Patient- versus physician-reported relapses in multiple sclerosis: insights from a large observational study

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Abstract

Background and purpose: The patient’s perspective is becoming increasingly important for endpoints in studies on multiple sclerosis. However, relapse data generated from the patient’s perspective in combination with independent documentation by the physician are scarce. Our objective was to compare self-reported relapses by the patient to physician-documented relapses within a routine clinical practice setting of quarterly visits.

Methods: Two-year data (n = 1921 patients) were extracted from two prospective, non-interventional, multicentre cohort studies in Germany. The number of relapses independently reported by patients and physicians was analysed. In addition, inter-rater reliability and measures of validity were evaluated. Patterns of associations were investigated in subgroup analysis of sociodemographic, clinical and patient-reported outcome measures.

Results: Patients and physicians showed good overall agreement [κ = 0.78, 95% confidence interval (CI) 0.76–0.80]. Nevertheless, patients reported, on average, more relapses than physicians during follow-up (0.55 vs. 0.44; P < 0.001). Corresponding annualized relapse rates were 0.38 (95% CI 0.36–0.39) and 0.30 (95% CI 0.29–0.31), respectively. Differences between physicians and patients were particularly pronounced in patient groups with greater disability levels, decreased health-related quality of life or treatment satisfaction. The positive predictive value was 74.01% (95% CI 71.85–76.07), and the negative predictive value was 98.86% (95% CI 98.67–99.03).

Conclusion: Some disagreement on the occurrence of relapses appears in specific patient subgroups, where factors such as pseudo-relapses or confounding factors may have promoted over- or under-reporting.

Introduction

Multiple sclerosis (MS) is a chronic multifocal disease of the central nervous system, with a variable course and relapses as defining hallmarks [1]. Relapses are associated with a substantial functional and psychosocial burden and can significantly disrupt a patient’s life, for example, through ongoing anxiety about future relapses [2,3]. The prevention of relapses is a main target for disease-modifying therapies, and relapse-based outcomes serve as primary or secondary efficacy outcome measures in many clinical studies. Relapse-related outcomes include annualized relapse rates (ARRs), average number of relapses per patient, proportion of (non-)relapsing patients or the cumulative probability of (non-)relapse events.

Relapses are defined as patient-reported or objectively observed events of neurological disability with a duration of >24 h in the absence of infection or fever that are preceded by >30 days of clinical stability. However, definitions in clinical practice as well as in clinical studies often vary [4,5]. The timely and correct detection of an acute relapse is a prerequisite for rapid initiation of treatment (e.g. corticosteroids) in order to...
shorten the duration of symptoms and to avoid unnecessary physical and emotional strain in case of misclassification.

As the patients’ perspective gains increasing importance for endpoints in clinical and real-world studies, specific instruments for evaluating relapses from the patient’s point of view are surprisingly sparse [6,7]. Some patient-reported instruments have been shown to be sensitive to relapses [3], but only the Assessing Relapse in Multiple Sclerosis (ARMS) questionnaire could be identified as a specific tool for the assessment of relapses [8]. However, the ARMS questionnaire has rarely been used in studies, and the gathering of relapse data from both patients and physicians in tandem has, to date, not been carried out.

We addressed this research gap by directly contrasting patient self-reports of relapses to physician-documented relapses within a comprehensive real-world study setting of quarterly routine visits.

The primary objective of the present study was to compare the number of reported relapses and to evaluate the inter-rater reliability between patients and their neurologists. A secondary objective was to analyse measures of validity, particularly the positive predictive value. Patterns of associations were also examined in subgroups of sociodemographic, clinical and patient-reported outcome variables.

**Methods**

**Study design, patients and ethics**

Pooled 2-year data were extracted from the PEARL study and the PANGAEA sub-study, two prospective, observational, non-interventional cohort studies. Study design and inclusion criteria have been described previously [9,10]. In brief, patients diagnosed with relapsing remitting MS, treated with interferon-beta preparations, glatiramer acetate or fingolimod, were recruited and no exclusion criteria except for the contraindications mentioned in the respective summary of treatment information were stated.

Approvals from independent, local competent ethics committees were obtained, and all participants provided written informed consent before entering the study.

**Main outcome measure**

Presence and absence of relapses were independently assessed by both patients and attending neurologists for each patient every 3 months (quarterly) during routine study visits, resulting in a closely monitored recall period of 2 years per patient. Quarterly relapse status was assessed according to the clinical judgement of physicians in the real-world setting, and also according to the perception of the patient ("did you experience/how many relapses did you experience within the last 3 months?").

**Clinical, sociodemographic and patient-reported outcomes**

Additional clinical data [Expanded Disability Status Scale (EDSS), Clinical Global Impression (CGI) severity scale] were collected by the treating neurologists [11]. Patient-reported data comprised health-related quality of life (HRQoL), treatment satisfaction, and disability. HRQoL was evaluated by the EuroQol-Visual Analogue Scale (EQ-VAS) and the Patient-Reported Outcome Indices for Multiple Sclerosis (PRIMUS) questionnaire, using the quality of life (PRIMUS-Q) and activity limitations (PRIMUS-A) subscales [12,13]. Treatment satisfaction was assessed using the global scale of the Treatment Satisfaction Questionnaire for Medication (TSQM-Global) [14]. Patients’ perceived disability was obtained through the summary score of the UK (Guy’s) Neurological Disability Scale (UKNDS-Sum) [15]. Additionally, the Multiple Sclerosis-Health Resource Survey (MS-HRS) was used to estimate resource consumption associated cost groups [16]. For subgroup analyses, each patient was assigned to one (of up to three) associated outcome categories based on intra-individual mean values during the data-gathering phase, resulting in independent patient groups.

**Statistical analysis**

The statistical significance of the difference in mean number of relapses (self- vs. physician-assessed) was determined using Wilcoxon’s signed-rank test. In addition, ARRs were calculated on the basis of the physician- and patient-reported relapse data from two separate negative binomial regression models. The McNemar test was applied to compare the relative numbers of relapse-free patients (vice versa: relapsing patients) between self- and physician assessments. Multivariable binary logistic regression analysis was performed to examine how clinical, sociodemographic and patient-reported outcome variables influenced the likelihood that patients would report more relapses than their physicians (over-reporting by the patient). Odds ratios (ORs) were presented, with adjustments made for gender, age, disability (EDSS), follow-up time and data source.
To evaluate the patient–physician agreement on the presence and absence of relapses, \( \kappa \) statistics were calculated. Thresholds for interpretation of \( \kappa \) were as follows: poor/slight agreement, below 0.20; fair, between 0.21 and 0.40; moderate, between 0.41 and 0.60; good/substantial, between 0.61 and 0.80; very good, above 0.81) [17]. For measures of validity [positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity; see Table S1 for definitions], the assessments by the neurologists served as the reference standard.

Results

Patients

For 1921 out of 2246 eligible patients, both physicians and patients reported the presence or absence of relapses and the respective number of these (Fig. 1). Exclusion of patients with incomplete relapse data (no paired assessments) did not affect either relapse rates (Fig. 1) or the distribution of demographic variables. Overall, 12 690 paired assessments for 1921 patients were available, which corresponds to an average of 6.61 paired assessments per patient.

Almost three-quarters of patients (73.5%) were female. At study onset, patients had a mean age of 41.59 ± 10 years and the mean disease duration at the time of documentation was 7.72 ± 6.21 years. The mean baseline EDSS score was 2.42 ± 1.58 (median 2.0). Table 1 shows the frequency distributions of clinical, sociodemographic and patient-reported outcome subgroups.

Reliability and validity measures

With regard to the question of whether or not a relapse emerged in the past quarter, there was 96.7% absolute (crude) agreement between patients and physicians [12 275/12 690 (95% CI 96.4–97.0%);
Table S1]. After adjustment for chance, inter-rater reliability corresponded to good agreement between examiners (κ = 0.78, 95% CI 0.76–0.80). In each patient subgroup, overall good agreement was quantified (κ range from 0.72 to 0.87; Table S2).

The PPV was 74.01% [806/1089 (95% CI 71.85–76.07%)]; Fig. 1, Table S1]; that is, the probability that patients who reported a relapse in the present study actually had a relapse in the corresponding quarter (as assessed by the attending physician) was 0.74. The NPV was 98.86% [11469/11601 (95% CI 98.67–99.03)], sensitivity was 85.93% [806/938 (95% CI 83.54–88.09%)] and specificity was 97.59% [11469/11752 (95% CI 97.30–97.86%)].

Number of relapses per patient

At the patient level, the average number of patient- and physician-reported relapses during follow-up was 0.55 and 0.44, respectively (P < 0.001; Table 1). For number of relapses in annualized terms, the ARR was 0.30 (95% CI 0.29–0.31) when calculated on basis of the physician documentation and 0.38 (95% CI 0.36–0.39) for self-reporting. Not only were more self- than physician-reported relapses observed in total, but also a greater number of active patients (i.e. those who experienced at least one self-reported relapse) was observed (P < 0.001; Table 1).

Subgroup analyses showed that younger patients and patients with more advanced disability (EDSS, CGI) were monotonically associated with an increased number of relapses, regardless of whether patient or physician assessments were considered as the data source. This was also true for self-reported outcomes and the associated subgroups of increased disability (UKNDS-Sum), resource use (MS-HRS), decreased quality of life (EQ-VAS, PRIMUS) and treatment satisfaction (TSQM-Global). More specifically, the differences between self-reported and physician-reported relapses were largely significantly higher towards self-reporting (Table 1).

Patterns of over-reporting by the patient

The results from multivariate logistic regression analyses showed that greater disability was associated with patterns of over-reporting by the patient across all subgroups, with ORs > 1 increasing further with consecutive disability groups (CGI, EDSS, UKNDS-Sum, MS-HRS; P < 0.05). Older age, better HRQoL and treatment satisfaction indicated lower odds (ORs < 1) of over-reporting (age, PRIMUS, EQ-VAS; P < 0.05).

In contrast, disease duration and gender did not influence over-reporting by the patient (P > 0.05; Table 1).

Discussion

Overall, patient–physician agreement on the presence or absence of relapses within a routine clinical practice setting was quantified as good (κ = 0.78). Considering physician assessment as the reference standard, the PPV was 74.01%. However, patients on average reported significantly more relapses than physicians. In younger patients, in subgroups of more advanced disability, worse HRQoL and worse treatment satisfaction, differences between self- and physician-reported relapses were especially higher in favour of self-reporting. Nevertheless, both self- and physician-reported ARRs in our analysis lay within the range observed in previous studies [5,18].

In contrast to the PPV reported in the present study, Tallantyre et al. [19] reported results from a rapid-assessment MS relapse clinic and found that physicians diagnosed a relapse in 58% of patient presentations at the clinic. However, the results of the two studies are difficult to compare because of their differing methodologies, including patient recruitment; patients mostly self-referred by telephone to the relapse clinic and subsequent outpatient assessments were only undertaken when a relapse was considered possible or likely, while, in the present study, the relapse status of each patient was assessed within routine study visits independently of any pre-suspicion or associated symptom. As a result, there was a far greater proportion of relapse-negative assessments in the present study, particularly true-negative assessments. PPV is therefore the most suitable measure to allow a rough comparison of both sets of results. As another approach, we created a proxy metric to approximate the study setting of Tallantyre et al. more closely (Table S1). Based on the PPV and by additionally including false-negative assessments (reflecting a certain degree of remaining uncertainty about the presence of relapse symptoms when actually attending the relapse clinic after the telephone triage), patient–doctor agreement reached a more comparable level of 66% (Table S1).

To the best of our knowledge, no study to date has aimed to compare self- and physician reports of relapses in a clinical practice setting comparable to that of the present study. Previous MS studies have evaluated differences between self- and physician-rated disability, while other research has focused on comparisons of perceptions concerning the disease course [20,21]. As a result, patients often classified themselves as having worse forms of illness than did their physicians, which is consistent with our findings with regard to number of relapses.

Not only do definitions of what constitutes a relapse differ, but also fixed protocol definitions can remain
| Characteristic       | Subgroup | N   | PHY | PAT | Δ    | p  | PHY | PAT | Δ    | p  |
|---------------------|----------|-----|-----|-----|------|----|-----|-----|------|----|
| Total               | —        | 1921| 0.44| 0.55| +0.11| <0.001| 70.4| 68.0| -2.4 | <0.001|
| Sex                 | Male     | 507 | 0.39| 0.45| +0.06 | 0.017| 73.2| 70.6| -2.6 | 0.041|
|                     | Female   | 1412| 0.46| 0.59| +0.13 | <0.001| 69.4| 67.1| -2.3 | 0.002|
| Age                 | 18-29 years | 233 | 0.63| 0.81| +0.18 | <0.001| 61.4| 58.8| -2.6 | 0.263|
|                     | 30-49 years | 1183| 0.45| 0.55| +0.10 | <0.001| 70.2| 68.0| -2.2 | 0.007|
|                     | 50+ years | 505 | 0.35| 0.44| +0.09 | <0.001| 75.2| 72.5| -2.7 | 0.024|
| Disease duration    | ≤5 years | 760 | 0.48| 0.62| +0.14 | <0.001| 68.3| 66.6| -1.7 | 0.105|
|                     | 6–10 years | 518 | 0.39| 0.47| +0.08 | <0.001| 72.2| 70.1| -2.1 | 0.071|
|                     | >10 years | 624 | 0.44| 0.53| +0.09 | <0.001| 72.1| 68.6| -3.5 | 0.003|
| Relapses 1 year     | 0        | 1041| 0.30| 0.35| +0.05 | <0.001| 77.9| 76.1| -1.8 | 0.011|
|                     | 1        | 524 | 0.55| 0.72| +0.17 | <0.001| 63.7| 61.8| -1.9 | 0.230|
|                     | 2+       | 329 | 0.69| 0.91| +0.22 | <0.001| 58.7| 53.8| -4.9 | 0.007|
| CGIa                | 1–2      | 396 | 0.35| 0.38| +0.03 | 0.028| 77.8| 77.0| -0.8 | 0.549|
|                     | 3–4      | 1240| 0.46| 0.58| +0.12 | <0.001| 69.4| 66.9| -2.5 | 0.003|
|                     | 5+       | 277 | 0.53| 0.70| +0.17 | <0.001| 64.3| 59.9| -4.4 | 0.012|
| EDSSe               | 0–1.5    | 663 | 0.32| 0.38| +0.06 | <0.001| 77.7| 76.8| -0.9 | 0.418|
|                     | 2–3.5    | 825 | 0.52| 0.61| +0.09 | <0.001| 66.3| 64.5| -1.8 | 0.072|
|                     | 4+       | 425 | 0.50| 0.72| +0.22 | <0.001| 66.8| 60.9| -5.9 | <0.001|
| UKNDS-Sumb          | 0–5      | 789 | 0.36| 0.40| +0.04 | 0.012| 75.5| 74.5| -1.0 | 0.291|
|                     | 6–10     | 486 | 0.49| 0.60| +0.11 | 0.002| 67.7| 68.1| +0.4 | 0.864|
|                     | 11+      | 598 | 0.52| 0.70| +0.18 | <0.001| 66.1| 59.4| -6.7 | <0.001|
| PRIMUS-A∞           | 0        | 576 | 0.36| 0.40| +0.04 | 0.040| 75.7| 74.3| -1.4 | 0.215|
|                     | 1–3      | 622 | 0.43| 0.50| +0.07 | <0.001| 70.9| 69.6| -1.3 | 0.322|
|                     | 4+       | 710 | 0.53| 0.72| +0.29 | <0.001| 65.6| 61.3| -4.3 | <0.001|
| PRIMUS-Q²           | 0        | 404 | 0.32| 0.34| +0.02 | 0.032| 77.7| 77.2| -0.5 | 0.832|
|                     | 1–3      | 767 | 0.48| 0.53| +0.05 | 0.002| 69.2| 69.1| -0.8 | 0.999|
|                     | 4+       | 715 | 0.49| 0.69| +0.20 | <0.001| 66.9| 61.0| -5.9 | <0.001|
| EQ-VASb             | 0–60     | 573 | 0.52| 0.77| +0.25 | <0.001| 64.0| 58.5| -5.5 | <0.001|
|                     | 60–80    | 753 | 0.49| 0.56| +0.07 | <0.001| 69.5| 67.7| -1.8 | 0.072|
|                     | 80–100   | 585 | 0.31| 0.34| +0.03 | 0.040| 77.9| 77.6| -0.3 | 0.871|
| TSQM-globalb        | 0–60     | 264 | 0.62| 0.90| +0.28 | <0.001| 62.1| 55.7| -6.4 | <0.001|
|                     | 60–80    | 815 | 0.45| 0.58| +0.13 | <0.001| 69.7| 66.5| -3.2 | 0.001|
|                     | 80–100   | 841 | 0.38| 0.42| +0.04 | 0.117| 73.7| 73.4| -0.3 | 0.795|

(continued)
Table 1 (Continued)

| Characteristic       | Subgroup | N   | PHY | PAT | Δ   | P   | OR (95% CI) | OR (95% CI) |
|----------------------|----------|-----|-----|-----|-----|-----|-------------|-------------|
| Mean number of relapses per patient (categorical) |          |     |     |     |     |     |             |             |
| MS-HRS® (Euro)       | <20k     | 424 | 0.25| 0.29| +0.04| 0.008| 82.1 | 82.1 | 0.0 | 0.999 | 1.00 [Ref] | — |
|                      | 20–40k   | 1210| 0.48| 0.59| +0.11| <0.001| 67.9 | 65.2 | −2.7 | 0.002 | 1.82 (1.15–2.88) | 0.008 | 1.00 (1.00–1.00) | 0.004 |
|                      | >40k     | 287 | 0.56| 0.79| +0.23| <0.001| 64.1 | 59.2 | −4.9 | 0.011 | 2.15 (1.22–3.78) | 0.011 |

Proportion of relapse-free patients, %

Logistic regression models (PAT > PHY)^e

CGI, Clinical Global Impression (severity scale); CI, confidence interval; EDSS, Expanded Disability Status Scale; EQ-VAS, EuroQol-Visual Analog Scale; MS-HRS, Multiple Sclerosis-Health Resource Survey (total societal costs in Euro per year); OR, odds ratio; PAT, patient-reported relapses; PHY, physician-reported relapses; PRIMUS-A, Patient-Reported Outcome Indices for Multiple Sclerosis activity limitation subscale; PRIMUS-Q, Patient-Reported Outcome Indices for Multiple Sclerosis quality of life subscale; TSQM-Global, Treatment Satisfaction Questionnaire for Medication (global scale); UKNDS-Sum, UK (Guy’s) Neurological Disability Scale (sum score); D, PAT minus PHY. aHigher score worse. bHigher score better. cWilcoxon test (PHY vs. PAT). dMcNemar test (PHY vs. PAT). *Binary multiple logistic regression models on the likelihood that a patient reports more relapses than his/her physician (PAT > PHY vs. PAT ≤ PHY). Each model was adjusted for sex, age, disability (EDSS), follow-up time and data source, as appropriate. For categorical predictors (subgroups), reference categories for ORs are as specified in the table. In case of continuous treated predictors, ORs relate to an increase of one unit (score, year or Euro) in the associated variable.
surveys that they had not reported relapses to their physician in the past actively confirms the existence of further relapses, regardless of whether they were true or pseudo-relapses. As a consequence, study results are not necessarily contradictory as the inclusion of patients from the two aforementioned surveys in our study situation would probably have resulted in reporting of these missed relapses.

A limitation of the present study is that we did not systematically collect MRI data to additionally correlate our findings with MRI lesion accrual. Furthermore, the median EDSS score was 2, indicating under-representation of more severely disabled patients. Nevertheless, given the known demographic distribution in MS, our study population (73.5% female, mean age 41.59 years) represented a typical relapsing remitting MS population in clinical practice. Although case report forms (on the presence and absence of relapses) were filled in independently by physicians and patients, some distortion of independence may have resulted from what healthcare professionals last told the patient and vice versa (within and outside the study).

A strength of the present study was its large sample size, with the inclusion of 1921 patients with MS and 12 690 eligible paired assessments, supporting accuracy and external validity of the study.

In conclusion, some disagreement with regard to the number of reported relapses appeared in specific subgroups, where factors such as pseudo-relapses or symptom fluctuations may have promoted over- or under-reporting. Our results support the development and validation of multidimensional relapse assessment tools capturing the relapse experience from the patient’s perspective. These tools have the potential to improve recognition of relapses in routine clinical care when used to assist doctor–patient communication about relapse symptoms and confounding factors.

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Disclosure of conflicts of interest
The authors declare no financial or other conflicts of interest.

Data availability statement
The data are currently not publicly accessible for legal reasons. Anonymized, General Data Protection Regulation (GDPR) compliant data may be requested by qualified investigators.

Supporting Information
Additional Supporting Information may be found in the online version of this article:
Table S1. Inter-rater reliability and measures of validity (n=12690 paired assessments) for 1921 patients.
Table S2. Inter-rater reliability and measures of validity (n=12690 assessments).

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