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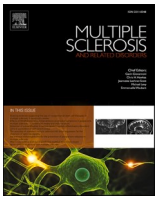

Application of definitions for conversion to secondary progressive MS in a Danish nationwide population

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ABSTRACT

Background: The number of patients with relapsing remitting multiple sclerosis (RRMS) who convert to secondary progressive (SP) MS is uncertain, and with emerging treatment options for SPMS, it is important to identify RRMS patients in transition to the SP phase. The objective of the present study was to characterize clinical parameters and use of disease modifying therapies in patients diagnosed with SPMS and RRMS patients already entered the SP phase by use of the Danish Multiple Sclerosis Registry (DMSR).

Methods: We used a cross-sectional design, including all living patients with MS as of June 30, 2020 from DMSR. First, we applied the MSBase definition of SPMS on all RRMS patients. Second, we applied the slightly modified inclusion criteria from the EXPAND clinical trial on patients with clinically confirmed SPMS and patients with RRMS fulfilling the MSBase definition of SPMS to identify SPMS patients recently progressed who may benefit from treatment with disease modifying therapy. We compared clinical characteristics and disease-modifying therapy use in the different patient groups.

Results: Among patients with clinically confirmed SPMS, application of a slightly modified EXPAND trial inclusion criteria for SPMS (m-EXPAND) captured patients who had converted to SPMS more recently and who had relapsed and initiated high-efficacy treatment more frequently. Moreover, our RRMS patients fulfilling the "SPMS"-criteria according to MSBase and recently progression according to m-EXPAND had similar characteristics and remarkably resembled the SPMS population in the EXPAND trial.

Conclusion: Our results indicate that data-driven diagnostic definitions might help identify RRMS patients at risk for SPMS and we highlight the challenges and reluctance in diagnosing SPMS in clinical practice.

Abbreviations: CNS, Central nervous system; DMSR, Danish multiple sclerosis registry; DMT, Disease-modifying therapy; EDSS, Expanded disability status scale; FS, Functional system; GDPR, General data protection regulation; He, High efficacy; IQR, interquartile range; Me, Moderate efficacy; m-EXPAND, Modified criteria used in the randomized clinical trial, EXploring the efficacy and safety of siponimod in PAtients with secoNDary progressive multiple sclerosis; MS, Multiple sclerosis; MSBase definition, A data-driven definition of conversion to SPMS as proposed by the MSBase Registry; RRMS, Relapsing remitting multiple sclerosis; SPMS, Secondary progressive multiple sclerosis; Yrs, Years.

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1. Introduction

Multiple sclerosis (MS) is an immune mediated disease of the central nervous system (CNS) characterized by inflammation, demyelination and axonal degeneration and is among the most common causes of neurological disability in young adults in the Western world (Reich et al., 2018). Accurate descriptions of the clinical disease course of MS are important for advising the patients on treatment decisions and prognosis.

At onset, most patients have relapses with focal neurological deficits, followed by complete or partial remission; i.e. relapsing-remitting MS (RRMS) (Lublin et al., 2014). This phase is believed to be driven by focal perivascular inflammatory demyelination involving lymphocytes and monocytes crossing the blood-brain-barrier from the circulation into the CNS. In 2% - 5% of patients per annum and typically after 10 - 15 years, patients may convert to a secondary progressive MS (SPMS) disease course, characterised by gradually accumulating irreversible disability in ambulatory, autonomic and cognitive functions (Rovaris et al., 2006; Vukusic and Confavreux, 2003; Weinshenker et al., 1989). This phase is thought to be driven by chronic and CNS-compartmentalized inflammation, slow rim-like plaque expansion and neuroaxonal degeneration (Bramow et al., 2010; Frischer et al., 2015, 2009).

Clinicians lack standardised criteria to define conversion from RR to SPMS and evidence on annual frequency of conversion to SPMS is limited (Scalfari et al., 2014; Tremlett et al., 2008; Weinshenker et al., 1989). A study from the MSBase Registry found that using criteria based on Kurtzke Expanded Disability Status Scale (EDSS) scores and EDSS worsening, the conversion to SPMS could be established several years before the clinicians labelled the disease course as SPMS (Lorscheider et al., 2016). With emerging treatment options for SPMS, it has become a matter of growing clinical concern how to identify RRMS patients at risk and when to diagnose conversion from RRMS to SPMS. Indeed, results from the randomized clinical trial (RCT) "EXploring the efficacy and safety of siponimod in PAtients with secoNDary progressive multiple sclerosis" ("EXPAND") (Kappos et al., 2018), indicate that siponimod may delay disability progression in patients with SPMS with or without relapses (Cree et al., 2020). Therefore, tools to identify patients eligible for siponimod and other therapies targeted for SPMS patients are needed. Studies of demographic and clinical data in registries such as the Danish Multiple Sclerosis Registry (DMSR) may help to provide such tools (Lorscheider et al., 2016; Manouchehrinia et al., 2019).

Most previous studies assessing diagnostic predictors of conversion to SPMS used clinically defined SPMS as outcome (Confavreux et al., 1980; Trojano et al., 1995; Vukusic and Confavreux, 2003). Consequently, using data from the DMSR, the objective of the present study was to characterize clinical parameters and disease-modifying therapy (DMT) use in patients with clinically assigned SPMS and those fulfilling the MSBase diagnostic definition for being in the SPMS course (Lorscheider et al., 2016). Furthermore, we aimed to compare SPMS patients with vs. without fulfillment of slightly modified inclusion criteria for SPMS in the EXPAND clinical trial.

2. Materials and methods

2.1. Study population

We used prospectively collected data from the nationwide population-based DMSR (Magyari et al., 2020). The DMSR regularly collects data on all Danish patients with MS during clinical visits at 13 departments of Neurology/MS clinics in public hospitals, which are exclusively authorized to prescribe and dispense DMT. It is mandatory to record data on treatments with DMT. Thus, data on patients treated with DMT is nearly complete. During visits starting from the diagnosis of MS, demographic, clinical and paraclinical data are recorded including EDSS score, Functional System (FS) score, relapses and adverse events. The registry is supplemented with data on death and emigration from The Danish Civil Registration System (Pedersen, 2011) by use of the 10-digit personal identification number attached to every citizen with residence in Denmark.

2.2. Study design

We applied a descriptive cross-sectional study design with date of data collection as index date (June 30, 2020) of all living patients with MS (Fig. 1).

We then stratified our MS population into SPMS and RRMS as assigned by the treating neurologist as of June 30, 2020 and applied the different diagnostic definitions.

In the group with a clinical diagnosis of SPMS, i.e. as assigned in the DMSR database by an MS-neurologist, we applied a slightly modified version of the EXPAND study inclusion criteria (m-EXPAND) to define patients with evidence of progression within the past two years (Fig. 2) (Kappos et al., 2018) and who may benefit from treatment with DMT.

Compared to the original EXPAND study, we defined the m-EXPAND criteria as presented in Fig. 2 that also included patients older than 60 years and those with relapses three months prior to index date, and required an EDSS of at least 3.0 at time of progression:

1) An EDSS from 3.0 to 6.5 (both inclusive) (at index date +/- six months), and
2) EDSS progression within the last two years before data extraction, defined as EDSS progression of 1 point or more in patients with an EDSS score of less than 6.0 or $\geq$ 0.5 point in patients with EDSS score $\geq$ 6.0, in the absence of relapses six months prior to progression and EDSS $\geq$ 3.0 at time of progression
3) Disability progression as described above confirmed over => six months

To capture patients with RRMS at high risk for conversion to SPMS, we first applied the MSBase diagnostic definition published by the MSBase collaboration (MSBase SPMS) (Lorscheider et al., 2016). The MSBase definition identified RRMS patients already progressed to the SP phase with an accuracy of 87%. Second, we applied the m-EXPAND criteria for recently progression on the RRMS patients fulfilling the MSBase definition. We applied the MSBase definitions on the RRMS population as described below and illustrated in Fig. 3.

We did not take the pyramidal FS score into consideration in the MSBase SPMS definition due to 18% missing values.

1) An increase in EDSS by $\geq$1.5 points if the last EDSS before conversion to SPMS was 0, an increase by $\geq$1.0 point if the EDSS was between 1.0 and 5.5, or an increase by $\geq$0.5 points if the EDSS was above 5.5 in the absence of relapses 30 days prior to progression
2) A minimum EDSS score of 4.0 at time of progression
3) Confirmation of disability progression over a minimum of three months

To assess different aspects of use of DMT in SPMS patients captured by the diagnostic definitions, we analysed:

1) Prevalent use of DMT (i.e. use at index date and regardless of treatment duration) in
   a SPMS patients, depending on fulfillment of the m-EXPAND criteria
   b MSBase "SPMS" patients depending on fulfillment of the m-EXPAND criteria
2) Recent commencement of DMT in patient diagnosed with SPMS by the treating neurologist depending on whether the m-EXPAND criteria for progression were additionally fulfilled within two years before the index date. Recent commencement of DMT was defined as DMT start within three years before the index date for

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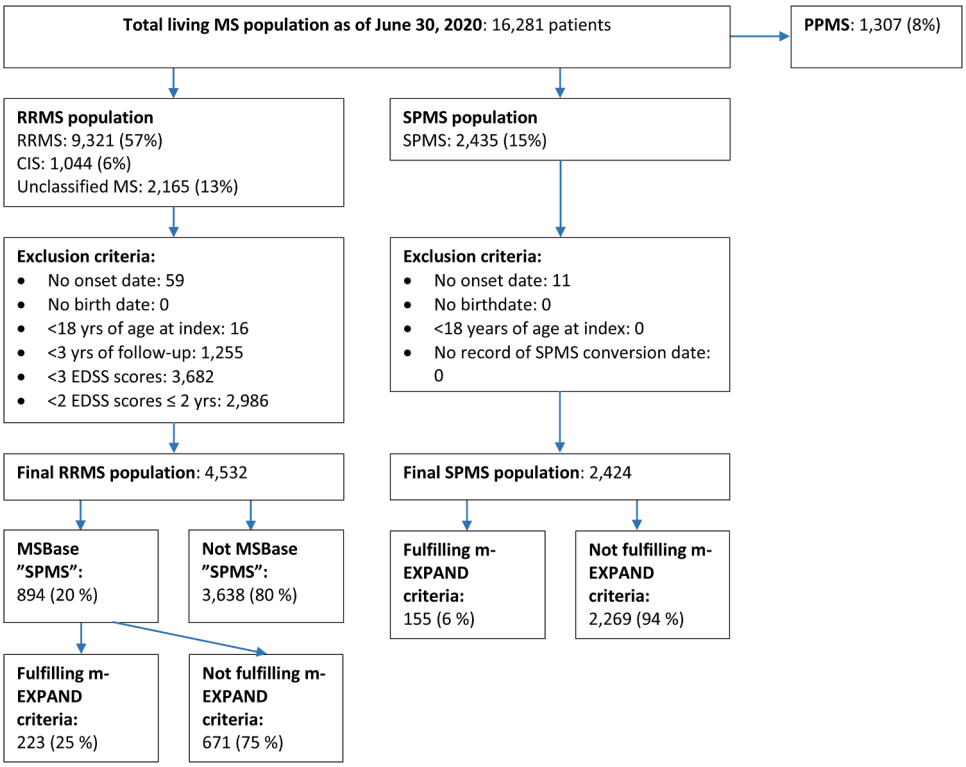

Fig. 1. Flowchart of the RRMS and SPMS population, respectively, including sub-groups of those fulfilling the diagnostic definitions.

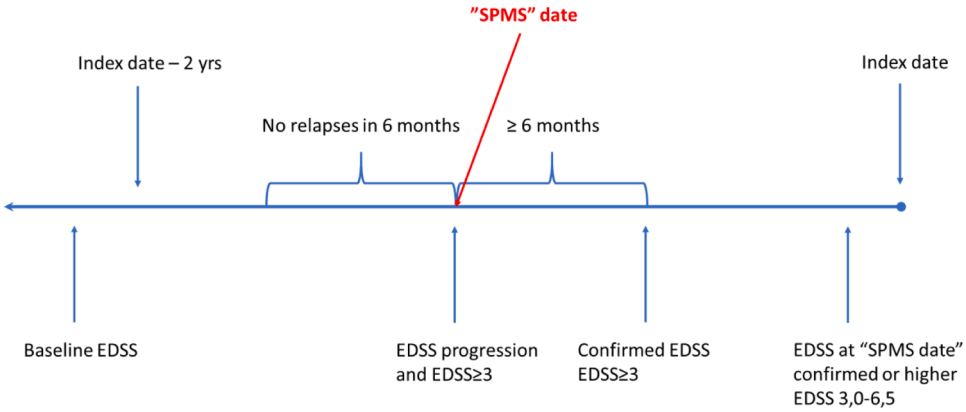

Fig. 2. Illustration of the modified EXPAND criteria (i.e. "retrospective algorithm").

all SPMS patients and thus reflects the choice of treatment at the time of SPMS conversion or later assigned by the neurologist in the same period of time.

We did not consider the following treatments in our analyses: Hematopoietic stem cell transplantation, azathioprine, intravenous immunoglobulins, and methylprednisolone (about 6% of the total number of treatments recorded in DMSR).

2.3. Statistical analyses

Statistical analyses were carried out using SAS Enterprise Guide 7.1 and R 3.5.1. Baseline demographic and clinical characteristics of the cohort at index date are presented as numbers with their percentages and medians with interquartile range (IQR).

3. Results

3.1. Clinical vs. MSBase spms populations

In total, 2424 patients with clinical SPMS and 4532 RRMS patients fulfilled the inclusion criteria (Table 1 and Fig. 1). Of the 4532 RRMS patients, 894 (20%) fulfilled the MSBase definition of having converted to SPMS. Compared to clinically assigned SPMS patients, patients with MSBase SPMS were younger at onset (31 vs 34 years), diagnosis (36 vs 40 years), SPMS conversion (44 vs 50 years) and index date (52 vs 61), had shorter disease duration at time of SPMS conversion (10 vs 14 years), more relapses after SPMS conversion (52 vs 17%), were more often treated with DMT (88 vs 32%) – especially high efficacy DMT (62 vs 18%), but the EDSS score was only 0.5 point lower at SPMS conversion (EDSS 4.5 vs 5.0) and 1.0 point lower at index date (EDSS 5.0 vs 6.0).

One hundred and fifty-five (6%) of the 2424 clinical SPMS patients

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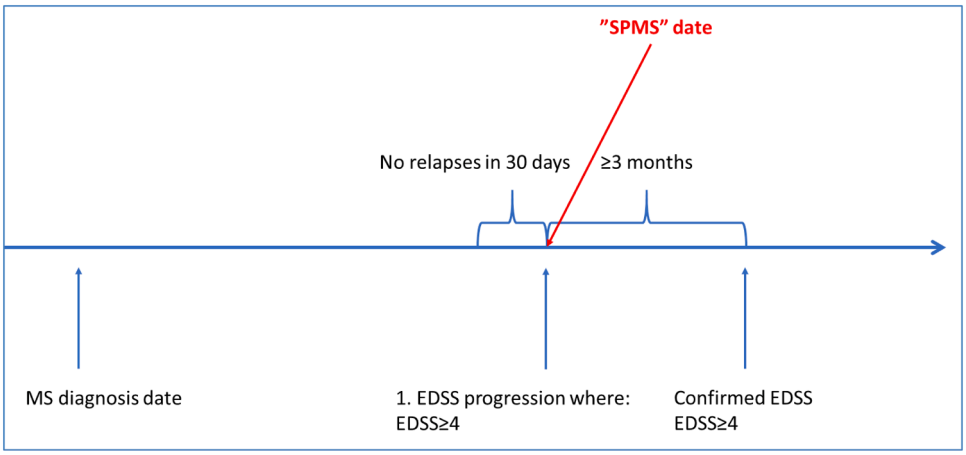

Fig. 3. Illustration of the MSBase definitions (i.e. "prospective" algorithm).

fulfilled the m-EXPAND criteria for progression in the past two years, whereas 223 (25%) MSBase SPMS patients fulfilled the m-EXPAND criteria (Table 2).

3.1.1. Clinical SPMS patients

We found remarkable differences when we compared the 155 SPMS patients fulfilling the m-EXPAND criteria for progression in the past two years to the 2269 patients not fulfilling the m-EXPAND criteria (Table 2). The patients fulfilling the m-EXPAND criteria were younger (55 vs 61 years), had shorter disease duration (19 vs 24 years), had slightly lower EDSS at SPMS conversion (EDSS 4.5 vs 5.0), more relapse activity after SPMS conversion (20% vs 17%) and in the 2 years pre-index (17 vs 5%), and received DMT more frequently at index date (67 vs 30%) than the patients not fulfilling the m-EXPAND criteria. Furthermore, the higher DMT frequency in the patients fulfilling the m-EXPAND criteria was accounted for by a markedly higher use of high-efficacy DMT (46 vs 16%) including particularly B-cell depleting agents (Table 2 and 3).

3.1.2. MSBase-"SPMS" patients

Among the 894 MSBase-"SPMS" patients, 223 patients (5% of all RRMS) also fulfilled the m-EXPAND criteria for progression in the preceding two years (Table 2). Compared to MSBase-"SPMS" patients not fulfilling the m-EXPAND criteria, patients fulfilling the criteria were slightly younger at index date (50 vs 52 years), had more recently converted to MSBase-"SPMS" (2 vs 7 years), had higher EDSS (EDSS 5.5 vs 4.5) and had more relapse activity in the two years pre-index (28 vs 20%). However, 62% of both groups received high efficacy DMT at index date.

Compared to patients with clinically assigned SPMS fulfilling the m-EXPAND criteria, the MSBase-"SPMS" patients fulfilling the criteria were more often female (70 vs 65%), were younger (50 vs 55 years), had shorter disease duration (17 vs 19 years), had more relapse activity in the two years pre-index (28 vs 17%) and were more likely to be on high efficacy DMT at index date (62 vs 46%).

3.2. Use of disease-modifying therapy in SPMS

Proportions of currently treated patients ranged from 30% of clinical SPMS patients not fulfilling the m-EXPAND criteria to 88% of MSBase-"SPMS" patients not fulfilling the m-EXPAND criteria (Table 3).

Patients fulfilling the m-EXPAND criteria more frequently received anti-CD20 therapy, in both clinical SPMS (30%) and MSBase-"SPMS" (30%). Fingolimod and natalizumab were also the second and third most preferred DMT among both groups of patients fulfilling the m-EXPAND criteria. The most frequently used DMT for clinical SPMS patients not fulfilling m-EXPAND criteria were injectable platform therapies (27%) followed by fingolimod (21%) and anti-CD20 therapies (16%). For MSBase-"SPMS" patients not fulfilling the m-EXPAND criteria, the most frequently used DMT was fingolimod (22%) followed by natalizumab (21%) and anti-CD20 therapies (20%).

3.3. Initiation of disease-modifying therapy in SPMS

Fifty-eight of the 155 SPMS patients fulfilling the m-EXPAND criteria (37%) had recently started a new DMT (i.e. within three years from index date), whereas this was the case for only 11% ($N = 260$) of the SPMS patients not fulfilling the m-EXPAND criteria (Table 4). Compared to clinical SPMS not fulfilling the m-EXPAND criteria, the clinical SPMS patients fulfilling these criteria had more frequently initiated anti-CD20 monoclonal antibody treatment (57 vs 47%) although this type of therapy was by far the most used in both groups.

4. Discussion

In the present study, we applied a slightly modified inclusion criteria from the EXPAND trial (Kappos et al., 2018) on the Danish nationwide MS population with a diagnosis of clinical SPMS assigned by an MS-neurologist and RRMS patients fulfilling the MSBase diagnostic definition for conversion to SPMS (Lorscheider et al., 2016). The m-EXPAND criteria identify patients with recent worsening on the EDSS score not explained by a recent relapse. The MSBase SPMS definition captured ~20% of Danish RRMS patients at putative high risk of converting to SPMS or who may already have converted to SPMS. These patients were younger, with shorter disease duration, with more disease activity, yet remarkably had only slightly less disability than patients with a clinically assigned SPMS diagnosis. We then applied the modified EXPAND criteria on the clinical SPMS population and the RRMS population fulfilling the MSBase-"SPMS" criteria in order to capture patients with recent progression in the absence of relapses. In these populations, the m-EXPAND criteria captured patients who were equally frequently treated with B-cell depleting therapy.

Recently published data from the Italian Multiple Sclerosis Registry argue against decision-making in SPMS based solely on discrete definitions: A data driven algorithm identified fewer SPMS patients than experienced MS-neurologists (Iaffaldano et al., 2020). Furthermore, their algorithm identified older, more disabled, faster progressing patients than the neurologists. This is partly in contrast to our study, where the MSBase definition identified an additional 20% patients with possible SPMS who were younger than patients with a clinical SPMS diagnose and appeared to have aggressive disease. The m-EXPAND criteria captured patients who were more likely to have recently

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Table 1
Clinical and demographic characteristics of the population stratified according to diagnosis of SPMS or RRMS and - for RRMS patients - fulfillment of the MSBase definition.

	Total SPMS population	RRMS population		
		Total RRMS population	MSBase "SPMS"	Not MSBase "SPMS"
Total number of patients	2424	4532	894 (20)	3638 (80)
Females, n (%)	1604 (66%)	3279 (72%)	641 (72%)	2606 (72%)
Age at index date, yrs, median (IQR)	61 (54–68)	47 (39–54)	52 (45–58)	45 (38–53)
Age at conversion to SPMS, yrs, median (IQR)	50 (43–57)	–	44 (37–51)	–
Age at clinical onset, yrs, median (IQR)	34 (27–42)	32 (25–39)	31 (25–40)	32 (25–39)
Age at MS diagnosis, yrs, median (IQR)[1]	40 (32–48)	35 (27–42)	36 (29–44)	35 (27–42)
Calendar year at clinical onset, median (IQR)	1996 (1988–2002)	2007 (2001–2012)	2002 (1996–2008)	2009 (2003–2013)
Calendar year at MS diagnosis, median (IQR)	2001 (1995–2007)[1]	2010 (2005–2014)	2005 (2000–2011)	2011 (2006–2014)
Calendar year at SPMS diagnosis, median (IQR)	2011 (2005–2017)	–		–
Disease duration from clinical onset until SPMS conversion, yrs, median (IQR)	14 (7.5–22)	–	10 (5–16)	–
Disease duration from clinical onset until index date, yrs, median (IQR)	24 (18–32)	13 (8–19)	18 (12–24)	11 (7–17)
Yrs since MS diagnosis until SPMS conversion, yrs, median (IQR)	9 (3–16)[1]	–	6 (3–11)	–
Yrs since MS diagnosis until index date, yrs, median (IQR)	19 (13–25)[1]	10 (6–15)	15 (9–20)	9 (6–14)
Time since SPMS conversion, yrs, median (IQR)	7 (3–13)	–	6 (3–10)	–
EDSS score at SPMS conversion	5.0 (3.5–6.5)[2]	–	4.5 (4.0–5.5)	–
(+/- 13 months), median (IQR)				
EDSS score at index (if any <2 yrs from index date), median (IQR)	6.0 (4.0–6.5)[3]	2.0 (1.5–3.5)	5.0 (3.5–6.0)	2.0 (1.0–2.5)
Patients with relapses after SPMS conversion, n (%)	418 (17%)[4]	–	466 (52%)	–
Patients with relapses in the 2 yrs pre-index, n (%)	138 (6%)[4]	764 (17%)	197 (22%)	567 (16%)
Time spent on active DMT treatment in % of time form diagnose until SPMS diagnosis/% of disease duration, median (IQR)	14 (0–55)	73 (49–88)	68 (46–85)	74 (51–89)
DMT use at index date, n (%):				
No DMT	1642 (68%)	493 (11%)	110 (12%)	383 (11%)
meDMT	348 (14%)	1785 (39%)	228 (26%)	1557 (43%)
heDMT[5]	434 (18%)	2254 (50%)	556 (62%)	1698 (47%)

For the RRMS population, the term SPMS is related to the MSBase definitions used for conversation to SPMS.
DMT, disease modifying therapy; EDSS, expanded disability status scale; heDMT, high efficacy DMT; IQR, interquartile range; meDMT, moderate efficacy DMT; SPMS, secondary progressive multiple sclerosis; yrs; years.
[1] Numbers with missing MS diagnosis date, $N = 215$.
[2] Numbers with missing EDSS at SPMS conversation within +/- 13 months, $N = 852$.
[3] Numbers with missing EDSS at index date, $N = 841$.
[4] Numbers with missing values on relapses, $N = 215$.
[5] Includes fingolimod, alemtuzumab, rituximab, cladribine, methotrexate, mitoxantrone, ocrelizumab, treosulfan, natalizumab and daclizumab. Alemtuzumab, natalizumab and ocrelizumab are considered an ongoing treatment once it is administrated, unless there is a record of discontinuation of treatment.

commenced and to be under current B-cell depleting therapy, although anti-CD20 drugs were also used in ~16% of SPMS patients who did not fulfill the m-EXPAND criteria. This is likely because the EXPAND criteria mainly capture patients who have recently progressed and not necessarily those with relapses or radiological disease activity.

Compared to patients included in the EXPAND trial (Kappos et al., 2018), our 155 clinical SPMS patients fulfilling the m-EXPAND criteria were older, had a longer disease duration and fewer relapses prior to the index date. This might reflect reluctance or a delay in SPMS diagnosis in clinical practice. Such reluctance could be due to fear of diagnosing a condition for which no approved and routinely reimbursed DMT exists. Interestingly, our subgroups of RRMS patients fulfilling both the MSBase SPMS definition and the m-EXPAND criteria were surprisingly comparable to the population labelled "typical SPMS" in the original EXPAND trial. 72% were relapse-free within 2 years before the index date

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Table 2
Clinical and demographic characteristics of patients with either clinical or MSBase "SPMS" stratified according to fulfillment of EXPAND criteria.

	Clinical SPMS ($N = 2424$) according to m-EXPAND criteria		MSBase "SPMS" ($N = 894$) according to m-EXPAND criteria	
	Yes	No	Yes	No
Total number of patients, (%)	155 (6%)	2269 (94%)	223 (25%)	671 (75%)
Females, n (%)	90 (65%)	1504 (66%)	155 (70%)	486 (72%)
Age at index date, yrs, median (IQR)	55 (48–63)	61 (54–68)	50 (44–55)	52 (45–59)
Age at conversion to SPMS, yrs, median (IQR)	51 (42–58)	50 (43–57)	45 (37–51)	44 (36–51)
Age at clinical onset, yrs, median (IQR)	33 (27–43)	34 (27–42)	30 (24–38)	32 (25–40)
Age at MS diagnosis, yrs, median (IQR)	40 (31–50)	40 (32–48)	35 (28–42)	36 (29–44)
Calendar year at onset, median (IQR)	2001 (1994–2008)	1996 (1988–2002)	2003 (1997–2008)	2002 (1996–2007)
Calendar year at MS diagnosis, median (IQR)	2006 (2000–2012)	2001 (1995–2007)	2007 (2000–2012)	2005 (2000–2010)
Disease duration from clinical onset until SPMS conversion, yrs, median (IQR)	15 (8–21)	14 (7–21)	12 (7–18)	10 (5–15)
Disease duration from clinical onset until index date, yrs, median (IQR)	19 (12–26)	24 (18–32)	17 (12–23)	18 (13–24)
Yrs since MS diagnosis until SPMS conversion, yrs, median (IQR)	9 (4–15)	9 (2–16)	8 (4–13)	6 (3–10)
Yrs since MS diagnosis until index date, yrs, median (IQR)	14 (8–20)	19 (13–25)	13 (8–20)	15 (10–20)
Time since SPMS conversion, yrs, median (IQR)	2 (1–5)	8 (3–13)	2 (1–8)	7 (4–11)
EDSS score at SPMS conversion (+/- 13 months), median (IQR)	4.5 (3.5–6.0)	5.0 (3.5–6.5)	5.0 (4.0–5.5)	4.5 (4.0–5.5)
EDSS score at index (<2 yrs from index date), median (IQR)	6.0 (4.5–6.5)	6.0 (4.0–7.0)	5.5 (4.5–6.0)	4.5 (3.5–6.0)
Patients with relapses after SPMS conversation, n (%)	31 (20%)	387 (17%)	90 (40%)	376 (56%)
	27 (17%)	111 (5%)	62 (28%)	135 (20%)
Patients with relapses in the 2 yrs pre-index, n (%)	54 (16–77)	10 (0–53)	65 (45–82)	69 (47–86)
Exposure to DMT (% of time from diagnose until index date/disease duration), yrs, median (IQR)				
DMT use at index date, n (%):				
No DMT	50 (33%)	1592 (70%)	32 (14%)	78 (12%)
meDMT	33 (22%)	315 (14%)	52 (23%)	176 (26%)
heDMT[1]	72 (46%)	362 (16%)	139 (62%)	417 (62%)

For the RRMS population, the term SPMS is related to the MSBase definitions used for conversation to SPMS.
DMT, disease modifying therapy; EDSS, expanded disability status scale; heDMT, high efficacy DMT; IQR, interquartile range; meDMT, moderate efficacy DMT; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; yrs; years.
[1] Includes fingolimod, alemtuzumab, rituximab, cladribine, methotrexate, mitoxantrone, ocrelizumab, treosulfan, natalizumab and daclizumab. Alemtuzumab, natalizumab and ocrelizumab are considered an ongoing treatment once it is administrated, unless there is a record of discontinuation of treatment.

compared to 62–63% in the EXPAND trial; disease duration was 17 years compared to 16.2–17.1 years in the EXPAND trial; and age at index date was 50 years compared to 49 years in the EXPAND trial (both placebo and Siponimod group). These similarities between our RRMS patients who fulfill both the MSBase SPMS definition and m-EXPAND criteria for SPMS i.e. as compared to the original EXPAND study population are in further support of a reluctance in diagnosing SPMS. In addition to such reluctance, genuine diagnostic uncertainty is likely to cause further delay and underestimation of the number of SPMS patients identified in the DMSR. As no major skew in the clinical characteristics was introduced by the m-EXPAND criteria, these criteria might help to reliably accelerate the identification of patients with RRMS at currently high risk for conversion to SPMS.

Taken together, our data underscore the relevance and potential of data-driven diagnostic definitions as a real-world diagnostic tool for a timely and more accurate SPMS diagnosis. Despite such potential, all known data-driven diagnostic definitions of conversion to SPMS have limitations: They all aim to detect the time of conversion to SPMS using the commonly available categorical clinical data such as relapses and ordinal/semi-quantitative scores such as the EDSS and FS-scores.

However, a clinical diagnosis of SPMS also involves several clinical and paraclinical parameters assessed during clinical visits not routinely registered in registries and databases. Such parameters include subtly increasing deficits in ambulation, cognitive function and upper extremity function, which might evade detection on the EDSS as well as MRI measures of brain and spinal cord atrophy. In clinical practice, these variables partly depend on thorough and repeated interviews and neurological evaluation and are integrated in a complex decision-making on whether and when to diagnose conversion from RRMS to SPMS. In addition, pathology studies show that in SPMS, active plaques still occur (Elkjaer et al., 2019), albeit often with slowly expanding plaques rather than classic active plaques, and remyelination becomes more incomplete as compared to RRMS (Frischer et al., 2015; Patrikios et al., 2006). Conversely, it was recently suggested that progression

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Table 3
Clinical and demographic characteristics of patients who were on any DMT at the index date (regardless of treatment duration) stratified according to SPMS definition and fulfillment of EXPAND criteria.

	SPMS patients		MSBase "SPMS"	
	Fulfilling m-EXPAND criteria	Not fulfilling m-EXPAND criteria	Fulfilling m-EXPAND criteria	Not fulfilling m-EXPAND criteria
On any DMT at index date disregarding treatment duration	105/155 (68%)[3]	677/2269 (30%)[3]	191/223 (86%)[3]	593/671 (88%)[3]
Characteristics among treated patients (N in sub-group)	$N = 105$	$N = 677$	$N = 191$	$N = 593$
Age at index date, yrs, median (IQR)	53 (47–59)	55 (48–61)	50 (44–55)	52 (45–58)
Age at diagnosis of SPMS, yrs, median (IQR)	49 (43–56)	49 (42–55)	44 (37–50)	44 (37–51)
EDSS score at index (<2 yrs from index date), median (IQR)	6.0 (4.5–6.5)	5.5 (3.0–6.5)[5]	5.5 (4.5–5.5)	4.5 (3.5–6.0)
Disease duration from clinical onset until index date, yrs, median (IQR)	17 (12–23)	20 (14–26)	17 (11–23)	18 (13–24)
Patients with relapses in the 2 yrs pre-index, n (%)	24 (23%)	81 (12%)	53 (28%)	119 (20%)
DMT treatments by efficacy among treated patients				
meDMT, n (% of whole group/% of treated in group)	33 (20%/29%)	315 (21%/41%)	52 (23%/27)	176 (26%/30%)
heDMT, n (%)	72 (51%/71%)	362 (30%/59%)	139 (62%/72)	417 (62%/70%)
DMT treatments, n (%of whole group/% of treated in group):				
Injectable platform therapies[2]	11 (7%/10%)	183 (8%/27%)	11 (5%/6%)	57 (8%/10%)
Teriflunomide	11 (7%/10%)	75 (3%/11%)	25 (11%/13%)	62 (9%/10%)
Dimethyl fumarate	11 (7%/10%)	57 (3%/8%)	16 (7%/8%)	57 (8%/10%)
Natalizumab	14 (9%/13%)	60 (3%/9%)	36 (16%/19%)	124 (18%/21%)
Fingolimod	18 (12%/17%)	141 (6%/21%)	35 (16%/18%)	132 (20%/22%)
Pulsed immune reconstitution therapy	5 (3%/5%)	16 (<1%/2%)	9 (4%/5%)	36 (5%/6%)
Anti-CD20 agents	32 (21%/30%)	111 (5%/16%)	57 (26%/30%)	120 (18%/20%)
Mitoxantrone	0	4 (<1%/<1%)	0	0
Others	3 (2%/3%)	30 (1%/4%)	<3[6]	5 (<1%/<1%)

For the RRMS population, the term SPMS is related to the MSBase definitions used for conversation to SPMS.
DMT, disease modifying therapy; EDSS, expanded disability status scale; heDMT, high efficacy DMT; IQR, interquartile range; meDMT, moderate efficacy DMT; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; yrs; years.
[1] Interferon-beta preparations including peginterferon-beta 1a and glatiramer acetate.
[2] Non-approved experimental drugs (Methotrexate and Treosulfan).
[3] Percentage of the respective population.
[5] Numbers with missing EDSS score, $N = 68$.
[6] Results with 1–2 patients are removed to adhere to GDPR.

Table 4
Clinical and demographic characteristics of clinical SPMS patients recently (i.e. < three years) starting on a new DMT treatment.

	Fulfilling m-EXPAND criteria	Not fulfilling m-EXPAND criteria
Numbers starting on a new DMT < 3 yrs from index date/all SPMS patients in group, N (%)	58/155 (37%)	260/2269 (11%)
Variables for further characterization of patients with SPMS who recently started DMT	$N = 58$	$N = 260$
Age at index date, yrs, median (IQR)	51 (46–57)	54 (46–59)
Age at diagnosis of SPMS, yrs, median (IQR)	47 (41–54)	48 (41–59)
EDSS score at index date, median (IQR)	6.0 (4.5–6.5)	6.0 (3.0–6.5)[4]
Disease duration from clinical onset until index date, yrs, median (IQR)	17 (11–23)	20 (13–25)
Patients with relapses in the 2 yrs pre-index, n (%)	19 (33%)	59 (23%)
DMT treatments by efficacy, n (% of whole group/% of treated within group)[1]:		
meDMT, n	25 (16%/43%)	107 (5%/41%)
heDMT, n	53 (34%/91%)	194 (9%/75%)
DMT treatments, n (% of group /% of newly treated within group)[1]:		
Injectable platform therapies[2]	7 (5%/12%)	46 (2%/18%)
Teriflunomide	8 (5%/14%)	30 (1%/12%)
Dimethyl fumarate	10 (6%/17%)	31 (1%/12%)
Natalizumab	4 (3%/7%)	16 (<1%/6%)
Fingolimod	11 (7%/19%)	38 (2%/15%)
Pulsed immune reconstitution therapy	3 (2%/5%)	6 (<1%/2%)
Anti-CD20 agents	33 (21%/57%)	121 (5%/47%)
Mitoxantrone	0	3 (<1%/1%)
Others	<3[3]	10 (<1%/4%)

DMT, disease modifying therapy; EDSS, expanded disability status scale; heDMT, high efficacy DMT; IQR, interquartile range; meDMT, moderate efficacy DMT; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; yrs; years.
[1] Each patient can have multiple treatments; therefore, the number of treatments can be higher than the number of patients.
[2] Interferon-beta preparations including peginterferon-beta 1a and glatiramer acetate.[3] Non-approved experimental drugs (Methotrexate and Treosulfan) and daclizumab.
[3] Results with 1–2 patients are removed to adhere to GDPR.
[4] Numbers with missing EDSS score, $N = 10$.

independent of relapse activity may be much more common even in typical RRMS than generally appreciated (Kappos et al., 2020). It is unknown to which extent these observations are clinically reflected by more protracted and more poorly remitting relapses in RRMS as disease duration and the risk for SPMS conversion increase. Nonetheless, some MS patients report the experience of rare but protracted relapses. Thus, we cannot exclude that a continuous and gradual conversion from RRMS to SPMS, possibly through rarer and more protracted relapses, add to the complexity and difficulty in diagnosing conversion from RRMS to SPMS. The complexity of the diagnosis of progressive MS is to some extent reflected in the recently revised MS phenotypic classification which allow superimposed relapses and periods of stability in addition to the pathognomonic feature of gradual disability progression (Lublin, 2014; Lublin et al., 2020).

Given the retrospective, cross-sectional and descriptive nature of this study, our data have some limitations. The disease course at index date was assigned for 85% of the total DMSR cohort of 16.281 patients in the DMSR. This could contribute to under-representation of SPMS patients with longstanding disease. Our SPMS prevalence was only ~ 15% out of the total DMSR cohort. In comparison, previous geographically based studies of the MS natural history based on older cohorts have reported a prevalence of SPMS of ~ 27% out of all MS patients (Confavreux et al., 2000). Over time, as many as ~ 66% of RRMS patients may convert to SPMS within a mean of 7 years (Scalfari et al., 2010). These discrepancies to our lower SPMS prevalence could, in part, be accounted for by

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our more frequent use of high-efficacy treatment in recent decades, which in turn could have postponed or even prevented conversion to SPMS in some of our RRMS patients. Nonetheless, due to diagnostic reluctance and delay explained above, we cannot exclude under-diagnosis of SPMS in our cohort. This could have inflated the frequency differences in anti-CD20 treatment among our SPMS patients. However, the m-EXPAND criteria also captured increased use of anti-CD20 therapies among our RRMS patients fulfilling the MSBase SPMS criteria. This suggests that the m-EXPAND criteria generally select for MS-patients with high disease activity and that bias by SPMS under-diagnosis is unlikely to account for our results.

A strength of the study is the nationwide, population-based and nearly complete data source which profits from mandatory data collection during clinical visits for all patients on DMT and for patients with newly diagnosed MS.

In conclusion, we propose further research in including diagnostic definitions as a diagnostic screening tool for systematic real-world application on clinical databases of well-characterised MS patients to accelerate accurate identification of RRMS patients in whom to suspect high risk of conversion to SPMS and in whom to consider a therapeutic strategy which may prevent or postpone conversion to SPMS or, if converted, slow progression.

Role of the funding source

This work was supported by Novartis Denmark. The sponsor reviewed the final draft manuscript for submission, but had no role in study design, in the collection, analysis and interpretation of data, and in the writing of the report.

Availability of data and material

Because of data protection regulation, data cannot be shared directly by the authors. Data is accessible to authorized researchers after application to the Danish Health Data Authority and the board of the Danish Multiple Sclerosis Group.

Ethics approval

Ethics approval is not required in Denmark for studies based on national health registries. Approval to store and analyze data was given by the Capital Region of Denmark under the Danish Data Protection Agency (journal no. P-2019–734).

Consent to participate

Consent to participate is not required in Denmark for studies based on national health registries.

CRediT authorship contribution statement

Tine Iskov Kopp: Conceptualization, Formal analysis, Methodology, Writing – original draft. **Stephan Bramow:** Investigation, Writing – review & editing. **Zsolt Illes:** Investigation, Writing – review & editing. **Matthias Kant:** Investigation, Writing – review & editing. **Claudia Kristensen:** Investigation, Writing – review & editing. **Peter Vestergaard Rasmussen:** Investigation, Writing – review & editing. **Finn Sellebjerg:** Conceptualization, Investigation, Writing – review & editing. **Melinda Magyari:** Conceptualization, Funding acquisition, Methodology, Resources, Investigation, Writing – review & editing.

Declaration of Competing Interest

T. I. Kopp has served on scientific advisory board from Novartis and received support to congress participation from Biogen. S. Bramow received financial support for congress participation and consultancy honoraria from Biogen. Z. Illes has served on scientific advisory boards, served as a consultant, received support for congress participation, received speaker honoraria, and received research support among others from Biogen, Merck-Serono, Sanofi-Genzyme, Novartis, Roche, Lundbeckfonden, Alexion. M. Kant has nothing to declare. C. Kristensen has served on scientific advisory board for Biogen, Sanofi, Roche, Novartis and Merck, has received honoraria for lecturing from Biogen and Merck and has received support for congress participation from Biogen and Roche. P.V. Rasmussen has served on scientific advisory board for Biogen, Sanofi, Roche, Novartis, Merck, and Alexion, has received honoraria for lecturing from Biogen, Merck, Novartis, Roche, has received support for congress participation from Biogen, Genzyme, Roche, Merck, Novartis. F. Sellebjerg has served on scientific advisory boards for, served as consultant for, received support for congress participation or received speaker honoraria from Alexion, Biogen, Merck, Novartis, Roche and Sanofi Genzyme. His-laboratory has received research support from Biogen, Merck, Novartis, Roche and Sanofi Genzyme. M. Magyari has served on scientific advisory board for Biogen, Sanofi, Roche, Novartis, Merck, Abbvie, Alexion has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, Genzyme, has received research support and support for congress participation from Biogen, Genzyme, Roche, Merck, Novartis.

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