Clinical predictors and neural correlates for compromised swallowing safety in Huntington disease

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Abstract

Background and purpose: Dysphagia is one of the most common and important complications in Huntington disease (HD), frequently leading to aspiration pneumonia and mortality. Objective estimates of prevalence using instrumental diagnostics and data on neural correlates of dysphagia in HD are scarce or lacking entirely. Similarly, its correlation with other clinical markers is still not fully known. We aimed at defining clinical risk factors and neural correlates for compromised swallowing safety in HD more precisely.

Methods: Thirty-four HD subjects (16 female, Shoulson & Fahn Stage I–IV, two premanifest) underwent a full clinical–neurological examination including the cranial nerves, the Unified Huntington’s Disease Rating Scale total motor score, and the Mini-Mental State Examination. Fiberoptic endoscopic evaluation of swallowing (FEES) was performed by a trained speech and language therapist. Twenty-six subjects additionally underwent a high-resolution anatomical magnetic resonance imaging (MRI) scan (T1, 3-T Siemens Prisma). Moreover, we correlated clinical and atrophy (MRI) measures with swallowing safety levels as judged by the validated Penetration–Aspiration Scale.

Results: FEES showed penetration or aspiration in 70.6%. Using partial correlation, no significant correlations were found between swallowing safety and any of the clinical markers after correcting for disease duration and CAG repeat length. Voxel-based morphometry demonstrated atrophy associated with compromised swallowing safety in a network of parietothalamocerebellar areas related to sensorimotor communication, notably excluding striatum.

Conclusions: Our results characterise dysphagia in HD as a disorder of communication between sensory and motor networks involved in swallowing. This finding and high rates of silent aspiration argue in favor of instrumental swallowing evaluation early in the disease.

Keywords
aspiration, dysphagia, fiberoptic endoscopic evaluation of swallowing, Huntington disease, voxel-based morphometry
Huntington disease (HD) is an autosomal dominant neurodegenerative disease caused by an expansion of CAG repeats located on the short arm of chromosome 4. The neuropathological features of HD are progressive striatal degeneration and cortical atrophy during the course of the disease. Clinically, HD is characterised by motor dysfunction (especially involuntary choreatic movements), cognitive decline, and psychiatric symptoms.

Dysphagia, or swallowing disorder, is one of the most common and important complications in patients with HD. It frequently leads to pneumonia, which has been identified as the most frequent cause of death in this patient population [1]. Despite its high prevalence and clinical relevance, there are few data directly addressing dysphagia in HD, mostly in terms of case reports or case series. Few studies, including three retrospective series, comprise larger sample sizes and employ instrumental diagnostics such as videofluoroscopic swallowing study (VFSS) or fiberoptic endoscopic evaluation of swallowing (FEES) [2–5]. In these studies, abnormalities of swallowing were found in every phase of oral food ingestion. However, there is a lack of knowledge about mechanisms and neural correlates of dysphagia in HD, both of which could critically inform clinical algorithms for screening for, diagnosing, and treating dysphagia in HD.

Voxel-based morphometry (VBM) of structural magnetic resonance imaging (MRI) data has been employed successfully in HD previously and is able to replicate neuropathological postmortem findings accurately [6,7]. Furthermore, it has been shown that atrophy of specific brain regions correlates with clinical features of the disease, as evidenced by a meta-analysis [8]. In regard to neural correlates of swallowing safety in HD, no studies have been performed so far.

By defining dysphagia and swallowing safety in HD objectively by using FEES and correlating findings with atrophy patterns as revealed by VBM, we aimed at elucidating pathophysiological mechanisms and neural correlates of dysphagia in HD.

METHODS

Data were collected within a cross-sectional study using a descriptive approach. Subjects with genetically confirmed HD were recruited from the Euregional Huntington Centre at the Department of Neurology, RWTH Aachen University Hospital between 2015 and 2019. The study was conducted according to Helsinki criteria and received approval by the local ethics committee of the RWTH Aachen University Hospital (EK 235-15). All patients gave written informed consent. Criteria for inclusion were: (i) age of 21 years or older, (ii) CAG repeat length of more than 39, (iii) (preliminary) stage of disease I–IV or premanifest (defined as ≤4 on the Diagnostic Confidence Level of the Unified Huntington's Disease Rating Scale [UHDRS]), and (iv) capacity to give written informed consent. Exclusion criteria were: (i) other neurological or psychiatric conditions and (ii) a pre-existing swallowing disorder due to other causes.

Neurological and cognitive testing

All subjects underwent a full clinical–neurological examination by a board-accredited neurologist specializing in HD including the cranial nerves, the UHDRS total motor score, and total functional capacity (TFC) score [9]. Cognitive data were collected using the Mini-Mental State Examination (MMSE) [10]. We also documented medication status. Neuroleptic drugs were converted to “olanzapine equivalents” using the DDD (defined daily dose) approach as proposed by Leucht et al. [11] for each patient.

Swallowing testing

Swallowing function was assessed by a trained speech and language therapist performing FEES (Rehder/Partner). Our standardised protocol included a preswallow evaluation of pharyngeal/laryngeal anatomy and physiology as well as the presence of secretions, followed by a swallow evaluation of three different bolus consistencies (puree, thin liquids, solid) in a standardised order: 3 teaspoons (5 ml) of plain yoghurt, 2 teaspoons (5 ml) of blue dyed water, one half glass of blue dyed water (90 ml), two slices of bread with butter (ca. 3.5 × 2.5 × 0.8 cm). No instructions were given to the patients, to maintain natural swallowing behavior. All examinations were video recorded and assessed by two experienced raters who were blinded to the results of the other clinical tests. Divergent ratings were reviewed by the raters and discussed afterwards to reach consensus. Swallowing safety was judged by the validated and reliable Penetration–Aspiration Scale (PAS) [12] which is frequently used as a marker for dysphagia severity or as an outcome measure for the efficacy of swallowing treatments. We aggregated PAS scores into four groups of ascending severity according to Steele and Grace-Martin [13] (A: PAS scores = 1, 2, 4; B: PAS scores = 3, 5, 6; C: PAS score = 7; D: PAS score = 8). This was done because ordinality of the PAS is not necessarily continuous (e.g., a PAS score of 4 might be considered less problematic than a score of 3).

Statistical analyses

To test whether compromised swallowing safety is related to motor or cognitive abilities of the patients independently of common drivers of pathology such as CAG repeat length and disease duration, we performed a partial correlation between swallowing safety as measured by the PAS groups and clinical parameters such as cognitive performance (MMSE), motor disabilities (UHDRS total motor score), and general abilities in daily life (TFC score) as well as age, but partialing out disease duration and CAG repeat length. This was done to avoid pseudocorrelations, as all clinical parameters in HD tend to get worse over time, given its progressive nature. The rationale for including both CAG repeat length of the pathological allele and disease duration is that both factors contribute to disease progression in an at least partially
independent manner [14–17]. They have previously been shown to predict neuropathology in both striatum and cortex [18], whereas the frequently used Disease Burden Scale (DBS) has been shown to be related to striatal pathology only, with no data on cortex [19]. A sensitivity analysis partia ling out DBS instead of CAG and duration, however, yielded very similar results (see Table S1). To visualise the partial correlation strengths between factors, we created a plot using Gaussian graphical modelling [20]. The threshold for statistical significance was set at 0.05. Interrater reliability for the swallowing measures was assessed using Krippendorff α [21]. Statistical analyses and plots were conducted using SPSS Statistics 25.0 (IBM) and R as implemented in jamovi 1.6.9 (https://jamovi.org).

MRI data acquisition

For each subject, we acquired high-resolution T1-weighted magnetisation-prepared rapid acquisition gradient echo images using a 3-T Prisma MRI scanner (Siemens Medical Systems) with the following parameters: repetition time = 1900 ms, echo time = 2.5 ms, matrix size = 256 × 246, 176 sagittal slices, voxel size = 1 × 1 × 1 mm³, field of view = 250 × 250 mm².

MRI data analysis

MRI images were analysed using an optimised VBM approach [22] using FSL tools version 6.0.3 (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl, [23]). Structural images were first skull-stripped and then segmented into maps containing grey matter, white matter, and cerebrospinal fluid, respectively. The resulting grey matter partial volume images were aligned to Montreal Neurological Institute (MNI) 152 standard space using affine registration and averaged to create a study-specific template. All native grey matter images were non-linearly registered to the study template. Following that, the registered grey matter images were modulated by multiplying each image with the Jacobian of the warp field to correct for local expansion or contraction due to the nonlinear component of the spatial transformation. Images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm. Correlations between grey matter values and clinical variables of interest were tested for significance by applying voxel-wise general linear model using permutation-based nonparametric testing [24].

To increase statistical validity with respect to the relatively small sample size, we binarised our cohort into two groups. The first group contained all subjects with intact swallowing safety, as indicated by a PAS score of 1, 2, or 4 according to group A by Steele and Grace-Martin [13]. The second group comprised all subjects with compromised swallowing safety (PAS score of 3, 5, 6, 7, or 8 according to groups B–D by Steele and Grace-Martin). Thus, a comparison between patients exhibiting intact and compromised swallowing safety was made possible. We contrasted both groups and compared grey matter values across the entire brain looking for atrophy associated with unsafe swallowing (one-sided t-test). To accommodate for multiple comparisons across space, threshold-free cluster enhancement (TFCE) [25] was applied using a p-value of 0.05. To further protect our results from spurious correlations with global drivers of neuropathology, we again included both individual CAG repeat length of the pathological allele and disease duration as covariates of no interest, as both CAG repeat length and disease duration have been shown to influence neuropathology independently [14–17]. Resulting statistical maps were colour-coded according to t-values and plotted on a subject’s T1 brain image (normalised into MNI standard space) after thresholding with p = 0.05 (TFCE-corrected) for illustration purposes. We report the local maxima of the significant clusters by using atlas tools provided by FSeyes visualisation software (coordinates in millimeters). For anatomical classification, we used the Talairach atlas [26] and the probabilistic cerebellar atlas [27].

RESULTS

Demographics

In total, 34 patients were included (16 female, mean age = 53.9 ± 9.5 years). Average disease duration was 6.6 ± 5.3 years; two patients were premanifest. Eleven patients took no neuroleptic medication. One patient declined the cognitive assessment. FEES revealed penetration or aspiration for at least one consistency in 24 of 34 patients (70.6%). Silent aspiration (PAS score = 8) was detected in eight (23.5%) patients, four of whom were at early stages of the disease (Stages I and II). For a distribution of the worst PAS scores per stage, see Figure 1. The results of Krippendorff α test showed a high interrater reliability for the worst PAS score (α = 0.85, 95% confidence interval = 0.71–0.96). All patients’ characteristics including average medication can be found in Table 1.

![FIGURE 1](https://example.com/fig1.png) Distribution of the worst Penetration–Aspiration Scale (PAS) score according to Shoulson & Fahn stage. Note the silent aspirators (PAS = 8) at Stages I and II.
Correlation between compromised swallowing safety and clinical features

After partialing out CAG repeat length and disease duration, we showed strong correlations between motor deficits, cognitive deficits, and deficits in global functioning. However, no relationship between swallowing safety and other clinical features could be found, even before correcting p-values for multiple comparisons (Table 2). Gaussian graphical modelling revealed swallowing safety to be almost completely isolated from the other factors, with only a very weak and insignificant correlation with UHDRS total motor score ($r_s = 0.239, p = 0.187$, uncorrected; Figure 2). No correlation was found between neuroleptic drug dosing (in olanzapine equivalents) and swallowing safety ($r_s = 0.071, p = 0.700$).

MRI results

Of our cohort, 26 subjects were able to undergo MRI (13 female, mean age = 51.4 ± 9.3 years, mean CAG repeats = 43.7 ± 3.4, UHDRS total motor score = 31.2 ± 17.5, MMSE = 25.0 ± 4.7). Subjects undergoing MRI scanning were significantly younger than the other eight subjects (51.4 vs. 60.8 years, $p = 0.015$, Mann–Whitney U test), but crucially did not differ significantly in any of the other clinical features, such as gender, CAG, disease duration, motor or cognitive scores, and our outcome measure for swallowing safety. A linear contrast of HD subjects with compromised swallowing safety against HD subjects with intact swallowing safety in the VBM analysis yielded several cortical and subcortical areas of atrophy associated with compromised swallowing safety (Table 3, Figure 3). In particular, we found cortical atrophy in the left parietal lobe (left superior parietal

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### TABLE 1 Characteristics of all subjects with Huntington disease ($n = 34$, unless otherwise indicated)

| Characteristics                                      | Distribution                      |
|-------------------------------------------------------|-----------------------------------|
| Age, mean years (SD) [range]                          | 53.9 (9.5) [31–68]               |
| Sex, n (%)                                            |                                   |
| Female                                                | 16 (47.1)                         |
| Male                                                  | 18 (52.9)                         |
| Stage per Shoulson & Fahn, n (%)                      |                                   |
| Premanifest                                           | 2 (5.9)                           |
| I, early                                              | 5 (14.7)                          |
| II, early                                             | 13 (38.2)                         |
| III, mid                                              | 12 (35.3)                         |
| IV, advanced                                          | 2 (5.9)                           |
| Disease duration, mean years (SD) [range]             | 6.6 (5.3) [0–20]                  |
| CAG repeat length, mean (SD) [range]                  | 43.3 (3.1) [40–55]                |
| TFC, mean (SD) [range]                                | 7.4 [3.5] [2–13]                  |
| UHDRS total motor score, mean (SD) [range]            | 33.8 [19.4] [1–83]                |
| MMSE, mean (SD) [range]; $n = 33$                     | 25.0 [4.5] [15–30]                |
| Neuroleptic medication, DDD (in olanzapine equivalents, mg), mean (SD) [range] | 5.5 [5.6] [0–19] |
| Worst PAS score, n (%)                                |                                   |
| 1                                                     | 10 (29.4)                         |
| 2                                                     | 4 (11.8)                          |
| 3                                                     | 5 (14.7)                          |
| 5                                                     | 5 (14.7)                          |
| 6                                                     | 1 (2.9)                           |
| 7                                                     | 1 (2.9)                           |
| 8                                                     | 8 (23.5)                          |

Abbreviations: DDD, defined daily dose; MMSE, Mini-Mental State Examination; PAS, Penetration–Aspiration Scale; TFC, total functional capacity; UHDRS, Unified Huntington’s Disease Rating Scale.

### TABLE 2 Partial correlation matrix controlling for CAG repeat length and disease duration

|                  | Age    | UHDRS motor | MMSE   | TFC    | DDD    | Swallowing safety |
|------------------|--------|-------------|--------|--------|--------|-------------------|
| Age              | Spearman Rho p-value | -       |        |        |        |                   |
| UHDRS motor      | Spearman Rho p-value | 0.336   | -      |        |        |                   |
| MMSE             | Spearman Rho p-value | -0.298  | -0.438 | -      |        |                   |
| TFC              | Spearman Rho p-value | -0.381  | -0.606 | 0.518  | -      |                   |
| DDD              | Spearman Rho p-value | 0.192   | 0.092  | -0.220 | -0.102 | -                 |
| Swallowing safety| Spearman Rho p-value | 0.064   | 0.239  | -0.228 | -0.229 | 0.071             |

Note: Swallowing safety was judged according to Penetration–Aspiration Scale groups by Steele and Grace-Martin [13].

Abbreviations: DDD, defined daily dose; MMSE, Mini-Mental State Examination; TFC, total functional capacity; UHDRS, Unified Huntington’s Disease Rating Scale.

*Significant for $\alpha = 0.05$.; **Significant for $\alpha = 0.002$ with Bonferroni correction for multiple ($n = 21$) comparisons.
lobule, comprising primary somatosensory cortex BA2 on the lateral aspect and cytoarchitectonic area 5Ci on the mesial aspect; Figure 3A) as well as in the right inferior temporal lobe. Additionally, we detected bilateral thalamic atrophy, accompanied by cerebellar atrophy (Figure 3B). Striatal atrophy was not associated with compromised swallowing safety, even after relaxing the threshold to $p = 0.001$ uncorrected (data not shown).

**DISCUSSION**

Our study shows that dysphagia is a common and important complication occurring early in HD. This is in agreement with previous studies using instrumental diagnostics to characterise dysphagia in HD [2–5]. Nonetheless, the high prevalence of penetration and aspiration is remarkable, given that 20 of 34 (58.8%) patients in our cohort were at an early stage of disease (Stage II or earlier). Eight of 34 patients (23.95%) aspirated silently (PAS score = 8), which occurred even at the early stages of disease (11.8% of the patients at Stages I and II). This and the finding that almost all other pathological PAS scores were also characterised by insufficient protective reflexes both point towards a prominent deficit in sensory processing in deglutition in HD. Therefore, cough reflex testing, as previously investigated in patients with Parkinson disease [28], might be a first step to better understand the underlying mechanisms of airway protection deficits in HD. Nonetheless, it is not clear at which point aspiration leads to pneumonia in HD patients. Longitudinal studies are necessary to examine the progression of dysphagia to define managing strategies. The high prevalence of silent aspiration shows that clinical assessment of dysphagia including swallowing questionnaires is not sufficient to detect swallowing dysfunction reliably in this patient population.

In our study, neither motor nor cognitive deficits were associated with swallowing safety after correcting for general disease severity. This points towards dysphagia in HD being a pathophysiologically distinct entity, independent from global motor and cognitive manifestations. Instead, certain aspects of motor phenotype such as dysarthria might be a clinical clue. However, the global motor phenotype does not seem to be suitable to predict dysphagia in HD, particularly at early stages. The same seems to hold true for cognitive deficits, which admittedly might have a greater impact on swallowing function in the progression of the disease (e.g., influencing eating behavior, as has been described as early as 1985 by Leopold and Kagel [2]).

Previous studies have reported correlations between dysphagia and motor or functional deficits and/or disease duration using instrumental diagnostics such as FEES [4], VFSS [5] or clinical assessment [29] seemingly contradicting our results. However, given

**TABLE 3** Locations of atrophy as revealed by voxel-based morphometry analysis

| Cluster index | $T$, Max | Max $X$, mm | Max $Y$, mm | Max $Z$, mm | Anatomy                  |
|---------------|----------|-------------|-------------|-------------|--------------------------|
| 1             | 6.84     | −28         | −38         | 50          | L superior parietal lobe  |
| 2             | 5.69     | 0           | −52         | −26         | L cerebellum I–IV        |
| 3             | 5.22     | 20          | −20         | 14          | R thalamus, lateral posterior nucleus |
| 4             | 5.11     | 40          | −60         | −12         | R inferior temporal lobe, fusiform gyrus |
| 5             | 4.86     | −14         | −4          | 10          | L thalamus, ventral anterior nucleus |
| 6             | 4.7      | −20         | −20         | 14          | L thalamus, lateral posterior nucleus |
| 7             | 4.51     | −14         | −44         | 44          | L parietal lobe, precuneus cortex |
| 8             | 4.11     | −22         | −70         | −14         | L cerebellum VI          |

Note: Coordinates are in Montreal Neurological Institute space (in millimeters). Abbreviations: L, left; Max, maximum; R, right; $T$, corrected $t$-value.
the strong link between disease duration, CAG load, and general functional decline in HD, we argue that disease duration and CAG load should be considered as confounders when examining associations between motor or functional deficits and dysphagia to avoid pseudocorrelations. Additionally, different scales have been used to describe swallowing dysfunction. Schindler et al. graded dysphagia severity in 61 HD patients comparing scores on the Dysphagia Outcome and Severity Scale (DOSS) to clinical features [4]. The DOSS is a scale that was developed to rate and document the functional severity of dysphagia while taking into account also diet recommendations based on FEES [30]. Thus, it is influenced by additional factors and does not reflect pathophysiology in the same way as a purely pathophysiological swallowing scale such as the PAS. Therefore, the significant correlation between the Huntington’s Disease Dysphagia Scale (HDDS) [29] and the DOSS levels in this study is probably best explained by the global functional deficits patients and caregivers perceived. It also seems likely that the HDDS is unable to detect patients at risk of (silent) aspiration, as it has not been validated by instrumental diagnostics. Notably, two patients in this cohort by Schindler and colleagues reported no dysphagia on the HDDS but consecutively scored highly on the DOSS.

Keage et al. [5] described swallowing function retrospectively in 49 individuals with HD, with repeated VFSS data for seven patients. The authors found that there did not appear to be a systematic way in which dysphagia worsened over time. Instead, some individuals’ scores even seemed to stabilise or improve. Considering the retrospective design and small sample size for the patients with repeated VFSS, these findings are still remarkable and support the theory of dysphagia as an entity that is distinct from the other clinical features of HD. Future studies should focus on collecting longitudinal data on swallowing behavior in relation to disease progression.

Further support for our hypothesis comes from neuroimaging. VBM has previously been used successfully to analyse grey matter atrophy in HD and related clinical features [6,7]. Here, striatal atrophy was a predominant finding that correlated with deficits in the motor domain, as evidenced by a meta-analysis [8]. In our study, however, striatal grey matter loss was not associated with compromised swallowing safety. However, we identified a network of cortical, thalamic, and cerebellar areas where atrophy was significantly correlated with compromised swallowing safety. This network can arguably be seen as a network of sensorimotor transformation in deglutition. Superior parietal lobule has been associated with general motor control as part of a corticostriatal circuit [31]. Mesial parietal cortex and precuneus have consistently been shown to belong to an orbitofrontoparietal network associated with deglutition [32] and in particular pharyngeal sensory processing [33]. Notably, activation of precuneus was stronger in tasks involving swallowing than tongue elevation alone [34]. Similarly, the right inferior temporal lobe has been shown to be part of lateral orbitofrontoparietal networks associated with processing of language and faces [32]. The cerebellum, too, is a recognised part of the swallowing network [35] Importantly, the atrophied regions in our study have been previously implied in cough and cough suppression [36] and motor responses to noxious stimuli in general [37], highlighting the importance of the cerebellum in protective motor responses. The thalamus, finally, is part of a motor control loop linking the cerebellum to the frontal and prefrontal cortex. Ventral anterior thalamus (VA) has been implied in cognitive motor
control and automated motor skills [38]. Accordingly, atrophy of the VA has been associated with reduced gait speed in the elderly [39]. For lateral posterior thalamus, a loss of functional MRI activation with self-initiated movements has been shown in the elderly compared with young subjects [40].

Taken together, atrophy in a parietothalamic cerebellar network that has been implied in sensory and motor functions in general or with deglutition in particular is associated with compromised swallowing safety in HD. Main functions associated with the nodes in this network are sensory processing, sensorimotor transformation, and cognitive control. No atrophy was detected in areas typically associated with classical motor dysfunction, such as the striatum. This fits with our behavioral data showing insufficient reactions to pathological stimuli by penetrating or aspirated bolus material and our notion that dysphagia in HD could potentially represent a distinct clinical domain based on atrophy of a defined neuronal network, in addition to recognised clinical domains such as motor function, cognition, and emotion. Additionally, our imaging data might serve as a potential explanation for the notoriously bad insight in dysphagic symptoms of patients with HD. A lack of agreement both between caregiver and self-report [29] and between self-report and objective dysphagia measures [4] has been reported previously. Reduced insight is a general feature of HD [41]. We showed atrophy in precuneus, parietal and inferior temporal cortex, where aberrant imaging parameters have previously been shown to be associated with anosognosia in Alzheimer disease [42].

CONCLUSIONS

This is the first study combining instrumental swallowing diagnostics with findings from MRI in HD. Our study demonstrates that aspiration occurs even at early stages of HD and is not predicted well by clinical markers like UHDRS total motor score, MMSE, TFC, or disease duration when taking onto account general disease burden. FEES results revealed a high prevalence of silent aspiration in this patient population, indicating a prominent role of sensory deficits. Arguably, dysphagia should not be referred to as a classical motor symptom, but could rather be seen as an independent clinical entity, based on its strong sensory component, its independence from motor dysfunction, and its reliance on a distinct neuronal network revealed by our MRI data. We therefore recommend the regular use of instrumental diagnostics to detect swallowing dysfunction even at early stages. FEES has been shown to be a safe and revealing tool in this patient population.

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CONFLICT OF INTEREST

The authors report no competing interests.

AUTHOR CONTRIBUTIONS

Beate Schumann–Werner: Conceptualisation (equal), data curation (lead), formal analysis (equal), investigation (lead), methodology (lead), project administration (lead), resources (lead), software (supporting), supervision (lead), validation (equal), visualisation (equal), writing–original draft (lead), writing–review & editing (lead). Imis Dogan: Investigation (supporting), resources (supporting), writing–review & editing (supporting). Shahram Mirzaadze: Investigation (supporting), resources (supporting), writing–review & editing (supporting). Bettina Mall: Investigation (supporting), resources (supporting), writing–review & editing (supporting). René Overbeck: Investigation (supporting), resources (supporting), writing–review & editing (supporting). Jörg B. Schulz: Funding acquisition (supporting), writing–review & editing (supporting). Kathrin Reetz: Conceptualisation (supporting), funding acquisition (lead), resources (supporting), supervision (supporting), writing–review & editing (supporting). Cornelius J. Werner: Conceptualisation (equal), data curation (supporting), formal analysis (equal), investigation (supporting), methodology (supporting), project administration (supporting), resources (supporting), software (lead), supervision (supporting), validation (equal), visualisation (equal), writing–original draft (supporting), writing–review & editing (supporting).

ETHICAL APPROVAL

The study was conducted according to Helsinki criteria and received approval from the local ethics committee of the RWTH Aachen University Hospital (EK 235–15).

DATA AVAILABILITY STATEMENT

The data are available to interested researchers upon request.

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