Journal Pre-proof

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PII: S2211-0348(24)00421-8
DOI: https://doi.org/10.1016/j.msard.2024.105844
Reference: MSARD 105844

To appear in: *Multiple Sclerosis and Related Disorders*

Received date: 6 May 2024
Revised date: 3 August 2024
Accepted date: 22 August 2024

Please cite this article as: Braune Stefan , Karamasioti Eleni , van Hoevell Philip , Bergmann Arnfin , Skuljec Jelena , Siva Aksel , NTD Study Group , Pul Refik , Accuracy of MSBase Criteria to Diagnose Secondary Progressive Multiple Sclerosis in Large German Real-World Patient Cohort, *Multiple Sclerosis and Related Disorders* (2024), doi: https://doi.org/10.1016/j.msard.2024.105844

Highlights

- MSBase criteria (MSBC) for the diagnosis of secondary progressive multiple sclerosis (SPMS) are not enabling earlier identification of patients with SPMS compared to treating physicians.
- 60.8% of patients switching to SPMS were diagnosed at least 3 months earlier by treating neurologists compared to the MSBC.
- MSBC showed a low sensitivity of 32.0% and an accuracy of 61.4%, but a high specificity of 89.6%.
- Test-retest variability identified 29.4% of patients diagnosed with SPMS by treating physicians did not fulfil the MSBC at a later point in time.

Accuracy of MSBase Criteria to Diagnose Secondary Progressive Multiple Sclerosis in Large German Real-World Patient Cohort

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Abstract

Background and Objectives: Accurate diagnosis of secondary progression in multiple sclerosis (MS) remains a challenge since standardized criteria are missing. In 2016, the MSBase registry presented an algorithm that enabled the diagnosis of secondary progressive multiple sclerosis (SPMS) more than three years earlier compared to diagnosis by neurologists. This work aimed to test whether this approach is equally effective in a real-world cohort of MS patients.

Methods: This longitudinal retrospective study analyzed clinical data of outpatients with MS recorded until October 2020 in the NeuroTransData registry, a Germany-wide network of 153 certified neurologists. Patient data had been captured in time during clinical visits employing a defined standardized clinical data set in the webbased NeuroTransData patient management platform DESTINY®. The time between the diagnosis of relapsing-remitting multiple sclerosis (RRMS) to SPMS onset was compared with one determined using MSBase criteria (MSBC). Group 1 consisted of patients diagnosed with SPMS during the observation period, whereas group 2 included RRMS patients who did not convert to SPMS during the observation period.

Results: Of 21,281 patients with MS included in our registry, 194 and 9506 patients were allocated to groups 1 and 2, respectively. 10.3% of patients with RRMS were diagnosed with SPMS simultaneously, whereas 60.8% were diagnosed with SPMS at least 3 months earlier by treating neurologists compared to the MSBC. In group 1, the MSBC showed a low sensitivity of 32.0% and an accuracy of 61.4% but a high specificity of 89.6%. In group 2, the MSBC identified 7.8% of patients with SPMS at some point during the observation time. Moreover, test-retest variability remains a challenge since 29.4% of patients diagnosed with SPMS by treating physicians did not fulfil the MSBC at a later point in time.

Discussion: These results are inconsistent with earlier SPMS diagnosis using the MSBC compared to clinical diagnosis by treating physicians. Therefore, there remains a need for an operational, structured, and validated approach to SPMS diagnosis.

Key words

Relapsing-remitting multiple sclerosis, transition, secondary progressive multiple sclerosis, diagnosis, real-world data.

Introduction

The transition to secondary progressive multiple sclerosis (SPMS) represents a formidable milestone in the course of each patient with relapse-remitting multiple sclerosis (RRMS) with consequences regarding a negative prognosis with irreversible, slowly progressive disability and sofar limited options for disease modifying therapies[1]. It also represents an essential parameter in clinical trials and studies. The most common method of assessing the time the patient has transitioned to SPMS is a retrospective clinical review of disability worsening independent of relapse activity[2]. However, although multiple attempts have been made to reach a consensus, diagnosing SPMS remains challenging in many ways[3]. Recent analysis of data from five European MS registries[4] showed an enormous range in the proportion of identified SPMS patients employing three objective classification methods including the MSBase algorithm[5]. Forsberg and colleagues[4] concluded a systematically underdiagnosis of SPMS in these registries. This is underlined by data from the Danish registry, reporting 20% of their RRMS being at risk for SPMS based on MSBC[6].

Previously, the duration of diagnostic uncertainty (the "transition phase") until a clinically accurate diagnosis of SPMS has been reported to last about 3 years[7,8,9]. The recent approval of siponimod as the treatment option for SPMS[10] represents a key turning point since there is now a medical need to identify the conversion to SPMS as early as possible to prevent or delay disease progression. This need will increase if further compounds, such as Bruton tyrosine kinases, receive approval for treating SPMS.

A proposal to shorten the time to diagnosis and to construct an operational framework for clinical trials has been introduced by Lorscheider and colleagues[5]. This comprised a diagnostic algorithm based on the Expanded Disability Status Scale (EDSS) and information about preceding relapses. In that study, among 576 candidate definitions, a longitudinal 3-strata progression paradigm and confirmed disability progression over three months were reported to provide the highest accuracy in terms of specificity and sensitivity referenced to a cohort of 200 patients with confirmed SPMS diagnosis. In half of the patients, the new algorithm based on MSBase criteria (MSBC), enabled SPMS diagnosis three years earlier than done by physicians. In the recent analysis of data from five European MS registries the MSBC did not identify a relevantly higher proportion of patients with SPMS compared to clinical judgement overall, although proportions differed substantially between countries[4].

In this study, we investigated the time between the RRMS diagnosis to SPMS onset, determined by practising neurologists of the Germany-wide NeuroTransData (NTD) network, and compared it to the applied MSBC diagnostic definition.

Methods

Data

Clinical real-world data recorded in the NTD multiple sclerosis (MS) registry were employed. NTD is a Germany-wide network of 153 neurologists in 78 offices, serving about 600,000 outpatients per year. They are certified according to network-specific and ISO 9001 criteria and inspected annually by an external audit organization. The registry included about 25,000 MS patients. Demographic and clinical parameters were captured in real-time over an average of 3.7 visits and Expanded Disability Status Scale (EDSS) assessments per year per patient[7] by certified evaluators, employing the web-based NTD patient management platform DESTINY®[11]. All personnel underwent regular training and monitoring to ensure data quality. All entries were checked for inconsistencies and mistakes, and automatic and manually executed queries were implemented to ensure data quality[12]. All data were pseudonymized and pooled to form the NTD MS database. The codes uniquely identifying patients were managed by the Institute for Medical Information Processing, Biometry and Epidemiology (IBE) at the Ludwig Maximilian University in Munich, Germany, acting as an external trust centre. For this study, data were extracted from the NTD MS database on October 1, 2020.

The date of the visit or inpatient stay when SPMS was diagnosed (FSD Date: first SPMS diagnosis date) was captured in the NTD registry. A visit-based dataset corresponding to the date when the NTD doctors documented a RRMS or SPMS diagnosis (index diagnosis date) was created. The index diagnosis date could be either the patient's first diagnosis or confirmation of a previous diagnosis. Documenting doctors are regularly asked via automated registry queries to confirm f.e. the persistence of SPMS. Thus, the dataset captures the time progression of all documented diagnoses for each patient, covering the total period during which each patient was monitored (observation period). Only patients with documented RRMS or SPMS diagnosis were included in the analysis, whereas other types of MS were excluded. For each index diagnosis date, it was checked whether the MSBC were met. For every visit of

every patient in this initial dataset, we evaluated the MSBC and produced the MSBC-based SPMS diagnosis corresponding to every visit during the observation times available. In case of insufficient data, the decision was denoted as non-available (NA). Notably, no data imputation was performed.

Patient Populations

This study focused on two different groups. **Group 1** included MS patients who transitioned from RRMS to SPMS during the observation period. The following inclusion criteria were applied: (i) FSD date is at least one year after the start and latest one year before the end of the observation period, respectively; (ii) the data contain at least two EDSS measurements, i.e. at least one value determined one year before and one year after the FSD date, respectively; (iii) the MSBC could be evaluated at least once during the observation period. Patients diagnosed with SPMS already before or during the first visit were excluded from analyses. **Group 2** included RRMS patients whose disease course did not transition to SPMS during the observation period. Following inclusion criteria were applied: (i) the data contained at least two EDSS measurements per year during the observation period; (ii) the MSBC could be evaluated at least once during the observation period.

Application of the MSBC

For each patient it was determined at every visit wether the MSBC were met. For the evaluation of the first MSBase criterion of 3-month confirmed disability progression (3mCDP) a roving EDSS reference value was employed. Data were screened starting from each visit to identify a possible 3mCDP, defined as an increase in the EDSS score of 1.5, 1.0, or 0.5 if the baseline EDSS score was 0, between 1.0 and 5.0, or greater than 5.0, respectively, in the absence of relapse. If 3mCDP was detected, the first date of a later confirmed increase of EDSS was captured as date of SPMS diagnosis by MSBC. To evaluate the second and third criteria, screening for a minimum EDSS score of ≥ 4.0 and the pyramidal functional system score of ≥ 2 was performed. The fourth criterion, which requires that 3mCDP is not associated with relapse activity, was determined by crosschecking with documented dates of relapse activity in the registry. Thus, SPMS diagnosis required the first three criteria to be met and the fourth criterion to be unmet. If one of the four criteria could not be assessed, the result was not

evaluated and was indicated as not applicable (NA). For the evaluation of the first criterion, cases were excluded if there were less than 3 EDSS measurements available since a baseline EDSS score before the index diagnosis date was required as a reference, a second EDSS score was used as an indicator for progression, and the third to determine 3mCDP.

MSBC were also applied to every visit of patients to evaluate the within-patient consistency of diagnostic assessments.

Accuracy Analysis of MSBC based SPMS Diagnosis versus Treating Neurologists´diagnosis

FSD dates determined by NTD neurologists and according to the MSBC were evaluated. Table 1 summarizes the approach on which the comparisons were based. For group 1, NTD and Lorscheider diagnosis dates were considered equal if they did not differ by more than 3 months. To visualize the comparison between MSBC based and the NTD neurologists´diagnoses, for every observation within the dataset (multiple diagnosis index dates for each patient), confusion matrices were generated for each of the two groups separately and for all patients together. These matrices served as a basis for the computation of performance metrics such as sensitivity, specificity, and accuracy. *Sensitivity* was defined as the ratio of true positives over the sum of true positives and false negatives. *Specificity* was defined as the ratio of true negatives over the sum of true negatives and false positives. *Accuracy* was defined as the ratio of the sum of true positives and true negatives over the total number of cases. True/false positives were the cases where the MSBC resulted in a correct/wrong SPMS prediction, whereas true/false negatives were the cases where the MSBC resulted in a correct/wrong RRMS prediction.

Standard Protocol Approvals, Registrations, and Patient Consents

The data acquisition protocol for the registry was approved by the Ethical Committee of the Bavarian Medical Board (Bayerische Landesärztekammer; June 14, 2012, approval number 11144) and re-approved by the Ethical Committee of the Medical Board North-Rhine (Ärztekammer Nordrhein; April 25, 2017, approval number 2017071). All patients provided written informed consent for the use of their clinical, laboratory, and imaging data.

Results

Demographic and Clinical Characteristics

Starting with the dataset of 21,281 MS patients, 13,631 patients remained after excluding those who had SPMS already diagnosed before the beginning of the observation period and where MSBC could not be applied due to insufficient data (Figure 1). After implementing the inclusion criteria mentioned above, groups 1 and 2 comprised 194 and 9506 patients, respectively (Figure 1). Demographic and clinical characteristics are summarized in Table 2. Patients in group 1 had significantly fewer visits per year but a longer observation period than those in group 2 (Table 2). As expected, patients in group 1 were older, with a median age of 52 years at the time of SPMS diagnosis, after a median disease duration of 13 years (Table 2). Nearly 45% of patients had no disease-modifying treatment (DMT) at the time of SPMS diagnosis (Table 2). The EDSS on the FSD date ranged from 0 to 9, with a median value of 5.0 (Table 2).

Comparison of the Earliness of SPMS Diagnosis

In 60.8% of the cases in group 1, the MSBC-based SPMS diagnosis was given later than that by the neurologists (Table 3). The mean period from the RRMS diagnosis to the FSD date was 171.9 (±105.0) months, as diagnosed by NTD neurologists. In contrast, an average of 185.8 (±113.8) months were calculated for the MSBC, representing a difference of 13.9 (±40.8) months. Moreover, in 28.9% of the cases, the MSBC estimated diagnosis was earlier than that given by the NTD neurologists, whereas an overlap between these two approaches was detected in only 10.3% of the patients (Table 3). In the sensitivity analysis, a 6-month tolerance was defined as the period in which the differences between the two approaches were considered equal. This resulted in a slight increase in the FSD overlap percentage from 10.3% to 18.0% in group 1, while all other results did not change significantly (Table 3), underlining the robustness of the data.

Evaluation of the MSBC Consistency

Applications of MSBC at every visit documented in the registry over the observation period revealed time-dependent fluctuations. 29.4% of patients in Group 1 and 4.1% of all patients did not consistently fulfil the MSBC for SPMS diagnosis even though these criteria were already met beforehand. The MSBC were not completed after the estimated FSD date in 18.0%, 6.7%, and 4.6% of group 1 SPMS patients when calculated FSD dates were earlier, later, or equal to those determined by the NTD neurologists, respectively. In contrast, NTD neurologists who diagnosed SPMS never reversed their diagnosis.

Evaluation of Sensitivity, Specificity, and Accuracy of MSBC

In group 1, a sensitivity of 32.0%, a specificity of 89.6%, and an accuracy of 61.4% were calculated for the FSD dates based on MSBC (Table 4). In group 2, which consisted of patients not diagnosed with SPMS by NTD neurologists, the application of the MSBC led to the diagnosis of SPMS in 7.8% of patients, while concordant judgement between the MSBC and neurologists was present in 92.2% (Table 5), corresponding to specificity and accuracy of 96.3%, respectively (Table 5).

To better understand discrepancies between the clinical identification of SPMS and MSBC, the false negative subpopulation of patients (n=2102) was analyzed, including patients being clinically diagnosed as SPMS but not by MSBC. In this group, 79% fulfilled three of the four MSBC, 15% two and 6% one of them. MSBC identified in only 14% of patients the 3mCDP based on EDSS, whereas the criteria of minimum EDSS total score of 4 and minimum EDSS pyramidal function score of 2 were identified in 78% and 86%, respectively. In almost all patients (95%), the lack of relapse-associated worsening was correctly employed in the MSBC algorithm.

Discussion

Defining the MSBC is the first substantial attempt to operationalize the SPMS diagnosis to enable SPMS diagnosis at an earlier stage than done by the treating physicians. MSBS used a reference group that consisted of 200 patients[5]. Their SPMS diagnosis was confirmed by an independent consensus of three neurologists, who also estimated the time point when patients

transitioned from RRMS to SPMS based on registry-captured clinical information. This work aimed to verify whether the claim of an earlier SPMS diagnosis based on MSBC also holds in a real-world MS cohort. In the present study, neurologists diagnosed SPMS on average 13.9 months earlier than the MSBC, suggesting no delay in diagnosing SPMS in routine clinical practice and that the application of the MSBC provides no advantage.

Using the SPMS diagnose dates determined by treating physicians as a reference, the specificity of the calculated dates based on MSBC was high (89.6%) in the group of patients diagnosed with SPMS and even higher (96.2%) if also RRMS patients without transition into SPMS were included. However, surprisingly low values of calculated sensitivity (32%) and accuracy (61.4%) for RRMS patients transitioning to SPMS imply a diagnostic discrepancy between the MSBC and neurologists. The low sensitivity mainly reflects a delay in MSBC-based SPMS diagnosis. The analysis of the false negative subpopulation, including patients being clinically diagnosed SPMS but not identified by MSBC, indicated that clinicians detected clinical worsening more precisely and beyond EDSS-based progression, as MSBC identified a formal 3mCDP in only 14% of patients. This reflects the limited sensitivity of EDSS to detect changes in disease progression[13]. How strongly this issue contributes is underlined by the observation that MSBC detected a minimum EDSS score of 4 and a pyramidal function score in 78% and 86% of patients, respectively, as well as 95% proportion with no association with relapse activity. The observation reported from the Danish registry, that only 25% of the 20% proportion of the RRMS population identified by MSBC as SPMS, also fulfilled the clinical diagnostic SPMS criteria used in the EXPAND clinical trial[6], underlines the sensitivity issue of the MSBC.

In line with our results, application of MSBC to the Swedish MS patient registry and demonstrated a lower classification accuracy (77.8%) and a longer estimated median time to SPMS from birth compared to clinical evaluations[14]. The authors have proposed a decision tree model for diagnosing SPMS, which was feasible due to the simplicity of the dataset, namely age and EDSS. The fundamental problem that recurs is that, also in this study[14], a comparison of the physicians' diagnoses was made with an algorithm based on the judgment of three independent neurologists as per MSBC[5]. The question arises as to who is more precise at recognizing SPMS; three neurologists who make their judgments selectively based on formal criteria extracted from clinical notes or the treating neurologists who evaluate patients and their disease dynamics more frequently. It is a conceptual problem because diagnosing SPMS is a heuristic construct using characteristics and dynamics of clinical deterioration as a surrogate

marker for a new phase in this autoimmune disease when neurodegenerative mechanisms simultaneously overtake inflammatory disease activity.

Furthermore, the present study identified another methodological drawback of the MSBC; a significant test-retest variability. 29.4% of patients who transitioned to SPMS and 3.6% who did not transition to SPMS did not fulfil the MSBC at a later visit because of a decrease in EDSS or its functional scores. Another methodological problem in this context is that the MSBC are not able to discriminate between progression independent of relapse activity (PIRA) and the "true beginning of a progressive MS"[15,16]. This is further complicated by the fact that neurodegeneration is not a static process and prolonged alternations between progression and stability may occur driven by a spectrum of overlapping pathological and reparative or compensatory processes[17].

Further divergent factors between the MSBase and the NTD population that can impact differences in these results include: (i) the different density of clinical visits (1.7 vs 3.5 P/A in group 1 and 5.2 P/A in group 2, respectively); (ii) the use of an estimated time of diagnosis of SPMS (mean 6.9 years in MSBase) vs a captured in-time documentation (mean 14.3 years in the NTD registry); (iii) the difference in annualized relapse rates in the year before SPMS diagnosis (mean 0.26–0.28 in patients diagnosed by the five shortlisted operational definitions versus 0.42, respectively); and (iv) age at SPMS diagnosis (not reported in the MSBase vs 51.9 years in the NTD registry).

This study's limitation is the disbalance in group sizes. Its strength is its size, with 194 patients converting to SPMS and a non-converting group of 9.506 patients with RRMS included for analysis. A further strength of this study is the structured and standardized approach of data collection using a defined data set per visit as part of a comprehensive digital platform by trained, certified neurologists, which supports high data source quality.

In conclusion, the MSBC do not enable earlier SPMS diagnosis compared to clinical evaluation by treating neurologists in a dataset of German neurology practises. The development and validation of algorithms for the transition from RRMS to SPMS is not straightforward due to the lack of sensitive instruments or biomarkers for capturing neurodegeneration that could help better define a threshold value from which neurodegeneration predominates the previous inflammatory course of MS. Nevertheless, the use of operationalized criteria is conceivable for the development of a graded probability-based algorithm that could help neurologists to predict disease progression.

Study Funding

This study was funded by NeuroTransData. JS was financially supported by a "Welcome Back" grant from the Medical Faculty of the University Duisburg-Essen, Germany.

Disclosure

S. Braune: received honoraria for clinical services from the Kassenärztliche Vereinigung Bayern und private health insurances, for clinical studies and lecturing from Biogen, CSL Behring, Novartis, Merck, Roche and Sanofi. He received honoraria for consulting from NeuroTransData and also as board member. E. Karamasioti Eleni and P. van Hoevell are employees of Rewoso, Zürich, Switzerland. A. Bergmann received consulting fees from advisory board/speaker/other activities for NeuroTransData. J. Skuljec received honoraria for lecturing from Merck and Sanofi, and travel grant from Novartis and Sanofi. A. Siva received research grants from The Turkish Multiple Sclerosis Society, and research grants from The Scientific and Technological Research Council Of Turkey & Istanbul University-Cerrahpasa Research Support Funds; honoraria or consultancy fees for participating to advisory boards, giving educational lectures and/or travel and registration coverage for attending scientific congresses or symposia from F. Hoffmann-La Roche Ltd, Novartis, Sanofi-Genzyme, Merck-Serono, Teva, Biogen Idec/Gen Pharma of Turkey, Alexion, and Abdi Ibrahim Ilaç, Turkey. R. Pul received honoraria for lecturing and consulting from Alexion, Bayer Healthcare, Biogen, Bristol-Mayers Squibb, Horizon, MedDay, Merck Serono, Mylan, Novartis, Roche, Sanofi Genzyme, and research funding from Teva, Merck Serono, and Novartis.

Acknowledgements

Authors thank all neurologists contributing to the data collection in the NeuroTransData registry. We also thank Dr. Nicholas Winzer for editing the manuscript for non-intellectual content.

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Group	Diagnosis of SPMS	Explanation
1	No transition to SPMS	The MSBC did not diagnose SPMS during the observation period; the FSD date is assumed to be after the physicians' FSD date
	Transition to SPMS	SPMS was diagnosed by both physicians and MSBC within the observation period. The MSBC-based calculated FSD date might be earlier, later, or at the same time as compared to clinical evaluation by physicians.
2	No transition to SPMS	Physicians and the MSBC are in agreement that there was no transition to SPMS during the observation period
	Transition to SPMS	Only the MSBC have diagnosed transition to SPMS; the MSBC-based FSD date is assumed to be earlier than the physicians-based FSD date.

Table 1: Classification of patients. Group 1: patients who transitioned from relapsing-remitting multiple sclerosis (RRMS) to secondary progressive multiple sclerosis (SPMS). Group 2: patients remaining with RRMS diagnosis during the observation period. Thus, FSD dates by physicians were not available for this group. MSBC = MSBase criteria; FSD = first SPMS diagnosis date.

		Patient populations	
Variable	**statistic**	**Group 1**	**Group 2**
Gender	Male	51 (26%)	2488 (26%)
	Female	143 (74%)	7018 (74%)
Total number of visits in observation period	N	194	9506
	Mean (SD)	32.53 (±15.49)	18.63 (±15.79)
	Median	29	14
	Q1 - Q3	20-41	6-27
	min, max	8, 83	2, 132
Visits per year in observation period	N	194	9506
	Mean (SD)	3.54 (±1.2)	5.16 (±8.89)
	Median	3.4	3.98
	Q1 - Q3	2.67-4.19	3.15-5.11
	min, max	1.15, 8.98	1.88, 365.25
Length of observation period [years]	N	194	9506
	Mean (SD)	9.47 (±4.08)	4.74 (3.77)
	Median	9.07	3.87
	Q1 - Q3	6.5-11.31	1.55-7.24
	min, max	2.39, 23.58	0.01, 24.83
Number of relapses during one year prior to FSD date	N	194	*NA*
	Mean (SD)	0.41 (±0.74)	
	Median	0	
	Q1 - Q3	0-1	
	min, max	0, 4	
Age on FSD date [years]	N	194	*NA*
	Mean (SD)	51.92 (±9.89)	
	Median	51.77	
	Q1 - Q3	45.58-57.53	
	min, max	29.12, 83.2	
EDSS on FSD date	N	194	*NA*
	Mean (SD)	4.82 (±1.51)	
	Median	5	
	Q1 - Q3	4-6	
	min, max	0, 9	
Disease duration prior to FSD date [years]	N	194	*NA*
	Mean (SD)	14.33 (±8.75)	
	Median	12.69	
	Q1 - Q3	7.63-19.62	
	min, max	1.19, 47.36	
DMT on FSD date	No	87 (44.8%)	*NA*
	Yes	107 (55.2%)	

Table 2: Descriptive characteristics of our real-world cohort.

Group 1 consists of patients with relapsing-remitting multiple sclerosis (RRMS) that transitioned to secondary progressive multiple sclerosis (SPMS). In contrast, group 2 contains patients with RRMS who did not progress to SPMS during the observation period (time between the first and the last documented visit). Visits per year were presented as the ratio of the total number of visits and the length of the observation period. Expanded Disability Status Scale (EDSS) on the first SPMS diagnosis (FSD) date was defined as the last EDSS measurement prior to the FSD date. Disease duration on the FSD date was considered the time from the date of RRMS diagnosis. DMT = disease-modifying treatment; SD = standard deviation; NA = non-applicable

	Group 1 patients			Group 2 patients		
Tolerance interval	**3 months**	**6 months**	**P value**	**3 months**	**6 months**	**P value**
Earlier: FSD date of MSBC earlier than CD	28.87%	25.26%	0.493	7.84%	7.84%	1
Later: FSD date of MSBC later later than CD	60.82%	56.7%	0.470	NA	NA	NA
Equal: FSD date of MSBC equal to CD	10.31%	18.04%	0.042	92.16%	92.16%	1
Number of patients [N patients]	194			9506		

Table 3: Comparison of the first secondary progressive multiple sclerosis diagnosis (FSD) dates assessed according to the MSBase criteria (MSBC) and obtained from the clinical diagnosis (CD) by the neurologists, taking into account tolerance interval of either 3 or 6 months within which the FSD dates were considered equal. Group 1: patients that transitioned from relapsing-remitting multiple sclerosis (RRMS) to secondary progressive multiple sclerosis (SPMS). Group 2: Patients with RRMS that did not worsen to SPMS diagnosis during the observation period. NA: not applicable

Group 1		MSBC diagnosis				Performance metrics
		RRMS **n=4986**	**SPMS** **n=1325**	Number of visits n= 6311	Number of NAs	Accuracy 61.38%
Clinical diagnosis	**RRMS**	*True negative* 45.70%	*False positive* 5.31%	3219	735	Specificity 89.59%
	SPMS	*False negative* 33.31%	*True positive* 15.69%	3092	0	Sensitivity 32.02%

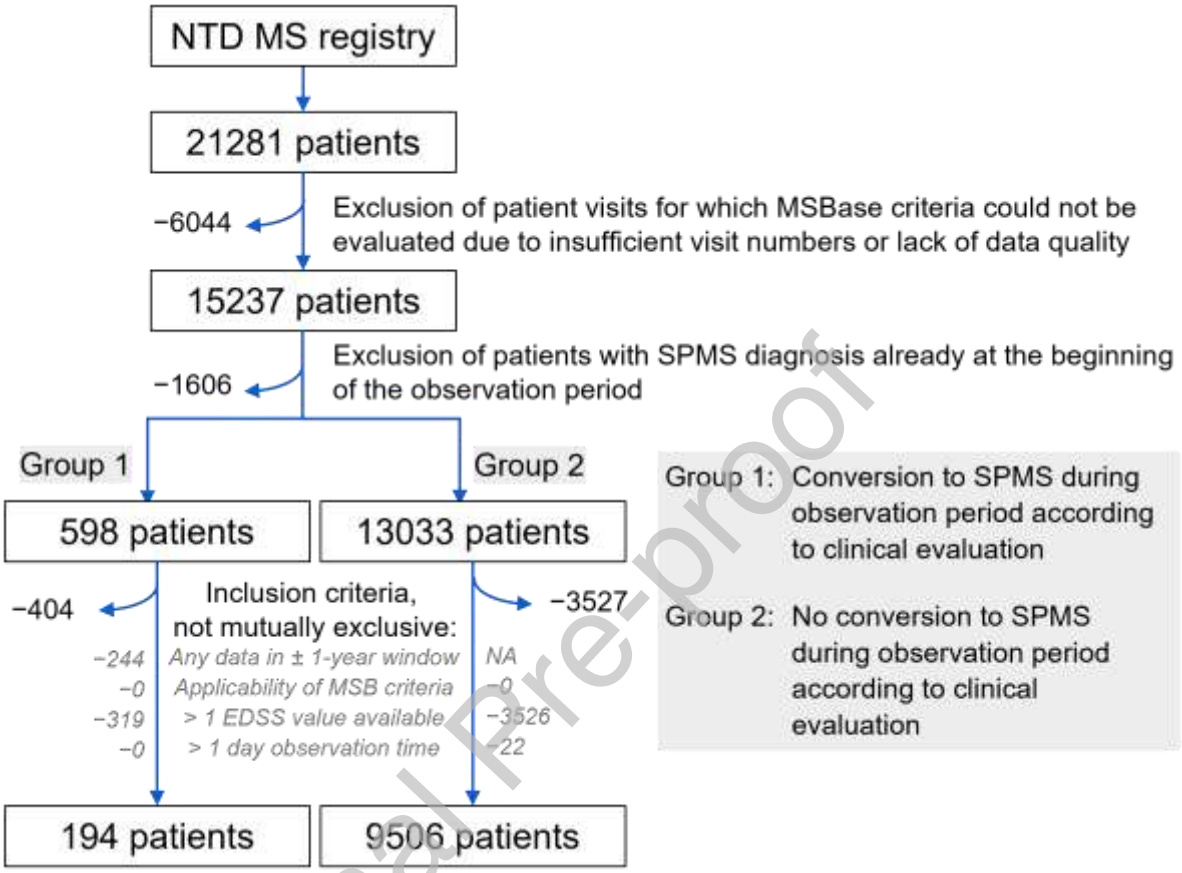
Table 4: Confusion matrix comparing diagnoses obtained by clinical diagnosis (CD) as reference versus the MSBase criteria (MSBC) for patients of group 1 (with transition from RRMS to SPMS). RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis. NA = not applicable

Group 2		MSBC diagnosis				Performance metrics
		RRMS **n=170533**	**SPMS** **n=6577**	Number of visits n=177110	Number of NAs	Accuracy 96.29%
Clinical diagnosis	**RRMS**	*True negative* 96.29%	*False positive* 3.71%	177110	30301	Specificity 96.29%
	SPMS	*False negative* 0%	*True positive* 0%	0	0	Sensitivity NA

Table 5: Confusion matrix comparing diagnoses by clinical diagnosis (CD) as reference versus the MSBase criteria (MSBC) for patients of group 2 (no transition from RRMS to SPMS during the observation period). RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; NA = not applicable.

Figure 1.

Patient flow chart for the NTD MS registry datasets.



Role of Funding Source

This study was funded by the physicians´ network NeuroTransData. JS was financially supported by a “Welcome Back” grant from the Medical Faculty of the University Duisburg-Essen, Germany.

Declaration of Interest Statement

All authors declare that there are no competing interests regarding this research project and manuscript.