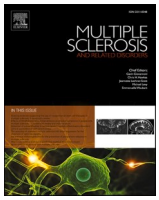
Multiple Sclerosis and Related Disorders 56 (2021) 103281

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard



# Characteristics of secondary progressive multiple sclerosis: Disease activity and provision of care in Germany – A registry-based/multicentric cohort study

Niklas Frahm [a,1,*], David Ellenberger [a,1], Firas Fneish [a], Kleinschnitz Christoph [b], Clemens Warnke [c], Uwe K. Zettl [d], Friedemann Paul [e], Benedict Rauser [f], Alexander Stahmann [a], Vroni Vogelmann [f], Peter Flachenecker [g]

[a] MS Forschungs- und Projektentwicklungs- gGmbH (MS Research and Project Development gGmbH [MSFP]), Hannover, Germany
[b] Department of Neurology and Center of Translational and Behavioral Neurosciences (C-TNBS), University Hospital Essen, Essen, Germany
[c] Department of Neurology, Medical Faculty, University Hospital of Cologne, Cologne, Germany
[d] Department of Neurology, Neuroimmunological Section, University of Rostock, Rostock, Germany
[e] Experimental and Clinical Research Center and NeuroCure Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité - Universitätsmedizin Berlin, Berlin, Germany
[f] Novartis Pharma GmbH, Nürnberg, Germany
[g] Neurological Rehabilitation Center Quellenhof, Bad Wildbad, Germany

ARTICLE INFO

*Key words:*
Multiple sclerosis
Secondary progressive
Disease course
Care
Disease activity
Classification

ABSTRACT

*Background:* The tailored immunomodulatory treatment strategy for secondary progressive multiple sclerosis (SPMS) depends on disease activity.
*Objective:* To assess the real-world situation in monitoring disease activity in SPMS patients and to identify associations of resulting subgroups with demographics, symptomatology, and therapy
*Methods:* This study included 4,263 SPMS patients from the German MS register (GMSR). For the classification into 'active' and 'inactive' according to relapse activity and MRI findings during the year prior to the latest clinical visit, we used the following definitions: active - gadolinium enhancing (Gd+)/new T2 lesions or ≥1 relapse, inactive - neither Gd+/new T2 lesions nor relapses. The active, inactive, and unclassifiable patients were compared in terms of clinical data, socio-demographics, symptomatology, healthcare, and DMT.
*Results:* Classification was possible for 1,513 (35.5%) SPMS patients, with 467 classified as active and 1,046 as inactive. For the classification, MRI data was available for 33.2% of the 4,263 patients. Higher MRI frequencies were observed for younger patients (OR 1.22 [1.12,1.33] per 10 years) with short disease duration (OR 1.19 [1.09, 1.30] per 10 years) ($p < 0.001$).
*Conclusion:* MRI coverage was low, especially in elderly SPMS patients. Roughly one third of the SPMS patients presented markers of disease activity in the last year. Overall, the clinical differences (concerning symptomatology and care) between patients with active and inactive SPMS were small.

## 1. Introduction

Treatment decisions for secondary progressive multiple sclerosis (SPMS) are a challenging area. The majority of disease-modifying therapies (DMTs) are only approved for relapsing-remitting disease courses (Gehr et al., 2019; Gholamzad et al., 2019; Saleem et al., 2019; Tintore et al., 2019). However, more recent approvals have also included SPMS patients, albeit only for those with an 'active' disease, i.e.

* Corresponding author at: Krausenstr. 50, 30171 Phone: editorial board member ORCID: 0000-0002-4655-774X.
*E-mail addresses:* frahm@msregister.de (N. Frahm), ellenberger@msregister.de (D. Ellenberger), fneish@msregister.de (F. Fneish), Christoph.Kleinschnitz@uk-essen.de (K. Christoph), clemens.warnke@uk-koeln.de (C. Warnke), uwe.zettl@med.uni-rostock.de (U.K. Zettl), Friedemann.Paul@charite.de (F. Paul), benedict.rauser@novartis.com (B. Rauser), stahmann@msregister.de (A. Stahmann), vroni.vogelmann@novartis.com (V. Vogelmann), peter.flachenecker@sana.de (P. Flachenecker).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.msard.2021.103281
Received 24 March 2021; Received in revised form 2 September 2021; Accepted 23 September 2021
Available online 26 September 2021

those with superimposed relapses (interferon beta, ocrelizumab, cladribine – approved for active relapsing MS) or at least inflammatory activity (siponimod – approved for active SPMS) as measured via MRI or relapse activity (Faissner and Gold, 2019). Detailed knowledge of the frequency and characteristics of active and inactive SPMS is required to provide suitable treatment strategies and to allocate the resources appropriately; however, the supporting data are lacking (Krieger et al., 2016). In view of this, we defined two groups, 'active SPMS' and 'inactive SPMS', based on both reported MRI data and relapse activity. Following this, we investigated whether these two groups differ in terms of patient characteristics, symptomatology, disease progression, or DMT usage, using a large sample of patients documented in the German MS Registry (GMSR).

## 2. Methods

The GMSR was initiated in 2001 under the auspices of the German MS Society (DMSG), Bundesverband e.V., to collect nationwide data from patients with MS. A detailed description of the methodology is provided elsewhere (Ohle et al., 2021) (www.msregister.de/en). In brief, the GMSR is aimed at collecting both epidemiological data and data related to disease course, healthcare, and the social situation of MS patients. The GMSR currently covers 189 centres, with more than 35,000 patients and over 160,000 visit datasets recorded across the whole of Germany since 2014.

### 2.1. Inclusion criteria

Patients whose most recent visit documentation was dated between January 2016 and April 2020 were included in this study (mandatory MRI and relapse information were only added to the registry dataset at the end of 2015).

### 2.2. Definitions of active and inactive SPMS

Disease activity was classified according to criteria adapted from the 2013 revisions of the clinical course descriptions of multiple sclerosis (Lublin et al., 2014):

*active SPMS:*

MRI: contrast (gadolinium) enhancing (Gd+) lesions and/or new T2 lesions

**or** at least one relapse

*inactive (or 'not active') SPMS:*

MRI: no Gd+ lesions and no new T2 lesions

**and** no relapses

*unclassifiable (or 'activity indeterminate') SPMS*

Patients not assessed with MRI **and** no relapses

The classification of SPMS patients was assessed either at the last recorded visit or, in the case of missing information (e.g. no MRI available), within the 12 months prior to the patient's last recorded visit. Lublin et al. recommend an at least annual assessment of disease activity by clinical and brain imaging criteria, but also consider longer assessment periods to be appropriate for 'certain situations', e.g. subgroups with progressive MS. To examine such deviations in our (sub)cohort for which the classification of the disease activity was not possible in this one-year period due to a lack of clinical visits or conducted MRI, or due to the non-occurrence of relapses, the classification was extended in an experimental approach to the patient's recent history of up to four additional years. The one-year period (time frame) was then enlarged to the last classifiable visit per MS patient in the last five years but never prior to the SPMS conversion date (see Supplementary Figure 1) in order to see whether information can be gained.

### 2.3. Statistical analysis

The main analyses involved the assessment of actual classifiability and the comparison of information of interest at the last visit or at the last assessable date and were exploratory in nature. This information included the following: gender; age; age at onset of MS; duration of disease since first symptoms; time to and since conversion to SPMS; symptoms at onset; current symptoms and symptomatic treatment, including physiotherapy and disability (as measured using the expanded disability status scale [EDSS]); multiple sclerosis severity score (MSSS); employment status, early retirement due to MS; frequency of DMTs; steroid-drug therapy; and documented off-label applications. Furthermore, the current type of care was evaluated in terms of family care, outpatient care, day care, short-term care, and full inpatient care. The required medical aids under assessment were walking aids, tub aids, wheelchairs, and rollators. The area of physiotherapy was analysed both in general terms and according to symptoms.

The statistical analyses included descriptive statistics including 95% confidence intervals for metric and categorical outcomes. Generalised additive models were used to investigate MRI frequencies and risk factors for low assessment rates as a function of age, disease duration, or calendar time. Estimated MRI coverages are visualized by contour plots. Due to the exploratory nature of the study, no adjustment for multiple testing was made and the analyses were performed at a confidence level of 95%. The data transformation, statistical analyses, and figure creation were performed using R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria, packages: mgcv_1.8-31, nlme_3.1-148, ms.sev_1.0.4, compareGroups_4.4.1).

The GMSR was registered with the German Register of Clinical Studies (DRKS, Deutsches Register Klinischer Studien, DRKS; No. DRKS00011257). Initial ethical approval was obtained from the institutional review board at the University of Würzburg. Anonymised data will be made available on request for any qualified investigator under the terms of the registries' usage and access guidelines and subject to the informed consent of the patients.

## 3. Results

We identified 4,263 SPMS patients with last recorded visit in the GMSR after January 2016. The details of the patients in the different subgroups are shown in Fig. 1.

Out of the total sample of 4,263 SPMS patients, 1,513 (35.5%) could be classified as either 'active' or 'inactive' MS, while 2,750 (64.5%) were 'unclassifiable' due to missing MRI data and the absence of relapses (the latter alone did not allow for the categorisation of 'inactive' since the absence of relapse does not mean the absence of subclinical [MRI] activity).

Out of the 1,513 SPMS patients with the required data available, 467 were classified as 'active SPMS' (30.9%) and 1,046 as 'inactive SPMS' (69.1%).

### 3.1. Persistence of activity classifications

A comparison of the classifiability of the patients according to the one-year criteria and the five-year criteria is presented in the Supplementary Fig. 1. \Fig. 2 shows a plot of the actual time (x-axis) since the last visit (occurrence of all relapses and MRI) as well as the (temporal) certainty of the classification (y-axis). This Fig. can also be read much like a (time)-reversed survival curve related to the delay of updated information for the subgroups due to the chronological order of the disease activity classification. The number of classifiable patients could be increased by 20% ($83.0\%^{-1}$, see Fig. 2) in the inactive patient group and by 34% ($74.6\%^{-1}$) in the active patient group when using a five-year window instead of the one-year window.

### 3.2. Frequency of MRI measures

As shown in Fig. 1, the classification as active SPMS was most frequently conducted considering recently acquired MRI data. The

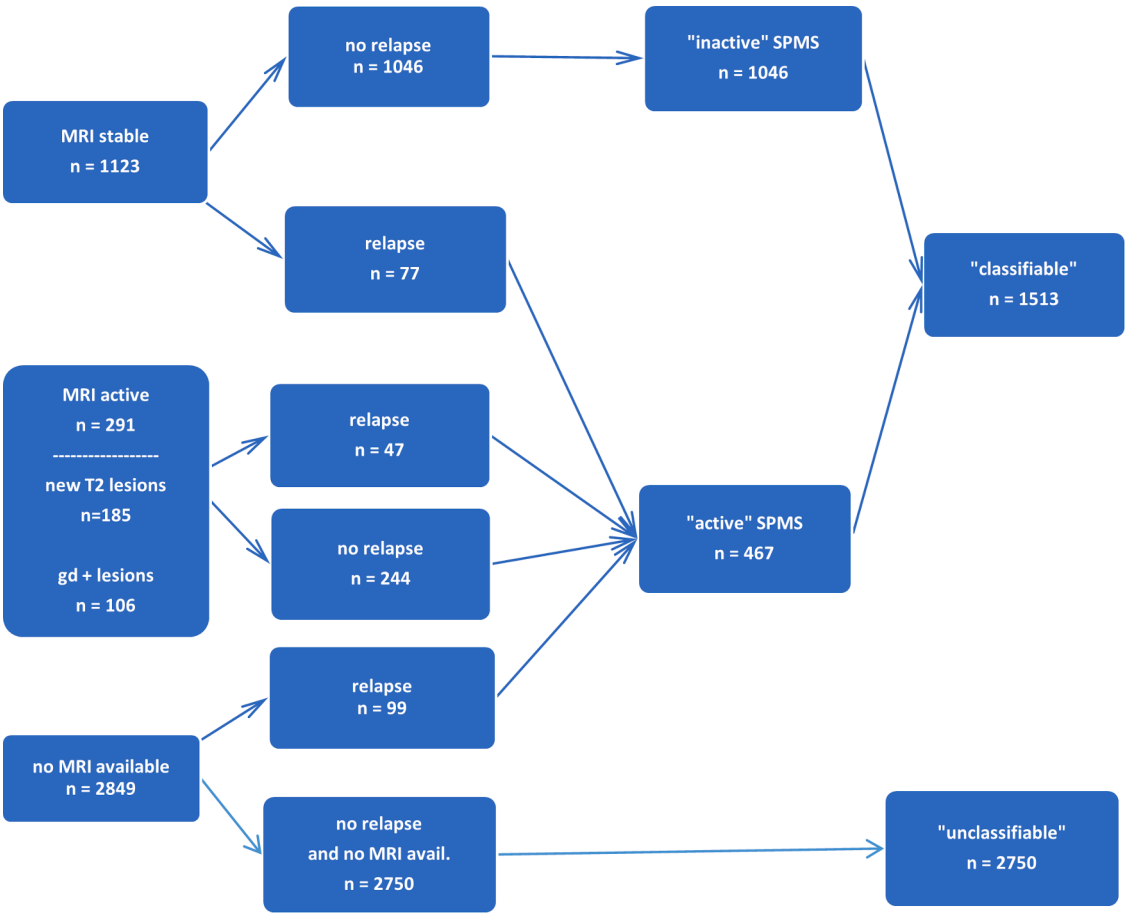



**Fig. 1.** Flowchart of all 4,263 SPMS patients. The MRI results and the occurrence of relapses were evaluated either at or within the year before the last visit of each PwMS (Supplementary Fig. 1 shows the extension to five years). MRI, magnetic resonance imaging; n, number of patients; PwMS, patient with multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

presence of relapses indicates active disease; however, only 223 of the analysed SPMS patients (5.2%) experienced relapses within the year before their last visit. MRI data were available for 1,414 SPMS patients (33.2%), which allowed for a more comprehensive classification. However, the relatively low rate of MRI measures in this population raised questions regarding how often MRI is carried out in actual clinical practice for SPMS patients in Germany and whether either age or disease duration influence the frequency. Therefore, we analysed the MRI proportions per visit in terms of age and disease duration, with the results of a generalised additive regression model shown in Fig. 3.

In our SPMS cohort, a younger age and a shorter disease duration were both associated with more frequently reported MRI. The MRI rate (at last visit) in the SPMS patients with a short disease duration ($\leq$10 years) was above 30%, while the patients suffering from MS for over >50 years generally had an MRI rate of below 20%. Furthermore, the MRI rate in the patients aged $\leq$40 years was around 40%, while the frequency in patients aged $\geq$70 years fell below 25% per visit. Effect sizes for age (odds ratio (OR) per 10 years: 1.22, 95% confidence interval: [1.12, 1.33], $p < 0.001$) and for disease duration (OR per 10 years 1.19 [1.09, 1.30], $p < 0.001$) were of similar extent.

### 3.3. Demographics, baseline disease characteristics, and current DMT use

In the next step of our analysis, we compared the demographic and baseline disease characteristics in terms of three patient subgroups (active SPMS, inactive SPMS, and unclassifiable). No significant differences were found between the patients with active SPMS and those with inactive SPMS with regard to sociodemographic and clinical characteristics ($p \geq 0.26$), see Table 1. However, the unclassifiable patients had a similar mean age at onset but a higher mean disease duration and were thus significantly older than the population in the classifiable groups.

The DMT rate in the unclassifiable group (43%) was significantly lower than in the classifiable groups (active: 56%, inactive: 57%). Detailed medication data were available for a subset of 113 active SPMS patients, 244 inactive SPMS patients, and 409 unclassifiable SPMS patients. With regard to the frequency of the use of single DMTs and steroid therapies (high-dosage pulse therapy, intrathecal steroids, or long-term therapy), no significant differences were found between the patients with active SPMS and those with inactive SPMS except a slight one in natalizumab (Table 1).

### 3.4. Frequency of symptoms, disability status, and healthcare utilization

As shown in Supplementary Table 1, SPMS patients with an active disease were slightly more likely to experience visual disturbances or blurred vision at MS onset (47% vs. 40%, $p = 0.025$ [Fisher exact test]), bladder dysfunction (19% vs. 13%, $p = 0.016$), and bowel dysfunction (8% vs. 3%, $p = 0.001$) in comparison to those with an inactive disease. No significant differences were found between the groups in terms of motor symptoms (weakness, paralysis), cerebellar disorders (coordination, fine motor disturbance, tremor ataxia), sensory disturbances (misperceptions, emotional disorders of different qualities), sexual disorders, brain stem function disorders (double vision, facial sensation, facial paralysis, hearing loss, speech disorder, dysphagia), depression, euphoria, concentration and/or memory disorders, or polysymptomatic

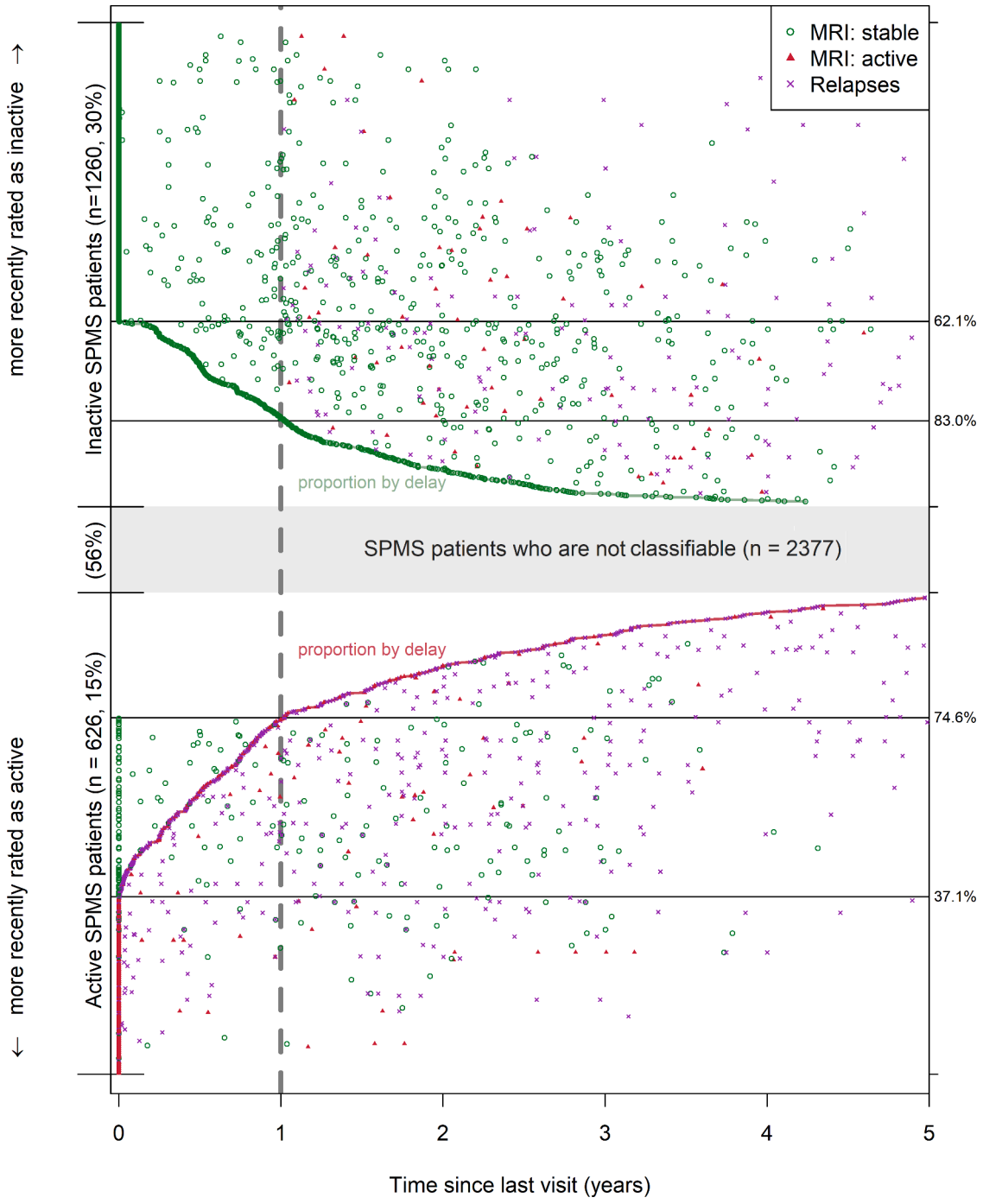



**Fig. 2.** Scatterplot showing the delay of relapses and/or MRI for classification since the last visit (SPMS patients, n=4,263). Occurrence of relapses and (updated) MRI visits are displayed for each patient as a horizontal timeline. The patients' timelines are thereby ordered vertically (y-axis) by the date of latest classifiability, with patients more recently rated as active towards the bottom and patients more recently rated as inactive towards the top. The subgroups were of different sizes and their total numbers are given. The x-axis shows the time since the patient's last visit up to 5 years. MRI with stable results is shown by the green circles, MRI with active results by the red triangles and relapses by the purple crosses. When using the (fixed) one-year window the classifiability of patients were 74.6% (active) or 83.0% (inactive) in relation to a five years extension. MRI, magnetic resonance imaging; n, number of patients; SPMS, secondary progressive multiple sclerosis.

onset and other onset symptoms. In terms of current symptoms, the active SPMS patients experienced a greater frequency of pain (46% vs. 40%, $p = 0.032$), cognitive dysfunction (45% vs. 36%, $p = 0.002$), and depression (33% vs. 28%, $p = 0.050$), while the inactive SPMS patients suffered more frequently from fatigue (60% vs. 66%, $p = 0.019$). There was no significant difference between the groups in terms of frequencies of spasticity, ataxia, micturition disturbances, defecation disturbances, sexual disorders, oculomotor disturbances, dysarthria, dysphonia, dysphagia, epileptic seizures, walking problems, and other paroxysms. Furthermore, in the year prior to the last visit, the active SPMS patients used wheelchairs more often (57% vs. 52%, $p = 0.045$) and required inpatient care more often (4% vs. 1%, $p = 0.008$) than the inactive SPMS patients. No significant differences were found in terms of disability (EDSS, MSSS), physiotherapy, or employment status between the two groups. When comparing the classifiable and unclassifiable patients, the latter had, besides higher disease duration, significantly higher EDSS

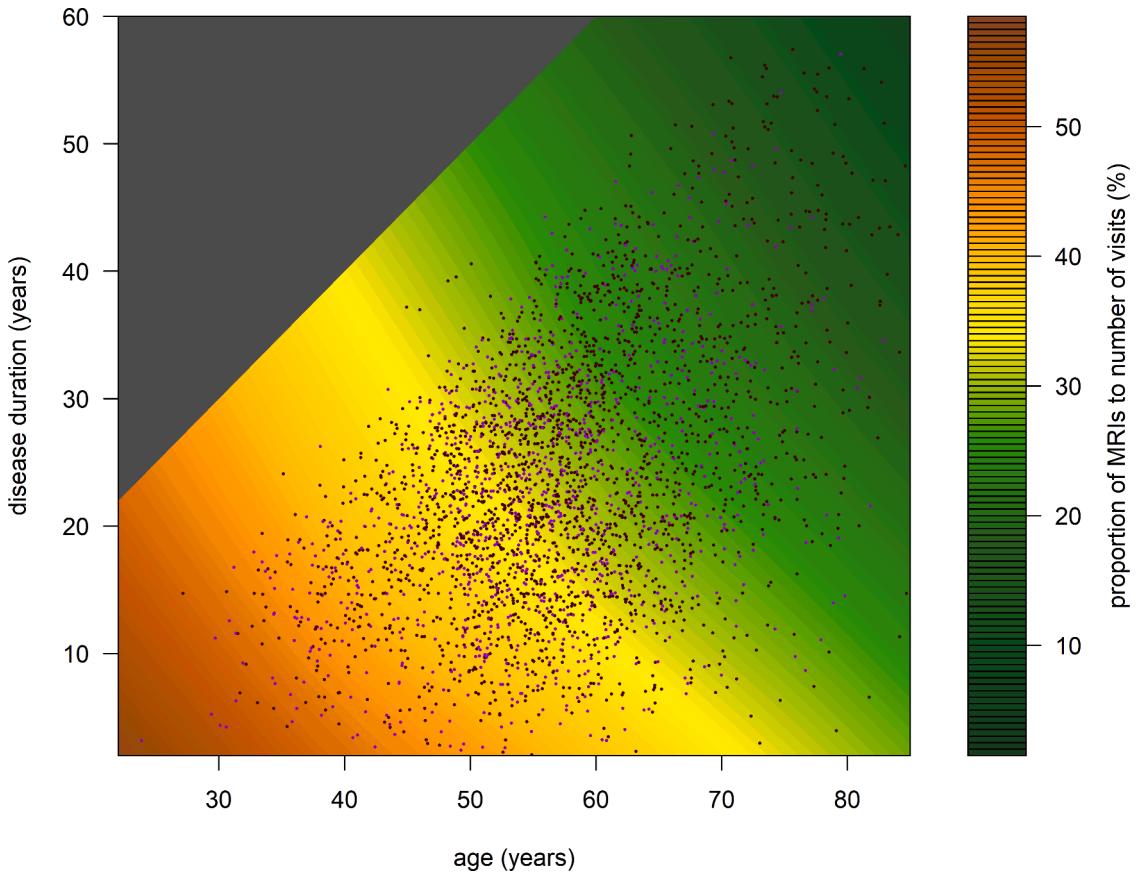



**Fig. 3.** Proportions of updated MRIs depending on age and disease duration. For the last recorded visit per SPMS patient, the orange and yellow areas indicate that more than 30% of visits were associated with an updated MRI status, while the green areas indicate rates of less than 30%. The light purple points indicate a visit with updated MRI information, while the dark brown points indicate visits without updated MRI information. MRI, magnetic resonance imaging.

scores, required more frequent outpatient care, and used a wheelchair more often.

## 4. Discussion

In this multicentre cohort study, a classification of SPMS patients was performed based on disease activity. The aims of the present investigation were to estimate the frequency of 'active' and 'inactive' SPMS and to identify the differences in terms of sociodemographic and clinical data, symptomatology, and healthcare utilisation between the two subgroups, based on real-world data.

The secondary progressive course of MS is both a diagnostic and a therapeutic challenge. On the one hand, the conversion of RRMS into SPMS is not clearly delineated because the transition phase runs smoothly without a clearly defined time point (Filippi et al., 2018; Giovannoni et al., 2016; Tremlett et al., 2008), while on the other hand, DMTs have largely been studied in patients with RRMS, meaning the immunotherapeutic options of SPMS with adequate efficacy are limited (Bhatia and Singh, 2019; Dargahi et al., 2017; Kappos et al., 2018). While Siponimod was the first drug specifically licensed for SPMS, its approval is limited to MS patients with an active disease (i.e. those with superimposed relapses and/or MRI activity) (European Medicines Agency, 2019). Meanwhile, interferon beta, cladribine, and ocrelizumab may also be used in patients with SPMS who exhibit clinical activity (relapsing MS, RMS), which means its use is, again, limited to MS patients with active SPMS. Treatments that effectively inhibit the continuous disability progression in SPMS patients in addition to reducing relapse activity would be long-awaited improvement in the therapy of SPMS patients.

One of our main findings was that according to the definition adapted from Lublin et al., 2014 only around one third of our SPMS patients could be classified as active, which indicates that there may still exist actual shortcomings in the classification of disease activity. Our results demonstrated that elderly patients with long disease durations are particularly less-frequently monitored via MRI, which may be associated with the small number of immunotherapeutic options for SPMS patients of an advanced age. Similar results regarding the frequency of MRI during the past year were found in Sweden, with a notable decrease with higher age and disease duration (Swedish MS registry, 2020). Furthermore, MRI capacities are subject to strong regional differences. However, regularly performed MRI plays an important role in the evaluation of disease activity (as shown both in our study and in others (Kaunzner et al., 2017)), since the relapse rate in progressing SPMS is generally low (Ontaneda, 2019). This finding was confirmed in our study, with only around 5% of our 4,263 patients experiencing relapses in the year prior to the evaluated medical examination. Regular monitoring and standardised MRI follow-up examinations (Rovira et al., 2015; Wattjes et al., 2015), especially at an advanced age, would provide new data and allow for a more appropriate and accurate identification of active SPMS patients.

It is worth noting that 'MRI activity' (new T2 lesions) in patients aged over 55–60 is likely to be confounded by lesions that are not MS-associated but are due to the increasing number of comorbidities (especially cerebrovascular) in elderly populations (e.g. hypertension) (Filippi et al., 2020; Guisset et al., 2020). Insufficient reproducibility of longitudinal MRI findings (especially beyond approval studies) has long been known as a problem in MRI follow-up investigations among clinical neurologists (Molyneux et al., 1999). Even relapses may lack discrimination from non-MS pathologies with increasing age. MRI data or relapse activity alone may thus have shortcomings in sensitivity as well

**Table 1**
Comparison of disease activity groups (number of cases, percentages, and mean ± SD are reported, t-test /Fisher's exact test).

| | SPMS population (n=4263) Classifiable n=1513 active SPMS (*n*= 467) | inactive SPMS (*n* = 1046) | p-value (active vs. inactive) | Unclassifiable n=2750 Last activity unknown |
|---|---|---|---|---|
| n | 467 | 1046 | | 2750 |
| (%) | 31% | 69% | | |
| Females (%) | 67% | 68% | 0.57 | 70% |
| Disease duration (years) | 22.6 (±11.0) | 21.9 (±9.7) | 0.26 | 24.2 (±10.4)* |
| Age at visit (years) | 55.6 (±10.6) | 55.8 (±9.4) | 0.66 | 57.6 (±9.9)* |
| Age at onset (years) | 33.2 (±10.8) | 33.7 (±10.5) | 0.42 | 33.5 (±10.5) |
| Years since conversion to SPMS | 5.8 (±6.5) | 6.2 (±5.6) | 0.61 | 7.8 (±6.9)* |
| Years from onset until conversion to SPMS | 15.1 (±9.1) | 14.7 (±9.2) | 0.71 | 15.7 (±9.4) |
| **DMT**[1] utilization rate | 56% (*n* = 113) | 57% (*n*= 244) | | 43%* (*n* = 409) |
| **Detailed DMT data for**[2]**:** | | | | |
| Azathioprine | 4.4% – (5) | 4.5% – (11) | 1.00 | 5.4% – (22) |
| Dimethyl fumarate | 5.3% – (6) | 3.38% – (8) | 0.39 | 3.4% – (14) |
| Fingolimod | 5.3% – (6) | 7.4% – (18) | 0.65 | 5.4% – (22) |
| Glatiramer acetate | 4.4% – (5) | 5.3% – (13) | 0.80 | 5.6% – (23) |
| Interferon beta | 17.7% – (20) | 12.7% – (31) | 0.25 | 18.1% – (74) |
| Mitoxantrone | 15.0% – (17) | 9.4% – (23) | 0.15 | 12.2% – (50) |
| Natalizumab | 0.9% – (1) | 5.7% – (14) | 0.04 | 1.7% – (7) |
| Ocrelizumab | 18.6% – (21) | 23.8% – (58) | 0.34 | 10.5% – (43) |
| Steroids | 18.6% – (21) | 12.7% – (31) | 0.15 | 22.2% – (91) |

DMT, disease-modifying therapy; n, number of patients; SD, standard deviation; SPMS, secondary progressive multiple sclerosis

* indicates that the unclassifiable group differs significantly from the classifiable groups at a type-I-error level of 1%, i.e. $p < 0.01$

[1] Ongoing DMT-treatment was captured as Yes/No/unknown for all patients (comparison of active vs. inactive SPMS: $p = 0.94$)

[2] Specific DMT details were captured at a reference date in a subset of centres (active vs. inactive SPMS: $p < 0.001$).

as in specificity for the classification of patients into active and inactive SPMS groups.

In summary, only marginal differences in the onset and current symptoms between the active and inactive SPMS groups were found and both groups are rather homogeneous. In terms of care and aids, wheelchair use was slightly more frequent among the 'active' SPMS patients than the 'inactive' patients (57% vs. 52%). This difference could be due to a temporary gait impairment related to relapses (Cameron and Nilsagard, 2018). This aside, the required aid did not depend as much on the disease activity as on age and disease duration. Overall, the lack of correlation with the evaluated demographic, symptomatic and status of care covariates is to be expected, as this suggests that MRI activity may provide an independent component of information which may not be available through these easy-access types of data.

The DMTs were only reported at a descriptive level since the activity of the disease and the treatment are co-dependent. In short, it was not clear whether disease activity triggered a change in the DMT or whether the administered DMT ensured that the disease remained inactive. Here, analyses using marginal structural models similar to those used by Spelman et al. (2020) for a given SPMS cohort would be of interest and could form the basis of follow-up research. In our study, ocrelizumab, interferon beta, and mitoxantrone were the most commonly used DMTs among both the active and inactive patients as well as those who could not be classified. These parallels in therapeutic strategies were likely due to the limited number of approved SPMS drugs (Dargahi et al., 2017; Kappos et al., 2018) and the fact that the licensure of cladribine and siponimod occurred during or after the observation period for our analysis. Considering the relatively high average age of 55 years, the disease duration of more than 20 years and the relatively high disability level, the DMT rate of more than 50% seems rather ambitious, especially when taking into account the fact that the clinical effectiveness of high-efficacy DMTs and low-efficacy DMTs does not differ in MS patients older than 40 years (Weideman et al., 2017). Nevertheless, targeted inclusion of older MS patients in DMT clinical trials is useful to investigate the effect of immune senescence and the possible accumulation of side effects (Papadopoulos et al., 2020; Vaughn et al., 2019). To date, study populations of clinical trials cannot be compared with real-world patient cohorts. Specific inclusion criteria of clinical trials, especially with respect to age, disease activity, and drug regimen, do not reflect the broad majority of MS patients (Jalusic et al., 2021).

One limitation of this study is that only 35.5% of our 4,263 SPMS patients could be classified as active or inactive. This low classification rate was largely due to the lack of MRI data, especially for older MS patients or for those with a longer disease duration, as was discussed in detail above. As such, the current registered number of SPMS patients with disease activity may have been underestimated. The selection of the time interval for classifying the disease activity in SPMS patients was a topic that had to be investigated separately. Here, with reference to Lublin et al. (2014), we used an interval of one year as the regular time frame; however, other periods can be considered suitable in certain situations. To experiment with a longer period, we looked at a larger time frame of up to five years. More patients could be reclassified but the data wasn't suggesting that an even five-year period will solve the mentioned shortcomings. Considering a one-year period seems thus reasonable. Nevertheless, our data suggest that too many patients do not receive regular MRI at all, as a real-world matter. In addition, there is the possibility of the under-reporting of SPMS, since the physicians may have avoided changing the diagnosis from RRMS to SPMS due to the lack of treatment options.

In conclusion, this paper provides an overview of the frequency and characteristics of SPMS patients according to disease activity. Today, MRI data play an important role in the classification of disease activity into 'active' and 'inactive'. However, despite this, the MRI rate tends to decline with an increase in age and longer disease durations.

## Role of funding

The German MS Registry of the German MS Society was initiated and funded by the German MS Foundation and the German MS Society in 2001. It is operated by a not-for-profit company, the MSFP. In 2021, Biogen, Celgene (BMS), Merck, Novartis, Roche and Sanofi are participating in the multi-stakeholder funding approach to support the registry's operation and to allow the collection and reporting of data required as part of the EMA-minimal data set. Industry funding does not result in restrictions to publishing data, nor do the funders have access to the raw data or have any influence over the scientific conduct of the registry.

The evaluations contained in this paper were supported and funded by Novartis.

## CRediT authorship contribution statement

**Niklas Frahm:** Writing – original draft, Writing – review & editing, Conceptualization. **David Ellenberger:** Project administration, Conceptualization, Formal analysis, Data curation, Writing – review & editing, Visualization. **Firas Fneish:** Formal analysis, Data curation.

**Kleinschnitz Christoph:** Writing – review & editing. **Clemens Warnke:** Writing – review & editing. **Uwe K. Zettl:** Writing – review & editing. **Friedemann Paul:** Writing – review & editing. **Benedict Rauser:** Writing – review & editing. **Alexander Stahmann:** Supervision, Conceptualization, Writing – review & editing. **Vroni Vogelmann:** Writing – review & editing. **Peter Flachenecker:** Supervision, Conceptualization, Writing – review & editing.

## Declaration of Conflicting Interest

DE and FF declare no competing interests.

NF received travel funds for research meetings from Novartis. None resulted in a conflict of interest.

CK has received speaker's fees, honoraria for attending advisory boards, and financial support for conducting research projects from Merck Serono GmbH, Germany and Merck KGaA, Germany. None resulted in a conflict of interest.

CW has received institutional support from Novartis, Alexion, Sanofi-Genzyme, Biogen, and Roche. None resulted in a conflict of interest.

UKZ received research support and lecture fees or travel funds from Alexion, Almirall, Bayer HealthCare, Biogen, Merck Serono, Novartis, Roche, Sanofi and Teva. None resulted in a conflict of interest.

FP has received speaking fees, travel support, honoraria from advisory boards, and/or financial support for research activities from Bayer, Novartis, Biogen, Teva, Sanofi-Aventis/Genzyme, Merck Serono, Alexion, Chugai, MedImmune, Shire, The German Research Council, Werth Stiftung of the City of Cologne, The German Ministry of Education and Research, the EU FP7 Framework Program, the Arthur Arnstein Foundation Berlin, the Guthy Jackson Charitable Foundation, and the National Multiple Sclerosis of the USA. FP serves as academic editor for PLoS ONE and associate editor for Neurology, Neuroimmunology and Neuroinflammation. None resulted in a conflict of interest.

BR is an employee of Novartis Pharma GmbH (Nürnberg, Germany).

VV is an employee of Novartis Pharma GmbH (Nürnberg, Germany).

AS has no personal pecuniary interests to disclose, other than being the lead of the German MS Registry, which receives funding from a range of public and corporate sponsors, recently including The German Innovation Fund (G-BA), The German MS Trust, German MS Society, Biogen, Celgene (BMS), Merck, Novartis, Roche and Sanofi. None resulted in a conflict of interest.

PF has received speaker's fees and honoraria for advisory boards from Almirall, Bayer, Biogen Idec, Celgene, Genzyme, Novartis, Merck-Serono, Roche and Teva. He has participated in pharmaceutical company sponsored trials by Roche. None resulted in a conflict of interest.

## Acknowledgments

We would like to thank all the patients who gave their informed consent. Furthermore, this study would not have been possible without the efforts of the centres participating in the registries. The centres are listed in the Supplement.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.materresbull.2021.111558.

## References

Bhatia, R., Singh, N., 2019. Can We Treat Secondary Progressive Multiple Sclerosis Now? Ann. Indian Acad. Neurol. 22, 131–136. https://doi.org/10.4103/aian.AIAN_345_18.

Cameron, M.H., Nilsagard, Y., 2018. Balance, gait, and falls in multiple sclerosis. Handb. Clin. Neurol. 159, 237–250. https://doi.org/10.1016/B978-0-444-63916-5.00015-X.

Dargahi, N., Katsara, M., Tselios, T., et al., 2017. Multiple sclerosis: immunopathology and treatment update. Brain Sci. 7, 78. https://doi.org/10.3390/brainsci7070078.

European Medicines Agency, 2019. Mayzent. https://www.ema.europa.eu/en/medicines/human/EPAR/mayzent (accessed 2 September 2021).

Faissner, S., Gold, R., 2019. Progressive multiple sclerosis: latest therapeutic developments and future directions. Ther. Adv. Neurol. Disord. 12, 1756286419878323 https://doi.org/10.1177/1756286419878323.

Filippi, M., Bar-Or, A., Piehl, F., et al., 2018. Multiple sclerosis. Nat. Rev. Dis. Primers 4, 43. https://doi.org/10.1038/s41572-018-0041-4.

Filippi, M., Preziosa, P., Barkhof, F., et al., 2020. Diagnosis of progressive multiple sclerosis from the imaging perspective: a review. JAMA Neurol. 78, 351–364. https://doi.org/10.1001/jamaneurol.2020.4689.

Gehr, S., Kaiser, T., Kreutz, R., Ludwig, W.D., Paul, F., 2019. Suggestions for improving the design of clinical trials in multiple sclerosis - results of a systematic analysis of completed phase III trials. EPMA J. 10, 425–436. https://doi.org/10.1007/s13167-019-00192-z.

Gholamzad, M., Ebtekar, M., Ardestani, M.S., et al., 2019. A comprehensive review on the treatment approaches of multiple sclerosis: Currently and in the future. Inflamm. Res. 68, 25–38. https://doi.org/10.1007/s00011-018-1185-0.

Giovannoni, G., Butzkueven, H., Dhib-Jalbut, S., et al., 2016. Brain health: time matters in multiple sclerosis. Mult. Scler. Relat. Disord. 9, S5–S48. https://doi.org/10.1016/j.msard.2016.07.003.

Guisset, F., Lolli, V., Bugli, C., et al., 2020. The central vein sign in multiple sclerosis patients with vascular comorbidities. Mult. Scler. 27, 1057–1065. https://doi.org/10.1177/1352458520943785.

Jalusic, K.O., Ellenberger, D., Rommer, P., Stahmann, A., Zettl, U., Berger, K., 2021. Effect of applying inclusion and exclusion criteria of phase III clinical trials to multiple sclerosis patients in routine clinical care. Mult. Scler. https://doi.org/10.1177/1352458520985118, 1352458520985118.

Kappos, L., Bar-Or, A., Cree, B.A.C., et al., 2018. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 391, 1263–1273. https://doi.org/10.1016/S0140-6736(18)30475-6.

Kaunzner, U.W., Al-Kawaz, M., Gauthier, S.A., 2017. Defining disease activity and response to therapy in MS. Curr. Treat Options Neurol. 19, 20. https://doi.org/10.1007/s11940-017-0454-5.

Krieger, S.C., Cook, K., De Nino, S., Fletcher, M., 2016. The topographical model of multiple sclerosis: a dynamic visualization of disease course. Neurol. Neuroimmunol. Neuroinflamm. 3, e279. https://doi.org/10.1212/NXI.0000000000000279.

Lublin, F.D., Reingold, S.C., Cohen, J.A., et al., 2014. Defining the clinical course of multiple sclerosis. Neurology 83, 278–286. https://doi.org/10.1212/WNL.0000000000000560.

Molyneux, P.D., Miller, D.H., Filippi, M., et al., 1999. Visual analysis of serial T2-weighted MRI in multiple sclerosis: intra- and interobserver reproducibility. Neuroradiology 41, 882–888. https://doi.org/10.1007/s002340050860.

Ohle, L.M., Ellenberger, D., Flachenecker, P., et al., 2021. Chances and challenges of a long-term data repository in multiple sclerosis: 20th birthday of the German MS registry. Sci. Rep. 11, 13340. https://doi.org/10.1038/s41598-021-92722-x.

Ontaneda, D., 2019. Progressive Multiple Sclerosis. Continuum (Minneap. Minn.) 25, 736–752. https://doi.org/10.1212/CON.0000000000000727.

Papadopoulos, D., Magliozzi, R., Mitsikostas, D.D., Gorgoulis, V.G., Nicholas, R.S., 2020. Aging, Cellular Senescence, and Progressive Multiple Sclerosis. Front. Cell. Neurosci. 14, 178. https://doi.org/10.3389/fncel.2020.00178.

Rovira, À., Wattjes, M.P., Tintoré, M., et al., 2015. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis-clinical implementation in the diagnostic process. Nat. Rev. Neurol. 11, 471–482. https://doi.org/10.1038/nrneurol.2015.106.

Saleem, S., Anwar, A., Fayyaz, M., Anwer, F., Anwar, F., 2019. An overview of therapeutic options in relapsing-remitting multiple sclerosis. Cureus 11, e5246. https://doi.org/10.7759/cureus.5246.

Spelman, T., Freilich, J., Anell, B., Wong, S.L., Hillert, J., 2020. Patients With High-disease-activity Relapsing-Remitting Multiple Sclerosis in Real-world Clinical Practice: A Population-based Study in Sweden. Clin. Ther. 42, 240–250. https://doi.org/10.1016/j.clinthera.2019.11.018.

Swedish MS registry, 2020. Web-based platform for live visualization and interactive statistical analysis. https://vap.carmona.se/open/msvap/graf/tillgang_mri/ (accessed 2 September 2021).

Tintore, M., Vidal-Jordana, A., Sastre-Garriga, J., 2019. Treatment of multiple sclerosis - success from bench to bedside. Nat. Rev. Neurol. 15, 53–58. https://doi.org/10.1038/s41582-018-0082-z.

Tremlett, H., Zhao, Y., Devonshire, V., 2008. Natural history of secondary-progressive multiple sclerosis. Mult. Scler. 14, 314–324. https://doi.org/10.1177/1352458507084264.

Vaughn, C.B., Jakimovski, D., Kavak, K.S., et al., 2019. Epidemiology and treatment of multiple sclerosis in elderly populations. Nat. Rev. Neurol. 15, 329–342. https://doi.org/10.1038/s41582-019-0183-3.

Wattjes, M.P., Rovira, À., Miller, D., et al., 2015. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis–establishing disease prognosis and monitoring patients. Nat. Rev. Neurol. 11, 597–606. https://doi.org/10.1038/nrneurol.2015.157.

Weideman, A.M., Tapia-Maltos, M.A., Johnson, K., Greenwood, M., Bielekova, B., 2017. Meta-analysis of the Age-Dependent Efficacy of Multiple Sclerosis Treatments. Front. Neurol. 8, 577. https://doi.org/10.3389/fneur.2017.00577.