

## LETTER TO THE EDITOR

### Aggressive multiple sclerosis: a matter of measurement and timing

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We read with great interest the recently published work of Malpas *et al.* (2020) in which the authors identified clinical markers of patients with aggressive multiple sclerosis in a cohort of relapsing remitting multiple sclerosis (RRMS) patients with 10 years of follow-up. The authors followed the definition a confirmed Expanded Disability Status Scale (EDSS) score  $\geq 6.0$  within 10 years of disease onset, which was initially applied by Tintore *et al.* (2019) to a cohort of patients with clinically isolated syndrome. In two independent databases, MSBase (2403 cases) and the Swedish MS Registry (556 cases), the authors confirmed a similar proportion of aggressive multiple sclerosis of  $\sim 6\%$ . Predictors for aggressive multiple sclerosis were age at onset  $\geq 35$  years, an EDSS of  $\geq 3.0$  and pyramidal symptoms within the first year.

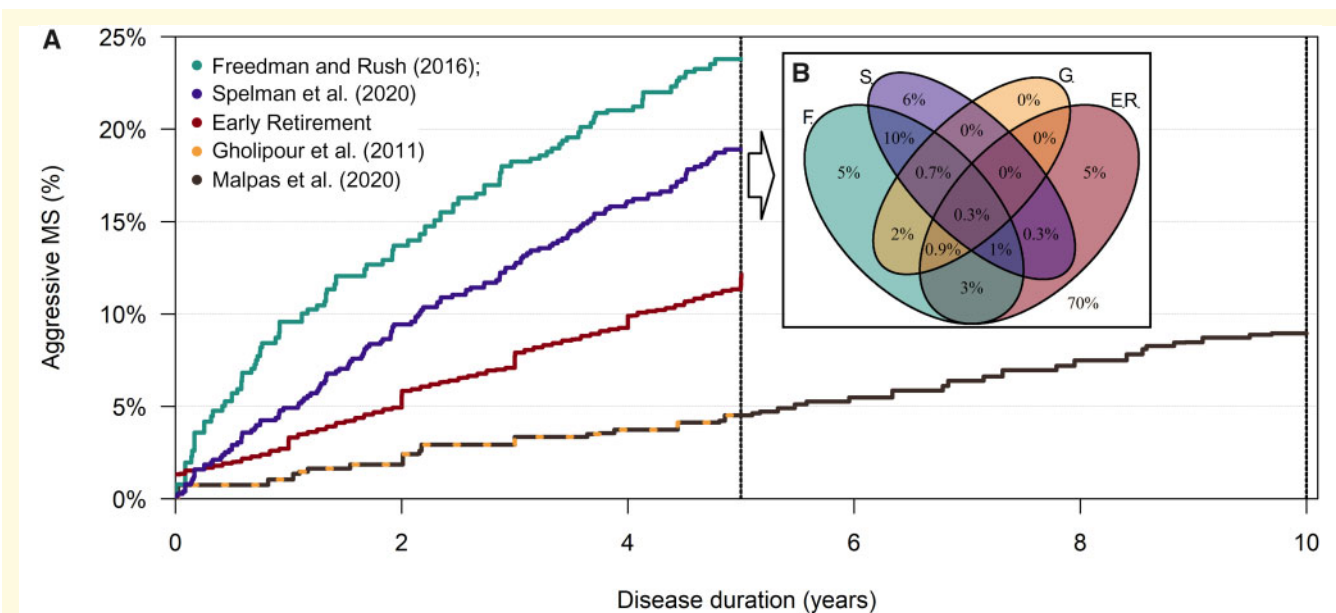
We tried to replicate the results of Malpas *et al.* within the data of the German MS Registry (GMSR), a nationwide registry including  $> 30\,000$  patients (with at least one follow-up since 2014) recruited from all sectors of care in over 190 centres.

By applying an interval-censored proportional hazards model, the estimated overall rate of aggressive multiple sclerosis in our GMSR cohort was 8.9% for all patients (including progressive cases;  $n = 17\,071$ ; Fig. 1) and 7.0% if only

including patients with relapsing course at onset, which is similar to previous studies. In univariate analysis of baseline covariates, age at onset [per 10 years with a hazard ratio (HR) of 2.02 and 95% confidence interval (CI) (1.91–2.14),  $P < 0.001$ ], the first year EDSS [per EDSS; HR: 3.45 (2.74–4.33),  $P < 0.001$ ] and pyramidal symptoms within the first year [HR: 4.51 (3.75–5.43),  $P < 0.001$ ] were associated with aggressive multiple sclerosis in RRMS. In multivariable analyses, however, only the EDSS after the first year and age at onset remained to be statistically significant for predicting an unfavourable course of multiple sclerosis.

Our data overall support the analysis of Malpas *et al.* and similar results were obtained when progressive patients were included. The progressive course *per se* had been identified as a risk factor for aggressive multiple sclerosis and affected patients should not be excluded unless specifically investigating forms of aggressive relapsing remitting multiple sclerosis (ARMS) (Jacobaeus *et al.*, 2020). TheECTRIMS Focused Workshop Group further points out that a plethora of definitions of aggressive multiple sclerosis exist and there is no generally accepted definition in the literature.

We have therefore carried out further analyses of GMSR data, comparing the results for different published aggressive multiple sclerosis or highly active multiple sclerosis



**Figure 1** Aggressive multiple sclerosis according to various definitions. (A) Proportions of aggressive multiple sclerosis (MS) patients over time according to different definitions. In this interval-censored Cox model, the rising proportions of patients in the GMSR classified as aggressive multiple sclerosis according to the definitions of Freedman and Rush (2016), Díaz *et al.* (2019), Spelman *et al.* (2020), Gholipour *et al.* (2011), Menon *et al.* (2017), Tintore *et al.* (2019) and Malpas *et al.* (2020) (10 years) were presented depending on the disease duration from symptom onset. Additionally, the proportion of early retired patients in the first 5 years is given. (B) Venn diagram showing overlapping proportions of aggressive multiple sclerosis patients according to various definitions in the first 5 years of the disease ( $n = 752$ ). Comparison of aggressive multiple sclerosis patients according to Freedman and Rush (2016) (F) Díaz *et al.* (2019), Gholipour *et al.* (2011) (G) Menon *et al.* (2017), Spelman *et al.* (2020) (S) and the early retired (ER) patients with aggressive multiple sclerosis.

definitions (Gholipour *et al.*, 2011; Freedman and Rush, 2016; Menon *et al.*, 2017; Díaz *et al.*, 2019; Tintore *et al.*, 2019; Malpas *et al.*, 2020; Spelman *et al.*, 2020). These definitions vary, in part considerably, regarding the parameters to be evaluated (in addition to EDSS, also relapses, MRI data, therapy response and the follow-up time needed):

- (i) Freedman and Rush (2016)/Díaz *et al.* (2019) (fulfilment of at least one criterion within first 5 years of multiple sclerosis):  $\geq 2$  relapses with incomplete recovery within 12 months;  $\geq 2$  MRI with new or enlarging  $T_2$  lesions or gadolinium enhancing (GD+) lesions during 12 months on DMT; no treatment effect during first year of DMT; and confirmed EDSS  $\geq 4.0$  after 5 years of disease onset.
- (ii) Gholipour *et al.* (2011)/Menon *et al.* (2017): confirmed EDSS  $\geq 6.0$  after 5 years of symptom onset.
- (iii) Spelman *et al.* (2020) [highly active (HA) multiple sclerosis; we considered fulfilment any HAMS indication within first 5 years as aggressive multiple sclerosis comparator]:  $\geq 2$  relapses within 12 months;  $\geq 1$  GD+ lesion(s); and  $\geq 9$   $T_2$  lesions (not used since  $\geq 9 / < 9$   $T_2$  not assessable).
- (iv) Tintore *et al.* (2019)/Malpas *et al.* (2020): confirmed EDSS  $\geq 6.0$  within 10 years of symptom onset; and RRMS: as a study inclusion criterion, not part of the aggressive multiple sclerosis definition.

Similar to Malpas *et al.*, only some of our patients could be classified and analysed in the GMSR, since, depending on

the definition, certain prerequisites regarding follow-up were required, e.g. in Freedman and Rush (2016)/Díaz *et al.* (2019), and Spelman *et al.* (2020) ( $n = 752$ ), accurate data in the first 5 years after disease onset. For criteria based exclusively on sustained and confirmed EDSS, we considered it sufficient to observe the end of the follow-up period, which leads to different numbers of patients being analysed for each definition. The proportion of aggressive multiple sclerosis/highly active patients varies significantly between the different definitions from 4.0% to 23.1% (Table 1 and Fig. 1A).

Direct comparisons of various criteria showed that there is little overlap between some definitions. For example, only 1% of our patients met the aggressive multiple sclerosis/highly active criteria of the three definitions of Spelman *et al.* (2020), Freedman and Rush (2016)/Díaz *et al.*, (2019), and Gholipour *et al.* (2011)/Menon *et al.* (2017) (Fig. 1B). In addition to clinical criteria such as relapses and EDSS, we tried to sharpen the clinical relevance of these definitions and have therefore included work ability. In this regard, the different definitions showed large variability within aggressive/highly active multiple sclerosis, ranging from 8.5% to 41.1% of patients who were not able to work (Table 1), with the highest numbers for those definitions based on EDSS.

In summary, the term ‘aggressive multiple sclerosis’ or ‘highly active multiple sclerosis’ is used differently in the literature and no agreement between multiple sclerosis experts exists on the criteria. Using the term should be carefully

**Table 1** Characteristics of patients with aggressive multiple sclerosis according to different definitions within the GMSR

|                             | Freedman and Rush (2016)/ Diaz <i>et al.</i> (2019) First 5 years covered | Spelman <i>et al.</i> (2020) First 5 years covered | Gholipour <i>et al.</i> (2011)/Menon <i>et al.</i> (2017) at 5 years | Tintore <i>et al.</i> (2019)/ Malpas <i>et al.</i> (2020) at 10 years | Early retirement at 5 years |
|-----------------------------|---|--|--|---|-----------------------------|
| Patients, <i>n</i>          | 752   | 752  | 4605   | 3949  | 4605                        |
| <i>n</i> with agMS          | 174   | 141  | 185  | 331   | 525                         |
| Proportion with agMS, %     | 23.1  | 18.8   | 4.0  | 8.4   | 11.4                        |
| Female, %                   | 70.7 (63.3–77.3)  | 73.0 (64.9–80.2)                                   | 61.6 (54.2–68.7)   | 58.6 (53.1–64.0)  | 67.4 (63.2–71.4)            |
| Progressive onset, %        | 5.7 (2.8–10.3)  | 0.7 (0.0–3.9)                                      | 22.2 (16.4–28.8)   | 13.3 (9.8–17.4)   | 7.8 (5.7–10.4)              |
| Mean age at MS onset        | 39.0 (37.1–40.8)  | 33.6 (31.7–35.5)                                   | 45.0 (43.3–46.7)   | 40.7 (39.5–41.9)  | 41.7 (40.8–42.5)            |
| Mean EDSS, last follow-up   | 3.5 (3.2–3.8)   | 2.1 (1.8–2.4)                                      | 6.6 (6.5–6.7)  | 6.7 (6.6–6.8)   | 3.9 (3.8–4.1)               |
| Retired early, % at 5 years | 23.0 (17.0–30.0)  | 8.5 (4.5–14.4)                                     | 41.1 (33.9–48.5)   | 29.0 (24.2–34.2)  |                             |

Descriptive statistics are presented as mean (95% confidence intervals). Clopper-Pearson variants for proportions. agMS = aggressive multiple sclerosis; EDSS = Expanded Disability Status Scale; GMSR = German Multiple Sclerosis Registry; MS = multiple sclerosis.

considered, taking into account the fact that there was little overlap among the known definitions for aggressive multiple sclerosis, even when the same dataset is used. Although it may be plausible to distinguish between a (short-term) relapse and MRI-based highly active multiple sclerosis and a long-term EDSS-based aggressive multiple sclerosis, we believe that patient-relevant outcomes, such as ability to work, may sharpen the meaningfulness of the definition.

We do not doubt the ability of the definitions to identify aggressive patients, but we believe that three aspects must be distinguished. First, there is a need to identify patients with rapid progression of the disease due to risk factors at an early stage (aggressive multiple sclerosis). Second, there is a need for long-term results that validate which patients have a high degree of disability or malignant course, e.g. measured by EDSS, as in Tintore *et al.* (2019) and Malpas *et al.* (2020). Third, it is necessary to continuously assess the severity of the disease (highly active multiple sclerosis). Well-defined definitions should be developed for all of these aspects. In addition, non-clinical factors, such as early retirement, would be important to better assess and predict the patient's status. A scoring system that includes several of the above-mentioned parameters could be helpful in predicting long-term outcomes and enabling evidence-based treatment decisions in the future.

## Data availability

Anonymized data will be made available on request by any qualified investigator under the terms of the registries' usage and access guidelines and subject to informed consent of the patients.

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and the German MS Society in 2001. It is operated by a not-for-profit company, the MSFP. In 2018, the MSFP received a grant from Merck and Novartis to support the extension of the registry and the implementation of EMA requirements. In 2019, Biogen and Celgene joined 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 dataset. Industry funding does not result in restrictions to publish data, nor do the funders have access to raw data or influence in the scientific conduct of the registry.

## Competing interests

P.F. 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. N.F. received travel funds for research meetings from Novartis. None resulted in a conflict of interest. K.H. has received speaking fees, travel support, and research honoraria from Biogen, Teva, Sanofi-Genzyme, Novartis, Bayer Healthcare, Merck Serono, and Roche. None resulted in a conflict of interest. F.P. 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, German Research Council, Werth Stiftung of the City of Cologne, German Ministry of Education and Research, EU FP7 Framework Program, Arthur Arnstein Foundation Berlin, Guthy Jackson Charitable Foundation, and National Multiple Sclerosis of the USA. He serves as academic editor for *PLoS ONE* and associate editor for *Neurology*, *Neuroimmunology and Neuroinflammation*. None resulted in a conflict of interest. A.S. has received institutional research support from Biogen,

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