Scale; HADS-A = Anxiety Subscale of HADS; HADS-D = Depression Subscale of HADS; HRQOL = health-related quality of life; LISAT-9 = 9-item Life Satisfaction Questionnaire; MCS = mental component summary of SF-36; mRS = modified Rankin Scale; PCS = physical component summary of SF-36; ROC = receiver operating characteristic.

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in BSCM is 30.8% compared to 18.4% in nonbrainstem CCM.[1] The potential to cause permanent neurological damage by (repetitive) hemorrhages makes patients with BSCM candidates for neurosurgical resection of the lesion.[12] Surgical treatment rates of BSCM range around 20%–25% in larger series.[1] The indication for such treatment remains controversial, as resection of a brainstem lesion itself carries significant risks.[12] Early postoperative morbidity is 31%, and long-term morbidity is around 18% according to the largest meta-analysis.[10] As the natural course of a BSCM remains hard to predict, the indication for surgical treatment is highly individual and is balanced among the patient's present impairment due to the lesion, potential future hemorrhage events, and the estimated risks of surgical intervention.[12] To guide these decisions, more detailed postoperative outcome data are needed; however, such data are scarce. In addition, data are oftentimes limited to mere descriptive clinical or functional outcome (disability) scores. Also, various and/or subjective outcome endpoints are utilized.[10,13] Unfortunately, even functional scores may not completely reflect the patient's burden after treatment, particularly in those with minor functional impairment.[14–16] This is especially so for brainstem lesions in which the interaction of brainstem nuclei, cranial nerves, and fiber tracts can cause very complex symptoms interfering with the patient's everyday activities even if they are not highly functionally disabling (balance problems, double vision, sensory disturbances, etc.).[17] An optimal assessment of the patient's postoperative physical and psychological condition should therefore reflect such impairment, for example, by measuring health-related quality of life (HRQOL),[18] anxiety and depression,[19] or life satisfaction.[20] Although these measures are not disease-specific but are generic tools, they do provide information beyond mere ordinal functional scores and better reflect the patient's everyday life situation. So far, only a very few small studies have reported on, for example, postoperative HRQOL in BSCM.[21–23] Because our center has a relatively high number of patients with BSCM undergoing surgery, we performed a cross-sectional outcome study including multiple patient- and physician-reported outcome surveys (functional outcome as measured by the modified Rankin Scale [mRS], HRQOL per the SF-36 instrument and the 9-item Life Satisfaction Questionnaire [LISAT-9], anxiety and depression as measured by the Hospital Anxiety and Depression Scale [HADS], patient-reported cranial nerve and brainstem symptoms, and return-to-work status). We also evaluated how these different surveys correlated with each other and with established relative and absolute clinical outcome endpoints after BSCM surgery. To put the results in context, we finally compared our results with the HRQOL and HADS scores in a healthy population.

Methods

Study Design and Population

We performed a cross-sectional study of all patients surgically treated for BSCM in our department between January 1, 2003, and December 31, 2019. A standardized interview was performed (baseline medical information, socio-educational background, SF-36 questionnaire, Depression and Anxiety Subscales of the HADS [HADS-D and HADS-A, respectively], LISAT-9, and cranial nerve and brainstem symptoms questionnaire).

The study was conducted according to the principles expressed in the Declaration of Helsinki, and local ethics approval was obtained. Informed consent was obtained from all participants. The study was performed according to the STROBE protocol.

Inclusion Criteria

We included all patients aged 18–80 years who had undergone surgical treatment for BSCM in the given time period with a minimum postoperative interval of 3 months and who agreed to participate.

Exclusion Criteria

We excluded patients who had undergone an invasive medical treatment necessitating hospitalization within 3 months prior to the interview and those with insufficient knowledge of the German language.

Data Collection and Survey

Clinical baseline data on patients and CCM were obtained based on medical charts according to CCM reporting standards[6] both pre- and postoperatively (sex, age at surgery, CCM location in brainstem, history of multiple symptomatic hemorrhages, multiplicity of CCMs, known chronic disease [as defined by SF-36 criteria],[18] known psychiatric disease, and degree of disability on the mRS). An experienced neuroradiologist independently assessed further radiological data (size of CCM, associated developmental venous anomaly [yes/no], and completeness of resection on postoperative MRI). In a standardized postoperative interview, we assessed HRQOL using the German version of the SF-36. The SF-36 questionnaire addresses 8 domains (physical functioning, role physical, bodily pain, general health perception, vitality, social functioning, role emotional, mental health, and the two component summary scores of physical health [PCS] and mental health [MCS]). Additionally, we assessed the German HADS score to evaluate symptom-based depression and anxiety (14-item questionnaire) and the LISAT-9 score to estimate satisfaction with life. The LISAT-9 contains 1 question about life satisfaction as a whole and 8 questions about domain-specific life satisfaction (self-care ability, leisure time, vocational situation, financial situation, sexual life, partnership relations, family life, and contact with friends) and is scored on a 6-point scale ranging from very unsatisfied (1) to very satisfied (6).[24] During the interview, we also queried the presence of any residual brainstem or cranial nerve symptoms (facial nerve palsy, hearing problems, ataxia, hemiparesis, balance disturbances, disturbance of fine motor skills, vision problems, double vision, nystagmus, deglutition disturbance, dysarthria, neuropathic pain, sensibility disturbance, and sexual dysfunction). The different symptoms were outlined in detail for each patient in a standardized way. We did not perform quantification of symptoms. Preoperatively, the employed patients were asked if and when they planned to return to their former work or equivalent positions. The interval between the questionnaire and surgery was calculated (months).

Outcome Definitions

Relative Outcome

A minimum 1-point increase in the mRS score compared to the preoperative score at the time of the interview was defined as neurological deterioration/operative morbidity.

Absolute Outcome

According to previous studies,[25] an mRS score ≤ 2 was defined as a favorable outcome, and an mRS score > 2 was defined as an unfavorable outcome.

Life Satisfaction Outcome

According to previous studies,[24] LISAT-9 scores of 1–4 were defined as unsatisfied and scores of 5–6 as satisfied.

Reference Data

HRQOL in the study population was compared to that in an age- and sex-matched healthy German population.[18] HADS mean values in the study population were also compared to those in a healthy German population.[19]

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM Corp.). Nominal data were expressed as absolute numbers and valid percent, and continuous variables were expressed as means ± standard deviations. A Shapiro-Wilk test was used to test data for normal distribution. Additionally, histograms and Q-Q plots were used. We used parametric statistics for between-group comparisons. In comparing continuous variables, we used the unpaired t-test or Mann-Whitney U-test. For categorical variables, a chi-square or Fisher's exact test (expected frequencies < 5) was applied. Using a German reference sample, we created a sex- and age-matched 1:1 case control sample. A comparison of mean values (SF-36 scores) was performed using the Student t-test preceded by Levene's test. Effect size was reported using Cohen's d.

To identify parameters with an impact on outcome/scores, a bivariate correlation was performed. According to the variable character, Pearson's, Spearman's rho, or Kendall's tau-b test was used. Clinically relevant and significant parameters ($p < 0.05$) were included in a linear or logistic regression analysis in terms of a stepwise model selection. To evaluate the association of outcome endpoints or functional scores with HRQOL scores, we performed a linear regression analysis and calculated R^2 and the regression coefficient B. To visualize the associations, we calculated receiver operating characteristic (ROC) curves and analyzed the areas under the curve (AUCs). All tests were two-tailed (alpha = 0.05).

Results

Seventy-four of 95 patients were eligible for inclusion in the study. Of the 21 patients excluded, 4 did not agree to participate and 17 did not have a complete data set or did not respond. The initial patient characteristics and postoperative functional outcome did not differ significantly between participating and nonparticipating patients (see Supplemental Table 1). Forty-five of the included patients (61%) were female. The mean age was 40.4 ± 12.10 years (range 18–72 years). A chronic disease was found in 14 patients (19%). A psychiatric disease was found in none of the patients. A history of symptomatic hemorrhage was found in all patients, and multiple hemorrhages were found in 37 patients (50%). Eighteen patients (24%) were initially unemployed or already retired; 56 patients (76%) were employed. Table 1 shows further baseline patient and CCM characteristics.

Outcome Endpoints

Outcomes were measured at the last follow-up, which was at a mean of 53 ± 44.5 months (range 3–177 months). Fifteen patients (20%) showed functional deterioration as indicated by a comparison to their preoperative mRS score (relative outcome endpoint). Sixty patients (81%) showed a favorable outcome (mRS score ≤ 2, absolute outcome endpoint). The mortality rate was 0% among the included patients. Thirty-eight (68%) of the previously employed patients returned to their former positions; 18 (32%) were unable to return to their previous employment. In 1 patient (1%), resection of the CCM was rated as incomplete on postoperative MRI and revision surgery was performed. More details can be found in Table 1 and Fig. 1.

Predictors of a Favorable Outcome

Among the various parameters, only the size of the CCM, initial mRS score (≤ 2), and known chronic disease were significantly associated with a favorable outcome in the bivariate analysis. In the multivariate logistic regression analysis, only initial mRS score (≤ 2) stayed significant ($p = 0.002$, OR 10.89, 95% CI 2.36–50.25; Supplemental Table 2).

SF-36 Results

In the overall cohort, several SF-36 subdomains (physical functioning, role physical, general health perception, vitality, and social functioning) and the PCS showed significantly lower values compared to those in the healthy population. After stratification by outcome, patients with a favorable outcome showed results comparable to those in the healthy population, except for role physical (Cohen's d = small effect) and PCS (Cohen's d = small effect). Patients with an unfavorable outcome showed decreased scores in all items except bodily pain, and the effects were mainly medium and large (Table 2). As expected, PCS scores tended to increase as the time from surgery increased, reflecting the typical neurological recovery from temporary deficits after surgery. Such an effect was not observed for MCS (Supplemental Fig. 1).

HADS Results

In the overall cohort, the mean HADS-A scores were 5.7 ± 4.6 for male patients and 5.1 ± 3.3 for female patients. The mean HADS-D scores were 5.1 ± 4.7 and 5.0 ± 4.5, respectively. Differences with the healthy population (as measured by effect size) were negligible except for slightly increased depression symptoms in females. After stratification by outcome, patients with a favorable outcome showed normal values. Patients with an unfavorable outcome showed significantly increased anxiety and depression symptoms (male) or exclusively increased depression symptoms (female), all with a medium effect size (Table 2).

LISAT-9 Results

Results of the LISAT-9 are listed in Table 3. Patients with a favorable outcome showed significantly better results than the patients with an unfavorable outcome (except for partnership and family life). To put the results in context, we added "reference scores" for a healthy population sample[30] and a sample of patients 1 year after stroke.[31]

Patient-Reported Cranial Nerve and Brainstem Symptoms

Details of frequencies in patient-reported symptoms are listed in Table 4. Bivariate analysis showed significant associations for several symptoms, especially physical HRQOL (PCS). In the multivariate analysis, none of the associations remained significant. In a further sensitivity analysis, we assessed different combinations of symptoms (both being present in one patient). Here we found that especially balance disturbance (balance disorder and ataxia) was significantly associated with physical HRQOL (multivariate, $p = 0.000$, coefficient = –11.459; Supplemental Table 3).

Correlation of HRQOL With Established Outcome Endpoints

Postoperative mRS strongly correlated with PCS ($p = 0.000$, $R^2 = 0.49$) and less strongly with MCS ($p = 0.001$, $R^2 = 0.14$). However, the variance of mean PCS values significantly increased with the mRS score: from 4.2 (mRS 0) to 68.3 (mRS 1) to 98.8 (mRS 2) and to 118.7 (mRS 3).

Absolute outcome endpoint (mRS ≤ 2) strongly correlated with PCS ($p = 0.000$, $R^2 = 0.28$) and less with MCS ($p = 0.002$, $R^2 = 0.12$). These values were lower/not significant for the relative outcome endpoint (deterioration of at least 1 point in the mRS score; $p = 0.003$, $R^2 = 0.12$ and $p = 0.191$, $R^2 = 0.02$, respectively). Accordingly, AUC values in the ROC analysis showed good and fair values for the absolute outcome endpoint for PCS and MCS, respectively (AUC = 0.870 and 0.743). The relative outcome endpoint showed only fair and poor accuracy (AUC = 0.729 and 0.620; Fig. 2).

Discussion

We present a detailed outcome analysis of a large cohort of patients after surgery for BSCM. According to the most recent meta-analysis,[10] our series is the sixth largest single-center series of those published since 1986. The meta-analysis summarized 86 studies comprising 2493 patients (range 3–397 patients, median 11.5 per series), demonstrating how rarely surgery for BSCM is performed. Most series, however, have reported outcome solely based on functional scores or clinical evaluation. Further outcome measurements, including HRQOL, have only been reported in 3 other series with 17,[22] 22,[23] and 71[21] patients.

Compared to meta-analysis results,[9,10] the long-term

TABLE 1. Baseline characteristics and outcome in 74 patients with BSCM treated with surgery

Variable	Value
Baseline characteristics (n = 74)	
Female sex	45 (61%)
Mean age in yrs	40.4 ± 12.10
Chronic disease	14 (19%)
Psychiatric disease	0 (0%)
Multiple CCMs	5 (7%)
Multiple SHs	37 (50%)
Initial mRS score	
0	2 (3%)
1	26 (35%)
2	24 (32%)
3	13 (18%)
4	9 (12%)
5	0 (0%)
Mean BSCM size in mm	17.8 ± 7.3
Associated DVA	22 (30%)
Location	
Medullary	7 (9%)
Pontomedullary	15 (20%)
Pontine	30 (41%)
Pontomesenphalic	8 (11%)
Mesencephalic	14 (19%)
Ouctome (n = 74)	
Mean time since surgery in mos (range)	53 ± 44.5 (3–177)
Functional deterioration at last FU	15 (20%)
Functional score equal or better at last FU	59 (80%)
Favorable outcome	60 (81%)
Unfavorable outcome	14 (19%)
Mortality	0 (0%)
mRS score at last FU	
0	8 (11%)
1	27 (37%)
2	25 (34%)
3	7 (10%)
4	6 (8%)
5	1 (1%)
RTW	38 (68%*, 76%†)
Mean time to RTW in mos (range)	7.6 ± 5.7 (1–24)
Favorable outcome as stratified by initial mRS score	
0	2 (100%)
1	26 (100%)
2	21 (88%)
3	5 (38%)
4	6 (67%)

DVA = deep venous anomaly; FU = follow-up; n = number of patients; RTW = return to work; SH = symptomatic hemorrhage.
Values are expressed as number (%) of patients or mean ± standard deviation.
* Among the previously employed.
† Among those with a favorable outcome who were previously employed.

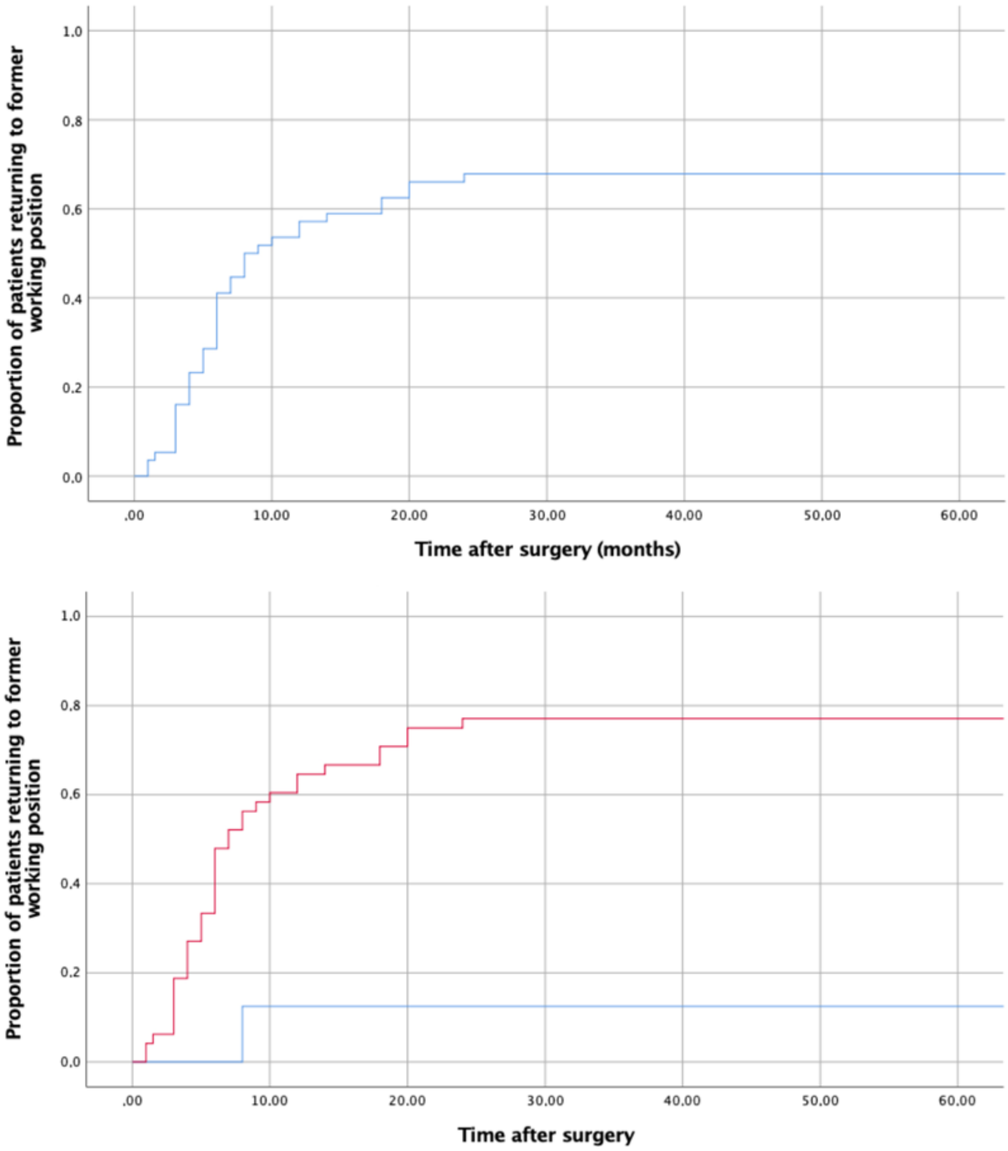

FIG. 1. Proportion of patients returning to former employment after surgery. **Upper:** Overall cohort. **Lower:** Patients stratified by outcome. *Red* = favorable outcome; *blue* = unfavorable outcome. Figure is available in color online only.

relative functional outcome in our series (20% functional deterioration) was within the same range (18.3% and 16%, respectively). Compared to the largest single-center series defining and reporting absolute functional score–based outcomes, our series showed identical results (19% vs 20.3%, respectively unfavorable outcome [mRS > 2]).[25] The mean age and distribution of CCM over the brainstem were also comparable to those in other large series.[25,26] Overall, our study lies within the range of functional outcomes and patient characteristics reported in other series, which increases the external validity of our additionally reported outcomes.

The overall cohort showed significantly impaired HRQOL subdomains and component scores compared to those in an age- and sex-matched healthy population. Scores were strongly decreased in patients with an unfavorable outcome. However, in patients with a favorable outcome, the PCS was slightly decreased compared to that in the healthy population. Notably, a decrease of 2 points in the component scores (and 5 points in the subdomains) is regarded as a clinically and psychosocially relevant decrease.[27,28]

The impact on patients with an unfavorable outcome is also reflected by the strongly increased depression and anxiety scores compared to those in the healthy population. Also, the relatively low rate of patients returning to their former employment reflects this (approximately 80% with a favorable outcome, approximately 10% with an unfavorable outcome). For example, after unruptured aneurysm treatment, this rate is around 90%.[29]

While satisfaction in life has not been previously assessed in BSCM and healthy population data are limited, the results are difficult to put into context. Compared with

TABLE 2. SF-36 and HADS-A and -D results for the entire cohort and subgroups

	Overall Cohort (n = 74)				Favorable Outcome (n = 60)				Unfavorable Outcome (n = 14)				Reference Sample* (n = 74)	
Scale	Mean	SD	p Value†	Effect Size‡	Mean	SD	p Value†	Effect Size‡	Mean	SD	p Value†	Effect Size‡	Mean	SD
SF-36 scores														
Physical health subdomains														
PF	68.37	32.90	**0.000**	Small	78.66	24.40	0.080	NA	24.28	28.20	**0.000**	Large	86.01	23.43
RP	53.26	45.53	**0.000**	Small	62.36	42.78	**0.003**	Small	14.28	36.31	**0.000**	Medium	82.77	33.59
BP	80.47	27.62	0.578	NA	83.31	25.39	0.248	NA	68.28	34.08	0.266	NA	77.89	28.47
GH	61.97	23.48	**0.003**	Small	66.82	20.43	0.111	NA	41.21	25.09	**0.000**	Medium	72.12	17.02
VT	52.56	20.24	**0.024**	Small	56.16	19.29	0.291	NA	37.14	17.17	**0.000**	Medium	59.52	16.80
Mental health subdomains														
SF	71.79	31.31	**0.001**	Small	80.00	26.85	0.173	NA	36.60	24.25	**0.000**	Medium	85.64	19.03
RE	71.62	41.17	0.125	NA	78.88	37.31	0.704	NA	40.47	43.71	**0.000**	Medium	81.27	34.24
MH	69.83	17.93	0.892	NA	73.46	16.20	0.247	NA	54.28	17.16	**0.001**	Medium	70.21	15.90
Component scores														
PCS	44.61	11.71	**0.000**	Small	47.59	9.98	**0.047**	Small	31.80	10.02	**0.000**	Medium	51.20	10.55
MCS	47.51	10.82	0.537	NA	49.32	9.82	0.643	NA	39.78	11.84	**0.003**	Small	47.51	9.28
HADS scores														
HADS-A														
M	5.7	4.6	0.253	NA	4.9	3.5	0.682	NA	9.1	3.9	**0.0001**	Medium	5.1	3.0
F	5.1	3.3	**0.011**	None	4.9	4.5	**0.019**	None	6.0	2.2	0.732	NA	6.3	3.2
HADS-D														
M	5.1	4.7	**0.014**	None	3.7	3.4	0.99	NA	10.3	4.3	**0.0001**	Medium	3.7§	2.7§
F	5.0	4.5	**0.001**	Small	3.7	3.8	0.322	NA	10.6	4.8	**0.0001**	Medium	3.2§	2.6§

BP = bodily pain; GH = general health perception; MH = mental health; NA = not available; PF = physical functioning; RE = role emotional; RP = role physical; SF = social functioning; VT = vitality.
Boldface type indicates statistical significance.
* Age- and sex-matched sample from German reference cohort.
† As compared to age- and sex-matched reference sample (Student t-test).
‡ As measured by Cohen's d: >0.2, small effect; >0.5, medium effect; >0.8, large effect.
§ Reference values for HADS-D are normative values from the German population.

TABLE 3. LISAT-9 results

Domain	Overall Cohort (n = 63)	Favorable Outcome (n = 52)	Unfavorable Outcome (n = 11)	p Value*	Nonspecific Patient Population (n = 69)†	Patients 1 Year After Stroke (n = 119)‡
Life as a whole	31 (49%)	31 (60%)	0 (0%)	**0.000**	75%	49%
Self-care ability	40 (63%)	37 (71%)	3 (27%)	**0.006**	100%	90%
Leisure time	30 (48%)	29 (56%)	1 (9%)	**0.005**	71%	48%
Vocational situation	27 (43%)	26 (50%)	1 (9%)	**0.013**	69%	55%
Financial situation	36 (57%)	33 (63%)	3 (27%)	**0.028**	48%	59%
Sexual life	30 (48%)	29 (56%)	1 (9%)	**0.005**	65%	33%
Partnership	46 (73%)	40 (77%)	6 (55%)	0.129	64%	72%
Family life	51 (81%)	44 (85%)	7 (64%)	0.107	74%	78%
Contact w/ friends	47 (75%)	44 (85%)	3 (27%)	**0.000**	81%	58%

Values are expressed as number (%), representing the satisfied patients. LISAT-9 scores of 5–6 were defined as satisfied. Boldface type indicates statistical significance.
* Favorable and unfavorable outcomes compared using the chi-square test.
† Patients reporting satisfaction before trauma surgery (normal population).
‡ Patients reporting 1 year after a stroke.

TABLE 4. Patient-reported cranial nerve and brainstem symptoms

Symptom	Frequency Among Overall Cohort (n = 74)	Frequency Among Favorable Outcome (n = 60)	Association w/ Impairment of Physical HRQOL* (bivariate)		Association w/ Impairment of Physical HRQOL* (multivariate)		Association w/ Impairment of Mental HRQOL† (bivariate)		Association w/ Impairment of Mental HRQOL† (multivariate)	
			Coefficient	p Value	Coefficient	p Value	Coefficient	p Value	Coefficient	p Value
Facial nerve palsy–dysarthria										
Facial nerve palsy	21 (28%)	6 (10%)	−0.196	**0.043**	−3.688	0.177	−0.058	0.550	NA	NA
Dysarthria	14 (19%)	8 (13%)	−0.298	**0.001**	0.027	0.994	−0.132	0.172	NA	NA
Hearing impairment	23 (31%)	18 (30%)	−0.061	0.529	NA	NA	−0.124	0.200	NA	NA
Motor symptoms										
Hemiparesis	18 (24%)	10 (17%)	−0.338	**0.000**	−4.885	0.087	−0.033	0.734	NA	NA
Fine motor skills impairment	45 (61%)	31 (52%)	−0.301	**0.002**	−0.272	0.919	−0.235	**0.015**	−2.434	0.403
Balance										
Balance disorder	44 (59%)	31 (52%)	0.364	**0.000**	−3.864	0.141	−0.194	**0.045**	−2.072	0.449
Ataxia	35 (47%)	21 (35%)	0.444	**0.000**	−5.351	0.071	−0.265	**0.006**	−2.241	0.451
Vision impairment										
Vision impairment	23 (31%)	12 (20%)	−0.239	**0.014**	−0.246	0.935	−0.277	**0.004**	−4.380	0.127
Double vision	30 (41%)	21 (35%)	−0.273	**0.005**	−1.622	0.548	−0.075	0.439	NA	NA
Nystagmus	13 (18%)	7 (12%)	−0.328	**0.001**	−5.654	0.133	−0.179	0.065	NA	NA
Surgery for double vision	9 (12%)	8 (13%)								
Caudal cranial nerve impairment	7 (9%)	5 (8%)	−0.005	0.963	NA	NA	−0.021	0.829	NA	NA
Sensory disorder										
Sensory disorder	38 (51%)	29 (48%)	−0.220	**0.023**	−2.451	0.329	0.021	0.825	NA	NA
Pain	19 (26%)	14 (23%)	−0.305	**0.002**	−1.050	0.707	−0.194	**0.045**	−3.211	0.127
Sexual dysfunction	14 (19%)	8 (13%)	−0.333	**0.001**	−2.458	0.476	−0.086	0.377	NA	NA

Values expressed as number (%), representing satisfied patients. Boldface type indicates statistical significance.
* Physical component score used.
† Mental component score used.

that in unaffected patients[30] or patients 1 year after stroke,[31] it is notable that especially satisfaction in self-care ability was low, even in cases with a favorable outcome. An unfavorable outcome led to a massive reduction in satisfaction in all domains of life (except family life and partnership).

Cranial nerve and brainstem symptoms in this series were assessed using patient-reported categorical data. This may have led to an overreporting of symptoms (whereas physician-reported outcomes are prone to underreporting of symptoms).[32] However, it has been shown that patient-reported symptoms enhance HRQOL assessment and outcome discrimination in clinical trials.[32] Most importantly, we found a strong association between balance disorders and HRQOL, meaning that among cranial nerve and brainstem symptoms, any disturbance in balance and the presence of ataxia reduced physical (and less mental) HRQOL most significantly. Additionally, to the best of our knowledge, sexual dysfunction (and satisfaction with sexual life), a potential postoperative complication and important aspect of HRQOL, has been assessed for the first time with this study.

Regarding outcome reporting after BSCM surgery in general, an important finding of our study was that HRQOL is more precisely reflected by using absolute outcome endpoints, that is, based on the mRS, rather than relative outcome endpoints. The general superiority of absolute over relative outcome measures in evaluating outcome has been discussed elsewhere.[33] To note, variance in the HRQOL component scores increased significantly as the mRS score increased. This means that in individual cases, lower mRS outcome scores of 1 or 2 were also associated with decreased HRQOL and vice versa in this study.

In summary, this study meticulously reflects the potential multidimensional impact on patients after surgery for BSCM. To note, nearly all patients with an unfavorable outcome were already initially severely disabled (mRS > 2) by the CCM hemorrhage itself. This is, in general, not infrequent after BSCM hemorrhage.[8] Only 6% of patients with a preoperative mRS score of 0–2 experienced an unfavorable outcome in this series. Accordingly, a preoperative mRS score of 0–2 was an independent predictor of a favorable outcome (p = 0.002, OR 10.89, 95% CI 2.36–50.25). However, the natural course even after a severe bleeding, as well as the potential recovery from symptoms, remains hard to predict and could be benign.[11] In addition, even patients with favorable outcomes frequently reported residual symptoms, especially those that were strongly associated with a decreased HRQOL (52% balance disorders). A satisfaction rate of only 71% in self-care ability also reflects substantial impairment in everyday life in these patients.

Although patients may live a relatively "normal" life after resection of their BSCM and attain a favorable outcome, the burden after surgery is substantial when this is not achieved. This dilemma emphasizes the importance

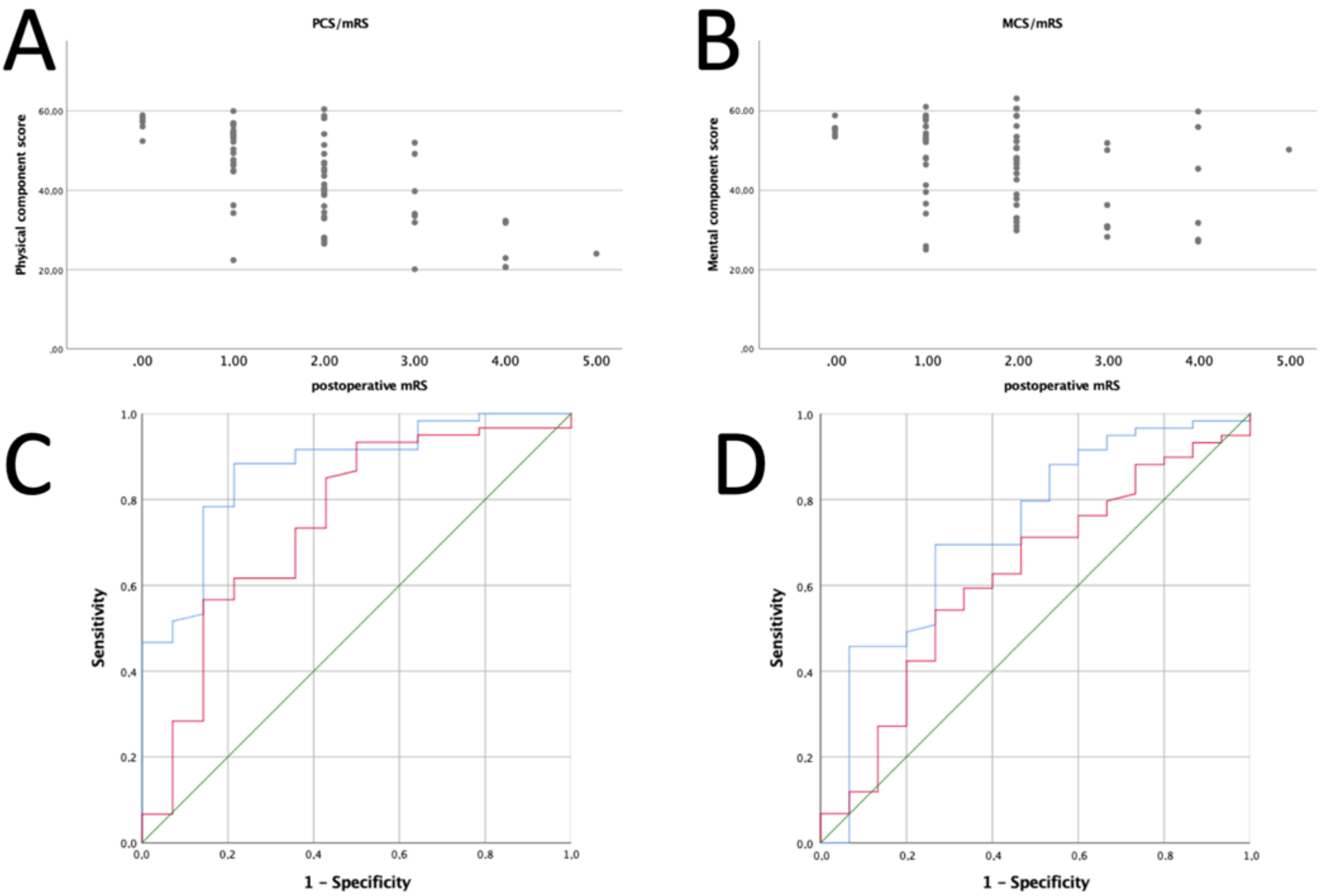

FIG. 2. Correlation of functional outcome and SF-36 scores. Scatter plots for PCS (**A**) and MCS (**B**) stratified by postoperative mRS score. Especially the PCS shows high variance at mRS scores 1 and 2. AUCs show the correlation of outcome endpoints with PCS (**C**) and MCS (**D**). Notably, the absolute outcome measurement (*blue*) correlates better compared to the relative outcome measurement (*red*). Figure is available in color online only.

in further improving the identification of "ideal" candidates for surgery and specifying these indications in future guidelines. Moreover, we should be aware that a "favorable outcome" after BSCM surgery as we define it does not necessarily reflect a good HRQOL or satisfaction in life in all patients (especially in those with an mRS score of 2). This is even more relevant when using relative outcome endpoints.

Study Limitations

This study has several limitations. It is not a comparative study with randomized treatment allocation. The presumed natural untreated course of patients remains unclear, and outcome cannot be compared to that in untreated or otherwise-treated BSCM. The initial selection for treatment was not based on predefined criteria, as such criteria do not exist yet.

Some data were assessed retrospectively and are thus susceptible to information and selection bias. Although this is a relatively large series, absolute numbers were small, probably over- or underestimating effects. Longitudinal data offer more information, but they were not available in our study. In addition, preoperative scores after diagnosis of symptomatic hemorrhage of a BSCM would be difficult to put into context, as these acute situations interfere with HRQOL perception.[18] Comparisons with healthy populations (as performed in this study) may deliver even more reliable results.

Conclusions

Our data can improve patient counseling and decision-making in BSCM treatment and may function as a benchmark. We report outcomes after BSCM surgery in high detail, emphasizing the impact of cranial nerve and brainstem symptoms on HRQOL. When reporting BSCM surgery outcomes, absolute outcome endpoints should be applied.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Dammann, Sure. Acquisition of data: Dammann, Herten, Chen, Forsting, Kleinschnitz. Analysis and interpretation of data: Dammann, Forsting, Kleinschnitz. Drafting the article: Dammann. Critically revising the article: Dammann, Santos, Kleinschnitz, Sure. Reviewed submitted version of manuscript: Herten, Santos, Rauschenbach, Chen, Darkwah Oppong, Sure. Approved the final version of the manuscript on behalf of all authors: Dammann. Statistical analysis: Schmidt. Administrative/technical/material support: Darkwah Oppong, Schmidt.

Supplemental Information

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Zusammenfassung

Die operative Versorgung von PatientInnen mit kavernösen Malformationen des Hirnstammes brainstem cavernous malformation (BSCM) ist Gegenstand intensiver Diskussion. Zur Stellung der Operationsindikation können verschiedene Klassifikationen zur Hand genommen werden, die das postoperative Outcome der PatientInnen vorhersagen und somit solche identifizieren, die von einer operativen Kavernomexstirpation profitieren könnten. Ungeklärt bleibt, wie zuverlässig diese Klassifikationssysteme arbeiten und inwieweit auch psychosoziale Einschränkungen in die präoperative Entscheidungsfindung integriert werden sollten. In der vorliegenden Studie wurden die verfügbaren Klassifikationen hinsichtlich ihrer Aussagekraft untersucht zunächst In einem ersten Schritt die prognostische Wertigkeit und die Reproduzierbarkeit von zwei Klassifikationssystemen. Anschließend wurde evaluiert, in-wieweit das postoperative Outcome mit dem Auftreten von psychosozialen Einschränkungen korreliert. Für diese Studie wurde eine Datenbank mit BSCM PatientInnen (⇥ 18 Jahre) herangezogen und durch 3 unabhängige Beobachter klassifiziert, welche zwischen 2003 und 2019 in der Abteilung der Autoren chirurgisch behandelt wurden. Perioperative klinische Aufzeichnungen sowie präoperative Magnetresonanztomographie -Untersuchungen wurden analysiert. Für einen Studieneinschluss wurde ein postoperatives Follow-Up von ⇥ 6 Monaten (prognostische Wertigkeit, Reproduzierbarkeit) bzw. ⇥ 3 Monaten (psychosoziale Einschränkungen) gefordert. Das funktionelle neurologische Outcome wurde anhand des Modified Rankin Scale (mRS)-Scores bewertet. Für die Bestimmung der psychosozialen Einschränkungen wurde die gesundheitsbezogene Lebensqualität (HRQOL) mit Hilfe des Short Form Health Survey-36 (SF-36) und des 9-item Life Satisfaction Questionnaire (LISAT-9) herangezogen/psychologische Outcome mit Hilfe der Hospital Anxiety and Depression Scale (HADS) und der Zeitpunkt der Rückkehr in die frühere Beschäftigung erhoben sowie für eine nähere Einordnung der SF-36- und HADS-Werte ein Vergleich zur Normalbevölkerung gezogen. Ingsgesamt wurden 67 PatientInnen in die Analyse eingeschlossen. Mehrfachblutungen, Kavernomdurchmesser und Patientenalter (>50 Jahre) wurden als Prädiktoren für ein ungünstiges postoperatives Funktionsergebnis beobachtet. Eine kombinierte Verwendung der beiden Klassifikationssysteme erhöhte die Aussagekraft deutlich. Für die Erfassung von psychosozialen Einschränkungen wurden 74 PatientInnen in die Analyse eingeschlossen. Die HRQOL war nach einer BSCM-Operation beeinträchtigt. Diese Beeinträchtigung war erheblich bei PatientInnen mit einem ungünstigen funktionellen Ergebnis (mRS > 2), war aber auch bei denen mit einem günstigen Ergebnis (mRS ≤ 2) in ausgewählten Bereichen vorhanden. Vor allem Hirnstamm- und Hirnnervensymptome wie Gleichgewichtsstörungen reduzieren die Zufriedenheit bei PatientInnen. Unsere Analyse zeigt, dass die derzeit verfügbaren Klassifizierungssysteme geeignete Instrumente sind, um das neurologische Ergebnis nach einer BSCM-Operation abzuschätzen, hierfür sollte eine Klassifizierung der BSCM Patienten präoperativ anhand verfügbarer Klassifikationssysteme erfolgen, absolute Endpunkte verwendet und psychosoziale Aspekte berücksichtigt werden .

Mit unseren Studienergebnissen hoffen wir, einen sinnvollen Beitrag zur Therapiestratifizierung von BSCM-PatientInnen zu leisten.

Summary

Treatment indications for patients with brainstem cavernous malformations (BSCMs) remain difficult and controversial. Some authors have tried to establish classification tools to identify eligible candidates for surgery. Authors of this study aimed to validate the performance and replicability of two proposed BSCM grading systems, the Lawton- Garcia (LG) and the Dammann-Sure (DS) systems, as well as assess the outcome after surgery BSCMs using functional, health-related quality of life (HRQOL), and psychological surveys to analyze the interrelation of these measurements, and to compare HRQOL and anxiety and depression scores with those in a healthy population. For this cross-sectional study, a database was screened for patients with BSCM treated surgically between 2003 and 2019 in the authors' department. Complete clinical records, preoperative contrast-enhanced MRI, and a post-operative follow-up ≥ 6 months were mandatory for study inclusion. The modified Rankin Scale (mRS) score was determined to quantify neurological function outcome. Three observers independently determined the LG and the DS score for each patient. Additionally, we assessed health-related quality of life (HRQOL) via the SF-36 and 9-item Life Satisfaction Questionnaire (LISAT-9), cranial nerve and brainstem function using a questionnaire, symptom-based psychological outcome via the Hospital Anxiety and Depression Scale (HADS), and timepoint of a return to previous employment. We analyzed the correlation between absolute (mRS score ≤ 2) and relative (postoperative deterioration in initial mRS score) outcome endpoints and the interrelation of the outcome measures and performed a comparison of HRQOL and HADS scores with findings in a healthy population. A total of 67 patients met selection criteria to validate the performance and replicability of proposed BSCM grading systems. Univariate and multivariate analyses identified multiple bleedings ($p = 0.02$, OR 5.59), lesion diameter (> 20 mm, $p = 0.007$, OR 5.43), and patient age (> 50 years, $p = 0.019$, OR 4.26) as predictors of an unfavorable postoperative functional outcome. Both the LG (area und the curve (AUC) = 0.72, $p = 0.01$) and the DS (AUC = 0.78, $p < 0.01$) scores were robust tools to estimate patient outcome. Subgroup analyses confirmed this observation for both grading systems (LG: $p = 0.005$, odds ration (OR) 6; DS: $p = 0.026$, OR 4.5), but the combined use of the two scales enhanced the test performance significantly ($p = 0.001$, OR 22.5). Moreover, 74 patients where eligible to assess possible psychosocial impairments after surgery. HRQOL was impaired after surgery for BSCM compared to that in a healthy population. This impairment was substantial in patients with an unfavorable functional out-come (mRS > 2) but was also present in those with a favorable outcome (mRS ≤ 2) in selected domains. Psychological impairment was negligible in patients with a favorable outcome and grave in those with an unfavorable outcome. LISAT-9 results revealed that brainstem and cranial nerve symptoms reduce satisfaction mainly in self-care abilities for both unfavorable and favorable outcome patients. Among the brainstem and cranial nerve symptoms, balance impairment showed the most significant impact on HRQOL. Absolute outcome endpoints were superior to relative outcome endpoints in reflecting impairment in HRQOL after surgery.

Currently available classification systems are appropriate tools to estimate the neurological outcome after BSCM surgery. Future studies are needed to design an advanced scoring system, incorporating items from the LG and the DS score systems. Moreover, we report outcomes after BSCM surgery in high detail, emphasizing the specific impact of cranial nerve and brainstem symptoms on HRQOL. When reporting BSCM surgery outcome, absolute out- come endpoints should be applied.

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