


# Factors associated with depressive mood at the onset of multiple sclerosis – an analysis of 781 patients of the German NationMS cohort

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## Abstract

**Background:** Depression has a major impact on the disease burden of multiple sclerosis (MS). Analyses of overlapping MS and depression risk factors [smoking, vitamin D (25-OH-VD) and Epstein-Barr virus (EBV) infection] and sex, age, disease characteristics and neuroimaging features associated with depressive symptoms in early MS are scarce.

**Objectives:** To assess an association of MS risk factors with depressive symptoms within the German NationMS cohort.

**Design:** Cross-sectional analysis within a multicenter observational study.

**Methods:** Baseline data of  $n=781$  adults with newly diagnosed clinically isolated syndrome or relapsing-remitting MS qualified for analysis. Global and region-specific magnetic resonance imaging (MRI)-volumetry parameters were available for  $n=327$  patients. Association of demographic factors, MS characteristics and risk factors [sex, age, smoking, disease course, presence of current relapse, expanded disability status scale (EDSS) score, fatigue (fatigue scale motor cognition), 25-OH-VD serum concentration, EBV nuclear antigen-1 IgG (EBNA1-IgG) serum levels] and depressive symptoms (Beck Depression Inventory-II, BDI-II) was tested as a primary outcome by multivariable linear regression. Non-parametric correlation and group comparison were performed for associations of MRI parameters and depressive symptoms.

**Results:** Mean age was 34.3 years [95% confidence interval: 33.6–35.0]. The female-to-male ratio was 2.3:1. At least minimal depressive symptoms (BDI-II > 8) were present in  $n=256$  (32.8%), 25-OH-VD deficiency (<20 ng/ml) in  $n=398$  (51.0%),  $n=246$  (31.5%) participants were smokers. Presence of current relapse [coefficient ( $c$ ) = 1.48,  $p=0.016$ ], more severe fatigue ( $c=0.26$ ,  $p<0.0001$ ), lower 25-OH-VD ( $c=-0.03$ ,  $p=0.034$ ) and smoking ( $c=0.35$ ,  $p=0.008$ ) were associated with higher BDI-II scores. Sex, age, disease course, EDSS, month of visit, EBNA1-IgG levels and brain volumes at baseline were not.

**Conclusion:** Depressive symptoms need to be assessed in early MS. Patients during relapse seem especially vulnerable to depressive symptoms. Contributing factors such as fatigue, vitamin D deficiency and smoking, could specifically be targeted in future interventions and should be investigated in prospective studies.

**Keywords:** CIS, clinically isolated syndrome, cohort study, depression, MRI, MS, neuropsychological symptoms, relapse, sex, smoking, vitamin D

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## Introduction

Lifetime prevalence of depression in persons with multiple sclerosis (MS) may range between 24% and 54%, thus exceeding the prevalence of 14 to 21% within the general population.<sup>1</sup> Depression can be present in all stages of MS, including clinically isolated syndrome (CIS),<sup>2</sup> and may be observed as one of a variety of prodromal signs of MS.<sup>3</sup>

Depressive symptoms have a major impact on well-being and quality of life in persons with MS. They reduce work productivity<sup>4,5</sup> and impact social participation,<sup>6</sup> but are not necessarily associated with a more severe disease course.<sup>7</sup>

Data on sex differences of depressive symptoms in MS have revealed contradicting results, whereas one study has reported a female preponderance and higher rates of somatic symptoms in women, another study did not detect sex differences for depression in MS representing a distinctive feature towards the general population.<sup>8,9</sup>

The interaction of fatigue and depression has been well established, but does not seem to be specific for MS.<sup>10,11</sup> A small study assessing patients during MS relapse has identified both age and relapse severity as independent predictors of depressive symptoms measured by Beck Depression Inventory-II (BDI-II), but not the disability level *per se*.<sup>12</sup> In line with this, a recent meta-analysis did not uncover clear associations of the prevalence of depression with disability level or disease duration. However, both parameters have been defined with binary cut-offs [more or less than expanded disability status scale (EDSS) score 3.0, and more or less than 10 years disease duration, respectively]<sup>13</sup> which might not be sensitive enough to detect differences and especially does not assess the phase around disease onset.

Modifiable factors well-known to increase MS susceptibility and progression, such as smoking<sup>14,15</sup> and vitamin D deficiency,<sup>16–18</sup> also in interaction with obesity,<sup>19</sup> have also been attributed to the risk of developing depressive symptoms.<sup>20,21</sup> The pathophysiological role of vitamin D deficiency in depression is described to be multifaceted: direct effects may play a role as vitamin D receptors are present in the brain, especially in the cortex, limbic system and hippocampus and as vitamin D regulates different neurotrophic factors

and modulates calcium toxicity and oxidative stress. In addition, it regulates neurotransmitter homeostasis for serotonin, dopamine and norepinephrine in the brain.<sup>22</sup>

Likewise, remote Epstein-Barr virus (EBV) infection has been associated with a higher risk of developing both MS<sup>16,23–25</sup> and major depressive disorders.<sup>26</sup>

Comprehensive analyses of the association of MS risk factors, including smoking, vitamin D (25-OH-VD) levels and EBV antibody levels, with depressive symptoms in patients with early MS are scarce.

Neuroanatomical correlations using different magnetic resonance imaging (MRI) techniques have been investigated for MS-related symptoms such as fatigue and depression. T2-hyperintense white matter lesions load, as a commonly used MRI parameter in MS, in varying brain regions such as the right temporal lobe,<sup>2,27</sup> amygdala/prefrontal tracts<sup>28</sup> has been associated with depression in MS, but another study has not detected a specific lesion pattern for both T1- and T2-weighted sequences.<sup>29</sup> In functional MRI analyses, patients with MS and depression had less capacities of neurocognitive emotion regulation corroborating the involvement of amygdala and prefrontal tracts as compared to patients with MS only.<sup>28</sup>

MRI-based volumetry has demonstrated associations of MS-related fatigue with specific subcortical gray matter areas, namely the basal ganglia, and the pons.<sup>30</sup> Another study reported the atrophy of several cortical gray matter areas to be associated with depression or a complex of fatigue and depression, but not fatigue alone.<sup>29</sup> No association of gray matter atrophy and related neurotransmitter maps has been detected for depression in a more recent analysis.<sup>31</sup>

With the increased risk of depression in MS patients, we hypothesised that common risk factors might play a role and wanted to investigate a set of markers to potentially identify populations at risk for depressive symptoms within a well-defined early MS cohort.

The aim of this study was thus to assess the potential association of MS disease characteristics and risk factors to depressive symptoms in participants of the German NationMS cohort.

## Methods

### Study design and setting

The German NationMS study is an ongoing multicentre prospective, longitudinal, observational cohort study as previously described.<sup>32</sup> The 22 participating centres across Germany represent tertiary care centres. Participants were recruited for the study between 2010 and 2017;  $n = 1374$  persons were included in the study. All data were entered in a centralised database, hosted by the Central Information Office Marburg, and regularly monitored for completeness and accuracy. For the present cross-sectional analysis, only data referring to the baseline visit for each participant were considered.

### Participants

In- and exclusion criteria for the German NationMS study are described in detail, elsewhere.<sup>32</sup> In brief, adult patients with newly diagnosed CIS fulfilling 3 of 4 Barkhof criteria<sup>33</sup> or 2 of 4 Barkhof criteria with additional cerebrospinal fluid or visual evoked potential findings suggestive of MS or with relapsing-remitting MS (RRMS) according to McDonald criteria 2005<sup>34</sup> or 2010,<sup>35</sup> naïve for treatment with disease-modifying drugs, were eligible for the study.

All patients with the available baseline data of interest including baseline results for 25-OH-VD serum concentration<sup>17</sup> and EBV nuclear antigen-1 IgG (EBNA1-IgG) serum antibody levels<sup>23</sup> were included in this analysis.

### Variables of interest for this study

The full assessment plan has been described.<sup>32</sup> In summary, it comprises yearly visits over the first 2 years and biannual visits thereafter. The standardised assessments include sociodemographic data (age, sex, ethnicity, education, employment status, social situation, smoking, alcohol consumption and other drugs), medical history (concomitant diseases and medications, family history), physical examination and MS-specific evaluations (MS history, relapse documentation, neurological status incl. EDSS and MS Functional Composite), a short cognitive testing (MS Inventory of Cognition), patient questionnaires [BDI-II, fatigue scale motor cognition (FSMC), PainDETECT] as well as a standardised brain MRI and collection of biomaterial.

Within this analysis, baseline data of participants were assessed for the following variables (measure):

- Sex (male, female)
- Age (years)
- Smoking behaviour (no, irregularly, daily)
- Diagnosis (CIS, RRMS)
- Current relapse at visit date (yes/no)
- Disability level (EDSS)
- Depressive symptoms (BDI-II)
- Fatigue (FSMC)
- Vitamin D level [25-OH-VD serum concentration in ng/ml, measured using a commercially available kit for liquid chromatography-mass spectrometry (LC-MS/MS)<sup>17</sup>]
- EBNA1-IgG serum levels [in U/ml, measured using Liaison (DiaSorin, Saluggia, Italy) automated quantitative chemiluminescence immunoassay (CLIA)<sup>23</sup>]

To address potential corticosteroid effects on depressive symptoms, time in days between last corticosteroid administration and the date of visit (available for  $n = 755$ ) was additionally analysed.

### MRI acquisition and morphometric analyses

Per NationMS study protocol, conventional MRI images were acquired at different 3T scanners with a 32-channel receive-only head coil, according to a standardised imaging protocol in all centres. This protocol included sagittal 3D T1-weighted magnetisation prepared rapid acquisition of gradient echo and T2-weighted fluid-attenuated inversion recovery sequences. Available morphometric data from previous NationMS studies has been re-used for this analysis. The detailed methodology can thus be found in Refs. 14 and 30.

The following MRI parameters have thus been integrated in the analysis:

- Global volumes: T2 lesion volume, gray matter volume and total brain volume (in ml).
- Region-specific volumes: thalamus volumes, hippocampus volumes and amygdala volumes as well as the total subcortical gray matter volume (in  $\mu$ l).

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### Statistical methods

Patient data were summarised descriptively, as given in Table 1. Categorical variables are listed with total number ( $n$ ) and relative frequencies (%). Continuous variables are expressed with mean and 95% confidence intervals (CI). In case of single missing items within a questionnaire, these data were imputed using mean imputation.<sup>32</sup>

As defined in the scoring manual, a BDI-II score of  $>8$  points was defined as 'at least minimal depressive symptoms'. 25-OH-VD deficiency was defined as values below 20 ng/ml as described in Ref. 36.

Multivariable linear regression (MLR) was performed using BDI-II score as the dependent variable and all named other factors as independent variables. Results are expressed as coefficient ( $c$ ) with 95% CI (Figure 1). Corresponding  $p$  values are provided in the respective text. The complete MLR model is given in Supplemental Table 1.

The expanded MLR model including the variable 'time in days between last corticosteroid administration and date of visit' is provided in Supplemental Table 2.

To identify potential morphometric parameters associated with the severity of depressive symptoms, a non-parametric correlation analysis (Kendall's Tau  $b$ ) and a non-parametric group comparison (Kruskal–Wallis test) using BDI-II categories as given in Table 1 were conducted. Multiple testing was accounted for using Bonferroni correction.

The reporting guideline STROBE is given as Supplemental Table 3.

### Results

Of the total German NationMS cohort ( $n = 1374$ ),  $n = 781$  individuals qualified for this analysis based on the availability of all required data. With a mean age of 34.3 years (33.6–35.0) and a female-to-male ratio of 2.3:1, the study sample reflects the characteristics of the whole cohort as described earlier.<sup>32</sup> The study cohort characteristics are summarised in Table 1.

At least minimal depressive symptoms were present in  $n = 256$  participants (32.8%).

Mean 25-OH-VD serum concentration was 22.2 ng/ml (21.2–23.2). 25-OH-VD deficiency,<sup>36</sup> was present in  $n = 398$  persons (51.0%) of which  $n = 124$  (15.9%) were severely deficient ( $<10$  ng/ml).

To analyze factors relevant to depression in MS, we applied MLR. Here, we did not find associations of sex, age, MS diagnosis (CIS *versus* RRMS), baseline EDSS, month of sampling or EBNA1-IgG levels with severity of depressive symptoms as measured by BDI-II score. In turn, the presence of a current relapse ( $p = 0.016$ ), higher severity of fatigue ( $p < 0.0001$ ), lower 25-OH-VD levels ( $p = 0.034$ ) and current smoking ( $p = 0.008$ ) were associated with a higher BDI-II score (Figure 1, Supplemental Table 1).

To assess whether the association of a current relapse and higher depressive symptoms might be related to a more recent corticosteroid administration, time in days between the last corticosteroid administration and visit date was included in the MLR model, resulting in a reduced number of  $n = 755$  patients, and showed no association [ $c$  0.001 (–0.004; 0.005),  $p = 0.756$ ]. The full MLR analysis including this item is given in Supplemental Table 2.

Variance inflation factors (all  $<1.3$ ) were not indicative of multicollinearity in either model (Supplemental Tables 1 and 2).

To test morphological factors potentially linked to depressive mood, we analysed global and region-specific MRI-volumetry in a subgroup of  $n = 327$  patients (Table 1).

Neither Kendall's Tau- $b$  correlation nor group comparison using the Kruskal–Wallis test identified global or regional MRI-markers of depressive symptoms in MS.

### Discussion

Depressive symptoms were detectable in more than 30% of patients in our study cohort (32.8% with at least minimal, 16.1% with at least mild, 6.9% with at least moderate and 1.7% with severe symptoms). As reported earlier, the majority of

**Table 1.** Cohort characteristics.

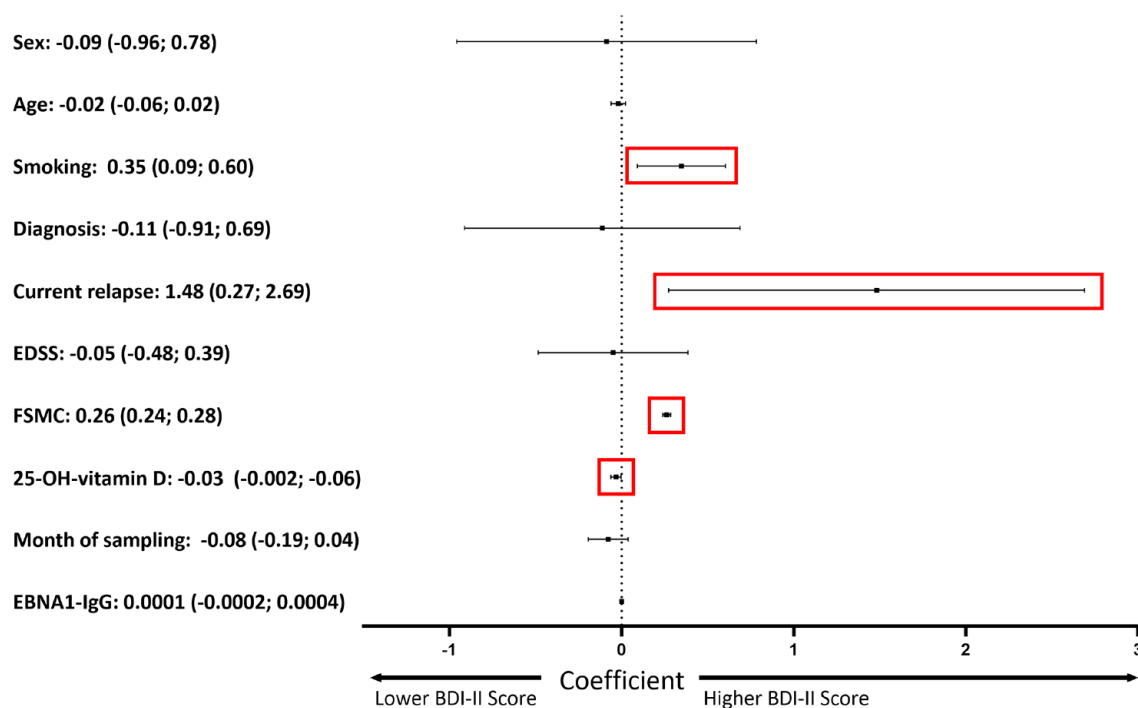
Variable	Indicator
Sex ( <i>n</i> , %)	
Female	546 (69.9)
Male	235 (30.1)
Age (years; mean, 95% CI)	34.3 (33.6–35.0)
Smoking ( <i>n</i> , %)	
No	535 (68.5)
Irregularly	56 (7.2)
Daily	190 (24.3)
Diagnosis ( <i>n</i> , %)	
CIS	327 (41.9)
RRMS	454 (58.1)
Current relapse ( <i>n</i> , %)	
No	683 (87.5)
Yes	98 (12.5)
EDSS (mean, 95% CI)	1.5 (1.4–1.6)
BDI-II (score; mean, 95% CI)	7.3 (6.8–7.8)
BDI-II score, cumulative frequencies* ( <i>n</i> , %)	
≤8 points	525 (67.2)
>8 points	256 (32.8)
>13 points	126 (16.1)
>20 points	54 (6.9)
>29 points	13 (1.7)
FSMC (total score; mean, 95% CI)	38.2 (36.9–39.5)
25-OH-VD (ng/ml; mean, 95% CI)	22.2 (21.2–23.2)
25-OH-VD deficiency (<20 ng/ml; <i>n</i> , %)	398 (51.0)
EBNA1-IgG (U/ml; mean, 95% CI)	1453.8 (1360.4–1547.2)

*(Continued)***Table 1.** (Continued)

Variable	Indicator
MRI volumetry parameters	
T2 lesion volume (ml; mean, 95% CI)	131.3 (–113.9–376.4)
Gray matter volume (ml; mean, 95% CI)	637.8 (629.0–646.6)
Total brain volume (ml; mean, 95% CI)	1388.1 (1370.8–1405.4)
Thalamus left (μl; mean, 95% CI)	7211.2 (7108.7–7313.7)
Thalamus right (μl; mean, 95% CI)	6851.3 (6757.5–6945.0)
Hippocampus left (μl; mean, 95% CI)	4010.7 (3962.7–4058.8)
Hippocampus right (μl; mean, 95% CI)	4131.8 (4082.6–4181.0)
Amygdala left (μl; mean, 95% CI)	1610.6 (1586.1–1635.1)
Amygdala right (μl; mean, 95% CI)	1759.9 (1733.6–1786.3)
Subcortical gray matter volume (μl; mean, 95% CI)	56,270.9 (55,722.5–56,819.3)
<p>*≤8 points, no depressive symptoms; &gt;8 points, minimal; &gt;13 points, mild; &gt;20 points, moderate; &gt;29 points, severe depressive symptoms.  BDI-II, Beck Depression Inventory-II; 95% CI, 95% confidence interval; CIS, clinically isolated syndrome; EBNA1-IgG, Epstein-Barr virus nuclear antigen-1 IgG; EDSS, expanded disability status scale; FSMC, fatigue scale motor cognition; MRI, magnetic resonance imaging; 25-OH-VD, vitamin D; RRMS, relapsing-remitting multiple sclerosis.</p>	

patients in this cohort had a very short disease duration of 0.33 years (median, interquartile range 0.20–0.70).<sup>32</sup> In this large German network cohort, we identified a negative impact of smoking and vitamin D deficiency on the severity of depressive symptoms.

Demographic characteristics (sex and age) and EDSS were not associated with the severity of depressive symptoms, which is in line with a small study in 37 individuals.<sup>2</sup> With the inclusion criteria



**Figure 1.** Factors related to depressive symptoms. Multivariable linear regression. Dependent variable: Severity of depressive symptoms as measured by BDI-II score. Regression coefficient with 95% CI given for each parameter. *p* values for sex, age, MS diagnosis (CIS versus RRMS), baseline EDSS, month of sampling and EBNA1-IgG levels:  $>0.05$ , for current relapse:  $p=0.016$ , higher severity of fatigue:  $p<0.0001$ , less 25-OH-vitamin D:  $p=0.034$ , current smoking:  $p=0.008$ . Linear regression model:  $R^2: 0.449$ . Coding: sex: 0 – female, 1 – male; age – years; smoking: 0 – No, 1 – Occasionally, 2 –  $\leq 5$  cigarettes per day, 3 – 6–10 cigarettes per day, 4 – 11–20 cigarettes per day, 5 –  $>20$  cigarettes per day; diagnosis: 0 – CIS, 1 – RRMS; current relapse: 0 – No, 1 – Yes; EDSS – score; FSMC – total score; 25-OH-vitamin D serum concentration – ng/ml; month of sampling – month; EBNA1-IgG titer – U/ml. BDI-II, Beck Depression Inventory-II; CIS, clinically isolated syndrome; EBNA1-IgG, EBV nuclear antigen-1 IgG; EDSS, expanded disability status scale; FSMC, fatigue scale motor cognition; RRMS, relapsing-remitting multiple sclerosis.

referring to older versions of the diagnostic criteria, the diagnosis of a CIS or RRMS appears to be an arbitrary distinction in our analysis. Previous studies investigating the effect of sex on depressive symptoms in MS have elicited contradictory results, pointing to a relevant gap of knowledge that should be addressed in further studies. The age range in our cohort is narrow, potentially explaining the lack of association, in contrast to a previous study that identified age as an influencing factor of depressive symptoms during relapse.<sup>12</sup> With the narrow age and disease duration ranges and the expected collinearity between these two parameters, we did not additionally include disease duration in our analysis.

The aforementioned study also described that not the EDSS score as such, but the relapse-associated EDSS worsening was related to depressive symptoms.<sup>12</sup> In that study, only patients during

relapse were investigated. Based on our results and those of a small study in CIS patients (according to Poser criteria),<sup>2</sup> this population represents a population at-risk as the presence of a current relapse was associated with higher BDI-II scores, irrespective of a more recent corticosteroid administration. This suggests the clinical need to assess depressive symptoms specifically in patients during relapse to enable early support by pharmacological and/or psychological interventions, if necessary. In our study, we specifically assessed the early stage of MS. A limitation of the current study is the absence of a longitudinal follow-up of depressive symptoms.

As all patients of our cohort were seropositive for remote EBV infection,<sup>23</sup> we included EBNA1-IgG titres in our MLR model which did not show an association to depressive symptoms. For both MS and depression, remote EBV infection has

been described as a risk factor.<sup>24,26</sup> Yet, real-world cohorts revealing 100% seropositivity as here represent EBV infection in adults.<sup>23</sup>

In contrast, in our cohort of early MS patients, lower vitamin D levels were associated with higher severity of depressive symptoms adding to the relevance of vitamin D deficiency in MS on multiple aspects.<sup>16–18,36</sup> This effect was not related to seasonal variation of vitamin D as the month of sampling was included in the MLR model and did not show an association to depressive symptoms. As the sampling date reflects the date of visit, the missing association between the month of sampling and depressive symptoms additionally demonstrates that depressive symptoms in our early MS cohort were independent of a seasonally altered affective state, but, in line with previous data, rather represents an early or even prodromal sign of MS.<sup>3</sup> This is of even more importance as the presence of depression has been shown to delay the diagnosis of MS.<sup>37</sup>

The lacking seasonality of depressive symptoms around MS onset interestingly – despite the association of fatigue and depression present in our cohort and other data<sup>10</sup> – represents a differentiating feature from fatigue: for MS-related fatigue, seasonality is a significant contributor to fatigue severity with more severe fatigue symptoms during summer.<sup>38</sup>

The negative impact of smoking and vitamin D deficiency is undisputed for both MS and depression.<sup>14–18,20,21,24</sup> Our analysis additionally underscores the negative impact of these modifiable factors for depressive symptoms in an early MS cohort. Our approach does not allow to draw causative conclusions. Yet, both factors can easily be addressed in clinical practice and individualised counselling, intervention and support might help to lower the burden of MS.

Within our dataset, we did not detect MRI-volumetric associations to the severity of depressive symptoms which is in line with another recent report.<sup>31</sup> To unravel the interrelations of depression in the context of MS-associated outcomes, functional MRI analyses might be more suited to identify depression with functional connectivity, temporal dynamics and neurotransmitter networks potentially paving the way for targeted drug treatment.<sup>28,39,40</sup>

As a clinical consequence of our work, depressive symptoms should be assessed in routine clinical care in early MS. Patients during relapse seem to be particularly vulnerable. Tackling modifiable contributors to depressive symptoms in early MS, such as fatigue, smoking and vitamin D deficiency, might have the potential to positively impact both the MS disease course and depression. The influence of specific interventions for these factors should further be addressed in prospective settings.

## Declarations

### *Ethics approval and consent to participate*

The cohort study German NationMS was approved by the ethics committee of Ruhr-University Bochum (registration no. 3714-10), and consecutively by all local committees of participating centers. All study participants provided written informed consent.

### *Consent for publication*

Not applicable.

### *Author contributions*

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**Robert Hoepner:** Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft.

**Vinzenz Fleischer:** Investigation; Methodology; Writing – original draft.

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#### Availability of data and materials

Anonymised data are available to every qualified researcher upon reasonable request to the corresponding author.

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#### Supplemental material

Supplemental material for this article is available online.

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