The occurrence of neuropathic pain following surgery of brainstem cavernous malformations

Annika Herten1 | Dino Saban1 | Alejandro N. Santos1 | Bixia Chen1 | Marvin Darkwah Oppong1 | Laurèl Rauschenbach1 | Ramazan Jabbarli1 | Karsten Wrede1 | Ulrike Bingel2 | Daniel Müller2 | Dagny Holle-Lee2 | Börge Schmidt3 | Yan Li4 | Ulrich Sure1 | Philipp Dammann1

1Department of Neurosurgery and Spine Surgery, University Hospital Essen, Essen, Germany
2Department of Neurology, Center for Translational Neuro- and Behavioral Sciences, University Hospital Essen, Essen, Germany
3Institute for Medical Informatics, Biometry and Epidemiology, University Hospital of Essen, Essen, Germany
4Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Essen, Germany

Correspondence
Annika Herten, University Hospital Essen, Department of Neurosurgery, Hufelandstrasse 55, 45147 Essen, Germany.
Email: annika.herten@uk-essen.de

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Abstract
Background and purpose: This study aimed to assess the occurrence and significance of postoperative neuropathic pain (NP) in patients with surgically treated brainstem cavernous malformations (BSCMs).

Methods: Seventy-four BSCM patients surgically treated between 2003 and 2019 were reviewed for the occurrence of postoperative NP and related treatment. The relevance of BSCM location, preoperative characteristics, influence on functional outcome, postoperative health-related quality of life (HRQOL) and life satisfaction was evaluated.

Results: Six out of 74 patients (8%) suffered from NP. The Leeds Assessment of Neuropathic Symptoms and Signs scores ranged from 12 to 16 (mean 14.28 ± 1.6). Visual analog scale pain was 5.2 ± 2.0. NP had no effect on preoperative characteristics or functional outcome. Bodily pain (HRQOL) and vocational time (life satisfaction) were significantly decreased in NP compared to non-NP patients. Specific BSCM location (regarding brainstem nuclei involved in pain processing) and other preoperative patient- and BSCM-related parameters were not associated with the occurrence of postoperative NP. Three out of six patients were currently under NP-specific treatment. The proportion of patients suffering from postoperative NP (8%) was substantially higher compared to previously published studies. The pain affected the HRQOL of patients, most of whom were insufficiently treated and not satisfied with treatment results.

Conclusion: Our findings may help to raise awareness for postoperative NP in BSCM, which is essential to improve diagnosis and initiation of proper treatment, as well as preoperative informed consent of patients.

Keywords
brainstem cavernous malformation, health-related quality of life, neuropathic pain
INTRODUCTION

Cerebral cavernous malformations (CCMs) occur with a prevalence of approximately 0.4%-0.8% in the general population [1-7] and account for 10%-25% of all intracranial vascular malformations [8,9]. They are found across the entire central nervous system, presenting as familial or sporadic disease [10]. The frequency of CCMs located in the brainstem (BSCM) varies between 10% and 35% in larger clinical series [1,3,9,11]. Whilst non-brainstem CCM are prone to intracerebral hemorrhage, the bleeding risk of a BSCM is still higher in comparison, with an estimated rate of 6% per patient per year [4,12]. The 5-year risk of a recurrent hemorrhage in BSCMs is reported as 30%, compared to 18% in those not located in the brainstem [9]. Based on their eloquent location, hemorrhages from BSCMs also cause more severe disability compared to supratentorial CCM [13-16]. These features render BSCMs potential candidates for neurosurgical treatment [17], the rate of which is approximately 20%-25% [1]. Due to significant operative risks, the indication for such treatment remains controversial [17]. Early postoperative morbidity is 31% and long-term morbidity is estimated to be 18% according to the largest meta-analysis [15].

Whilst a broad spectrum of symptoms may manifest after surgery for BSCM, few studies have reported the occurrence of neuropathic pain (NP). The largest series of surgically treated BSCMs, however, reported an occurrence of postoperative NP in <1% of cases [18]. This number appears surprisingly low considering that pain symptoms are reported in around 30% of symptomatic intramedullary CCMs [19,20] and given the fact that the prevalence of central poststroke pain, another example of central NP, is approximately 8% [21]. Since NP arises as a direct result of damage to or lesion of the somatosensory system [22,23], its manifestation is quite probable in the course of a bleeding or surgery of a BSCM. The diagnosis of NP is based on typical symptoms, in particular the combination of minus symptoms (sensitive deficits such as hypesthesia, hypalgesia) and plus symptoms (burning pain, especially at rest, shooting pain attacks, allodynia, hyperalgesia) [22-24]. Therefore, it may also be mistakenly interpreted and misclassified as a predominantly sensitive deficit and consequently be underreported. It is known of similar central poststroke pain that it is often not recognized as it is only disclosed by the patient when actively asked [25]. Under the assumption of a possible underdiagnosis of this severe symptom, a prospective cross-sectional study was performed in a previously described cohort of BSCM patients [26]. The aim was to evaluate the prevalence of postoperative NP, identify risk factors and evaluate its potential impact on postoperative outcome and health-related quality of life (HRQOL) and life satisfaction (LISAT).

METHODS

Study design and population

In a previously published cohort of 74 patients who were consecutively included between 1 January 2003 and 31 December 2019, undergoing surgery for BSCM and multi-modal outcome assessment (functional outcome, HRQOL, anxiety and depression scores) [26], 19 patients (26%) reported any kind of postoperative pain, including headache, joint pain, pain due to spasticity or paresis of one limb. In these patients, a standardized additional interview/examination was performed to diagnose and confirm postoperative NP and assess current related treatment. The study was conducted according to the principles expressed in the Declaration of Helsinki, and a local ethics approval was obtained (Review Board identification 19-8662-BO, 15-5751-BO). Informed consent was obtained from all participants. The study was performed according to the STROBE protocol.

Definition and assessment of neuropathic pain

Neuropathic pain was diagnosed and defined as probable or possible NP according to Treede et al. [23] and assessed according to the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale [24]. Intensity of pain was graded using the visual analog scale (VAS) (0-10). Examination was performed according to the proposal by Bates and colleagues [27]. Current treatment was evaluated and rated (3-point Likert scale: 1, not really satisfied; 2, neutral; 3, fairly satisfied).

Data collection and survey of the cohort

As previously reported [26], clinical baseline data of patients and BSCMs were collected preoperatively and postoperatively based on medical charts according to CCM reporting standards (sex, age at surgery, CCM location in brainstem, history of multiple symptomatic hemorrhages, known chronic disease [as defined by the Short Form 36 (SF-36) criteria [28]], known psychiatric disease, degree of disability on the modified Rankin Scale [mRS], postoperative complications and duration of hospitalization [29]). Radiological data (e.g., size of BSCM, presence of developmental venous anomaly, location in brainstem) were assessed by an experienced neuroradiologist. HRQOL was examined using the German version of the SF-36 [28] and the LISAT-9 score [30] (estimation of life satisfaction in different domains based on a 6-point score; 5-6 points defined as satisfied). Symptom-based depression and anxiety were assessed using the German Hospital Anxiety and Depression Scale (HADS-A/D) score [31]. Functional outcome was measured using the mRS.

location in relation to brainstem nuclei involved in nociception and pain processing

According to the proposal of Napadow et al. [32], the focus was on 11 brainstem nuclei in midbrain, pons and medulla. Direct proximity of the BSCM to (midbrain) dorsal raphe nucleus (DRN), periaqueductal grey (PAG), nucleus cuneiformis (NCF), (pons) median raphe
nucleus (MRN), parabrachial nucleus (PBN), locus coerulesus (LC), (ponto-medullary junction) nucleus raphe magnus (NRM), nucleus gigantocellularis (NGc), spinal trigeminal nucleus (SpV) and (medulla) ventrolateral medulla (VLM), dorsal reticular nucleus (DRt) and nucleus tractus solitarii (NTS) was evaluated by two raters (AH, PD) based on preoperative magnetic resonance imaging (MRI).

**Reference data**

Health-related quality of life was compared to an age- and sex-matched normal German population [28].

**Statistical analysis**

The characteristics and outcome of patients with and without postoperative NP were compared and potential predictors for postoperative NP were analyzed. Statistical analyses were performed using SPSS Statistics version 26 (IBM Corp.). Nominal data were expressed as absolute numbers and valid percentages, and continuous variables were expressed as mean ± standard deviation. A Shapiro–Wilk test, histograms and Q–Q plots were used to test data for normal distribution. Parametric statistics were used for between-group comparison. Comparing continuous variables, the unpaired Student’s t test or Mann–Whitney U test were used. For categorical variables, chi-squared or Fisher’s exact tests (expected frequencies <5) were applied. A sex- and age-matched 1–1 case–control sample was created based on the German reference sample. Comparison of mean values (SF-36 scores) was performed using Student’s t test preceded by the Levene’s test of variance homogeneity. Bivariate correlation was performed to determine parameters with an impact on pain occurrence. According to the character of the variables, Pearson’s r, Spearman’s rho or Kendall’s tau-b tests were used. All tests were two-tailed (alpha = 0.05).

**RESULTS**

**Baseline characteristics and outcome**

Six (8%) of 74 included patients fulfilled the definition of probable postoperative NP. None of these patients suffered from BSCM-related NP prior to the operation. LANSS pain scores ranged from 12 to 16 (mean 14.28 ± 1.6). Four patients developed NP within 6–12 weeks after surgery, three patients developed NP within 6 months and one patient within 12 months postoperatively. Five patients suffered from pain in the hemibody; three had one affected upper body limb. In this population three patients suffered from burning pain, of whom two described unpleasant sensations to light touch. Five patients had paraesthesia sensations. Averaged extent of pain as measured by the VAS was 5.2 ± 2.0 points and ranged from 3 to 7 points. In-between group comparison of NP and no-NP cohorts revealed no significantly different patient- or BSCM-related variables (Table 1).

**Health-related quality of life (SF-36), LISAT-9 and HADS-A/D results**

Short Form 36 values for the NP cohort, no-NP cohort, complete cohort and the reference sample from the normal German population are summarized in Table 2. As described before [26], patients after surgery for BSCM showed decreased values in several subdomains and the physical component score. In comparison to the no-NP cohort, patients with NP exhibited, as expected, significantly decreased HRQOL values regarding bodily pain. In other domains the groups did not differ significantly. No significant differences were found in LISAT and HADS-A/D values between patients with and without NP, except for the LISAT-9 domain “vocational time,” which was significantly decreased in the NP cohort (Table 3).

**Predictors and risk factors**

Bivariate correlation analysis between the occurrence of postoperative NP and clinical parameters (age, BSCM-related NP before surgery, multiple symptomatic hemorrhages before surgery, sex, pontine location, medullary location, mesencephalic location, known chronic disease, mRS score preoperatively, size of CCM, association with developmental venous anomaly, and favorable outcome) revealed no significant associations (Table S1). Similarly, bivariate correlation between the occurrence of postoperative NP and BSCM proximity to brainstem nuclei involved in pain processing (DRN, PAG, NCF, MRN, PBN, LC, NRM, NGc, SpV, VLM, DRt and NTS) demonstrated no significant correlation (Table S2).

**Current treatment**

Three patients reported treatment with gabapentanoids and serotonin-noradrenaline reuptake inhibitors (first-line treatment [27]) and two were treated with nonsteroidal anti-inflammatory drugs on demand (not established treatment in NP [27]), whereas one patient received no specific analgesic treatment. All patients reported that they were not really satisfied with the NP treatment results (100%).

**DISCUSSION**

In this study, a detailed outcome analysis of postoperative NP in a large cohort of patients after surgery for BSCM is presented according to NP reporting standards. In 8% of patients, probable postoperative NP was diagnosed. Of note, none of the patients suffered from NP before surgery. Although frequently described in patients...
| Baseline characteristics | Neuropathic pain (N = 6) | No neuropathic pain (N = 68) | Complete cohort (N = 74) | p* | Outcome | Neuropathic pain (N = 6) | No neuropathic pain (N = 68) | Complete cohort (N = 74) | p* |
|--------------------------|--------------------------|-----------------------------|--------------------------|----|---------|--------------------------|-----------------------------|--------------------------|----|
| Female sex               | 4 (67%)                  | 41 (60%)                    | 45 (61%)                 | >0.05 | Time since surgery (months) | 30.8 ± 18.0 | 55.0 ± 45.7 | 53.0 ± 44.2 | >0.05 |
| Age (years)              | 47.7 ± 11.11             | 39.8 ± 12.0                 | 40.4 ± 12.1              | >0.05 | Favorable outcome (mRS 0–2) | 4 (66%) | 56 (82%) | 60 (81%) | >0.05 |
| Chronic disease          | 0 (0%)                   | 14 (21%)                    | 14 (19%)                 | >0.05 | Unfavorable outcome (mRS >2) | 2 (33%) | 12 (18%) | 14 (19%) | >0.05 |
| Multiple CCM             | 1 (17%)                  | 4 (6%)                      | 5 (7%)                   | >0.05 | Mortality | 0 (0%) | 0 (0%) | 0 (0%) | >0.05 |
| Multiple SH              | 5 (83%)                  | 32 (47%)                    | 37 (50%)                 | >0.05 | Visual analog scale (VAS)  | 5.2 ± 2.0 | n/a | n/a | >0.05 |
| Initial mRS              |                          |                             |                          |      | mRS at last follow-up      | 0 | 0 (0%) | 8 (12%) | 8 (11%) | >0.05 |
| 0                        | 0                        | 2 (3%)                      | 2 (3%)                   | >0.05 | 1 | 1 (25%) | 25 (38%) | 27 (37%) | >0.05 |
| 1                        | 2 (33%)                  | 24 (35%)                    | 26 (35%)                 | >0.05 | 2 | 3 (38%) | 22 (33%) | 25 (34%) | >0.05 |
| 2                        | 1 (13%)                  | 23 (35%)                    | 24 (32%)                 | >0.05 | 3 | 2 (33%) | 5 (7%) | 7 (10%) | >0.05 |
| 3                        | 2 (33%)                  | 11 (16%)                    | 13 (18%)                 | >0.05 | 4 | 0 (0%) | 6 (9%) | 6 (8%) | >0.05 |
| 4                        | 1 (13%)                  | 8 (12%)                     | 9 (12%)                  | >0.05 | 5 | 0 (0%) | 1 (2%) | 1 (1%) | >0.05 |
| 5                        | 0                        | 0                           |                          |      | BSCM size (mm) | 19.4 ± 5.9 | 17.8 ± 7.5 | 18.0 ± 7.4 | >0.05 |
| DVA                      | 2 (33%)                  | 20 (29%)                    | 22 (30%)                 | >0.05 | 1 | 14 (21%) | 14 (20%) | 15 (20%) | >0.05 |
| Location                 |                          |                             |                          |      | Pontomedullary | 1 (13%) | 14 (21%) | 15 (20%) | >0.05 |
| Medullary                | 0 (0%)                   | 7 (11%)                     | 7 (9%)                   | >0.05 | Pontine | 2 (33%) | 28 (41%) | 30 (41%) | >0.05 |
| Pontomedullary           | 1 (13%)                  | 14 (21%)                    | 15 (20%)                 | >0.05 | Pontomesencephalic | 1 (13%) | 7 (11%) | 8 (11%) | >0.05 |
| Pontine                  | 2 (33%)                  | 28 (41%)                    | 30 (41%)                 | >0.05 | Mesencephalic | 2 (42.9%) | 12 (18%) | 14 (19%) | >0.05 |
| Pontomesencephalic       | 1 (13%)                  | 7 (11%)                     | 8 (11%)                  | >0.05 | Neurpathic pain before surgery | 0 (0%) | 2 (3%) | 2 (3%) | >0.05 |
| Mesencephalic            | 2 (42.9%)                | 12 (18%)                    | 14 (19%)                 | >0.05 | |

Abbreviations: BSCM, brainstem cavernous malformation; CCM, cerebral cavernous malformation; DVA, developmental venous anomaly; mRS, modified Rankin Scale; SH, symptomatic hemorrhage.

*Compared by chi-squared or Student’s t test.
after surgery for intramedullary CCM [19], in BSCM postoperative NP has either not been reported [15] or only rarely (<1%) described [18], which is in contrast to our findings.

When comparing patients with and without postoperative NP, no significant differences in preoperative characteristics or functional outcome were found. Regarding postoperative HRQOL, patients with NP showed strongly decreased scores in the subdomain “bodily pain.” Other subdomains as well as the component score showed comparable values. Selected LISAT domains were significantly lower in patients with compared to those without NP (“vocational time” 0% vs. 47%), in addition to an overall tendency for lower values in NP patients. Preoperative features and specific BSCM location showed no association with the occurrence of postoperative NP. The lack of a verifiable association between BSCM location and outcome, however, may be attributed to the relatively low overall number of patients analyzed.

Mean severity of pain as assessed using VAS (5.2 ± 2.0) was slightly lower compared to NP in patients with spinal cord injury [33]. Only three patients (50%) were properly treated according to NP treatment guidelines [27]. All patients specified to not being really

### TABLE 2 SF-36 values

| Physical health domains | Neuropathic pain (N = 6) | p* | No neuropathic pain (N = 68) | Complete cohort (N = 74) | p* | Reference sample (N = 74) |
|-------------------------|--------------------------|----|-----------------------------|--------------------------|----|--------------------------|
| PF                      | 70.83 ± 26.34            >0.05 | 68.16 ± 33.50               | 68.37 ± 32.90            | 0.0001 | 86.01 ± 23.43            |
| RP                      | 45.83 ± 51.03            >0.05 | 53.92 ± 45.38               | 53.56 ± 45.53            | 0.0001 | 82.77 ± 33.59            |
| BP                      | 38.00 ± 20.82            0.0001 | 84.24 ± 24.96               | 80.47 ± 27.62            | >0.05 | 77.89 ± 28.47            |
| GH                      | 64.33 ± 17.77            >0.05 | 61.77 ± 24.00               | 61.97 ± 23.48            | 0.003 | 72.12 ± 17.02            |
| VT                      | 50.00 ± 19.66            >0.05 | 52.79 ± 20.41               | 52.56 ± 20.24            | 0.023 | 59.52 ± 16.80            |

### TABLE 3 LISAT-9 and HADS-A/D results

| LISAT-9 domains | Neuropathic pain (N = 6) | No neuropathic pain (N = 57) | p* |
|-----------------|--------------------------|-----------------------------|----|
| Life as a whole | 2 (33%)                  | 28 (50%)                    | >0.05 |
| Self-care ability | 3 (50%)                  | 37 (64%)                    | >0.05 |
| Leisure time    | 3 (50%)                  | 27 (48%)                    | >0.05 |
| Vocational time | 0 (0%)                   | 27 (47%)                    | 0.026 |
| Financial situation | 2 (33%)                  | 34 (60%)                    | >0.05 |
| Sexual life     | 2 (33%)                  | 28 (49%)                    | >0.05 |
| Partnership     | 4 (66%)                  | 42 (73%)                    | >0.05 |
| Family life     | 4 (66%)                  | 47 (83%)                    | >0.05 |
| Contact with friend | 3 (50%)                  | 43 (75%)                    | >0.05 |

| Anxiety and depression | Neuropathic pain (N = 6) | No neuropathic pain (N = 68) | p* |
|-------------------------|--------------------------|-----------------------------|----|
| HADS-A                  | 6.0 ± 4.1                | 5.3 ± 3.8                   | >0.05 |
| HADS-D                  | 5.8 ± 3.8                | 4.9 ± 4.7                   | >0.05 |

Abbreviations: BP, bodily pain; GH, general health perception; MCS, mental component score; MH, mental health; PCS, physical component score; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; SF-36, Short Form 36; VT, vitality.

*Compared by Student’s t test. Bold significance indicates * p < 0.05.

*Compared by chi-squared or Student’s t test. Bold significance indicates * p < 0.05.
satisfied with NP treatment results, indicating a limited awareness/experience of practitioners in this regard and a probable underdos- ing of medication.

Whilst impairment of HRQOL in patients with BSCM (untreated [34] or after surgery [26]) is known, such a high proportion of pa- tients suffering additionally from HRQOL-decreasing NP has not been reported before. Considering the proximity of BSCM to several brainstem nuclei and pathways involved in pain processing [32], it seems likely that the low rates or lack of mention of postoperative NP in BSCM may be a form of underreporting. The difficulty of di- agnosing NP, particularly in the presence of other sensory deficits (which are commonly found subsequent to BSCM surgery [15,26]), may contribute to this issue.

In comparison to and in demarcation of NP in BSCM and cen- tral poststroke pain (CPSP) several aspects are relevant. CPSP, still lacking a universal definition and being sometimes challenging to diagnose, is a form of NP that is therefore diagnosed with a wide variety amongst stroke patients (8%–55%) [35]. Population-based data showed a prevalence of 8% [21]. Being initially thought to be limited to thalamic stroke patients (“thalamic pain”), newer theories state that involvement of spinothalamic and other sensory pathways (e.g., medial lemniscus pathway) and its associated nuclei groups may contribute to CPSP, perhaps in the form of a so-called “central imbalance” [35]. Overall, the exact mechanisms are poorly under- stood; however, a combination of deafferentation and subsequent development of neuronal hyperexcitability seems to be one crucial pathomechanism in the development of CPSP [36]. The complexity of the brainstem and diencephalic nuclei and pathways and the big challenge to verify/exclude the damage of (parts of) these structures by lesions (stroke, CCM hemorrhage, surgery) using MRI is a big methodological problem in CPSP research. Regarding BSCMs this is especially the case in larger BSCMs exceeding several centimeters, deviating normal anatomical structures. This difficulty in adjudicate the specific anatomical origin of the NP may have also contributed to the lack of a verifiable association between BSCM location and NP occurrence in our study design.

For NP in BSCM as analyzed in our study it is also difficult to distinguish whether the symptomatic hemorrhage of the BSCM or the surgical resection procedure was causative, as both events are normally very closely spaced in time (in general around 4–6 weeks or earlier). In CPSP, on the other hand, latency to onset of pain is reported as 3–6 months [37], which is more or less comparable to the latency in our study. Comparative observational studies are neces- sary to better compare NP outcome in treated or untreated BSCM patients.

Limitations

This is a single-center study. The occurrence and severity of postop- erative NP in BSCM surgery should be reviewed in other cohorts as single-center studies only allow limited generalizability. The evalu- ation of BSCMs regarding proximity to brainstem nuclei is limited since they cannot be visualized directly, rendering such localization prone to inaccuracy. In addition, BSCM hemorrhage leads to shifting of normal brain tissue, further limiting the localization of subtle anatomical structures. As no electrophysiological examinations as an important diagnostic tool in the assessment of the assumed NP were performed, it cannot be ruled out that additional peripheral neuro- pathic conditions may contribute to the extent of the reported NP.

Magnetic resonance imaging protocols were not equal in all pa- tients, which may have caused inter-patient variance in the local- ization of subtle anatomical structures. As mentioned before, an additional limitation is the low statistical power due to the small number of cases. Thus, only strong group differences become sta- tistically significant.

CONCLUSION

Our study revealed a profoundly increased proportion of patients suffering from postoperative NP in comparison with previously published studies (8% vs. <1%). Patients’ HRQOL was affected by the pain, and most patients were insufficiently treated and dissatisfied with treatment results. Our observations may help to raise aware- ness for postoperative NP in BSCM, which is essential to improve diagnosis and initiation of proper treatment, as well as preoperative informed consent of patients.

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CONFLICT OF INTEREST

Nothing to disclose.

AUTHOR CONTRIBUTIONS

Annika Herten: Conceptualization (lead); data curation (lead); for- mal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (lead); supervision (lead); validation (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead). Dino Vitali Saban: Conceptualization (supporting); data cu- ration (supporting); investigation (equal); project administration (supporting); resources (supporting); software (supporting); valida- tion (supporting); writing—original draft (supporting); writing— review and editing (equal). Alejandro Santos: Conceptualization (supporting); data curation (equal); investigation (supporting); project administration (supporting); software (supporting); validation (supporting); writing—original draft (supporting); writing—review and editing (equal). Bixia Chen: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); project admin- istration (supporting); software (supporting); validation (supporting); visualization (supporting); writing—review and editing (equal). Marvin Dakwah Oppong: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investiga- tion (supporting); resources (supporting); software (supporting);
visualization (supporting); writing—review and editing (equal). Laurêl Rauschenbach: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); methodology (supporting); software (supporting); supervision (supporting); writing—review and editing (equal). Ramazan Jabbarli: Conceptualization (supporting); data curation (supporting); investigation (supporting); software (supporting); visualization (supporting); writing—review and editing (equal). Karsten H Wrede: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (equal); supervision (supporting); visualization (supporting); writing—review and editing (equal). Ulrike Bingel: Conceptualization (supporting); data curation (supporting); methodology (supporting); software (supporting); supervision (supporting); validation (supporting); visualization (supporting); writing—review and editing (equal). Daniel Mueller: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); resources (supporting); software (supporting); writing—review and editing (equal). Dagny Holle: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); software (supporting); supervision (supporting); visualization (supporting); writing—review and editing (equal). Boerge Schmidt: Data curation (supporting); formal analysis (supporting); project administration (supporting); software (equal); validation (supporting); writing—review and editing (equal). Yan Li: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); methodology (supporting); software (equal); visualization (supporting); writing—review and editing (equal). Ulrich Sure: Conceptualization (supporting); data curation (supporting); formal analysis (supporting); funding acquisition (supporting); investigation (supporting); methodology (supporting); project administration (equal); resources (supporting); software (supporting); supervision (equal); validation (supporting); visualization (supporting); writing—original draft (supporting); writing—review and editing (equal). Philipp Dammann: Conceptualization (equal); data curation (supporting); formal analysis (supporting); funding acquisition (supporting); investigation (supporting); methodology (equal); project administration (equal); resources (supporting); software (supporting); supervision (equal); validation (equal); visualization (supporting); writing—original draft (supporting); writing—review and editing (equal).

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

ORCID
Annika Herten https://orcid.org/0000-0002-9698-4723
Dino Saban https://orcid.org/0000-0001-8645-3366
Alejandro N. Santos https://orcid.org/0000-0002-6616-5313
Marvin Darkwah Oppong https://orcid.org/0000-0003-1021-5024
Laurêl Rauschenbach https://orcid.org/0000-0001-8348-4298
Karsten Wrede https://orcid.org/0000-0001-7076-3503

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

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