Differentiating societal costs of disability worsening in multiple sclerosis

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Abstract
Background In multiple sclerosis (MS), confirmed disability progression (CDP) can be either the result of progression independent of relapse activity (PIRA) or relapse-associated worsening (RAW). However, the economic effect of PIRA and RAW on societal economic costs in patients with MS is not well understood.
Objective To determine societal economic costs of patients achieving disease activity free status (DAF) and compare them with those having PIRA and RAW events.
Methods We used a roving EDSS score analysis to detect PIRA and RAW events with confirmation after at least 6 months. We estimated the age-, gender-, EDSS-adjusted effects of PIRA and RAW on total, direct medical, direct non-medical and indirect societal economic costs. Patients achieving DAF were assigned to as reference.
Results Overall, 1959 patients were analyzed. Total mean quarterly societal economic costs including disease-modifying therapies (DMTs) were 6929€ (SD: 2886€) per patient averaged over a period of 2 years. Excluding DMTs, patients achieving DAF had total mean quarterly costs of 1703€ (SD: 2489€). PIRA caused 29% (IRR: 1.29; CI 1.06–1.50, p < 0.05) higher total costs compared to DAF. On the contrary, RAW increased total costs by factor 1.56 (CI 1.30–1.87, p < 0.001). The effect of PIRA and RAW was striking for direct medical costs which increased by factor 1.48 (95% CI 1.13–1.95, p < 0.01) and 2.25 (95% CI 1.72–2.94, p < 0.001), respectively.
Conclusion Disease progression increases societal economic costs significantly. Thus, delaying or even preventing disease progression in MS may reduce the societal economic burden of MS.

Keywords Multiple sclerosis · Progression · Worsening · Resource utilization · Cost of illness

Introduction
Multiple sclerosis (MS) is one of the most common causes of progressing neurological disability in young adults. Typically diagnosed between the ages of 20 and 40, the disease is associated with a lifelong high societal and economic impact [1]. About 85% of patients are initially diagnosed with relapsing remitting multiple sclerosis (RRMS) which is characterized by relapses that fully or partially resolve [2]. In the absence of disease-modifying therapies (DMTs), approximately half of RRMS patients transit to secondary progressive MS (SPMS) within 10 years resulting in an accumulation of irreversible disability [3, 4]. Recent data demonstrated that already in patients with RRMS, an essential proportion of the accumulated disability is due to a progressive course of the disease but not due to relapses itself [5].

In clinical studies, an accumulation of MS-related functional disability is most commonly indicated through confirmed disability progression (CDP) [6]. CDP is based on a predefined increase on the Expanded Disability Status Scale (EDSS) that is sustained over a predefined time period, usually 3 or 6 months [7, 8]. CDP may result either from relapse-associated worsening (RAW) or progression independent of relapse activity (PIRA) [9, 10]. While RAW can result from poor recovery from multiple or severe relapse activities, PIRA may indicate a progressive clinical course...
characterized by neurodegenerative processes independent of inflammation [11, 12]. For PIRA and RAW assignments, regular EDSS and relapse data collection is a prerequisite. While this is commonly ensured under clinical study conditions, EDSS assessment is not guaranteed in clinical practice on a regular basis. As a result, the detection of RAW and relapse without worsening (RWW) in clinical practice is more straightforward as relapses are the primary targets of current RRMS treatment regimens.

Health economic assessments are well established in MS and highly relevant due to the enormous societal economic burden. A widespread approach is to collect cross-sectional data based on a study-specific questionnaire commonly reported as costs stratified by EDSS. Estimates of annual costs in Germany vary between 21,174–28,200€ (EDSS 0–3) and 39,923–44,000€ (EDSS 4–6.5), independent of longitudinal evaluation of PIRA and RAW [13]. Furthermore, costs of relapses are estimated at 2468€ without taking into account affiliations to RAW or RWW [13]. Recently, the Multiple Sclerosis Health Resource Survey (MS-HRS) was published addressing the gap of a valid and easy to administer questionnaire to holistically assess resource utilization both in cross-sectional and longitudinal studies [14]. Consequently, this provides an opportunity to investigate the health economic impact of clinical endpoints using longitudinal data.

We hypothesized that disability progression leads to an increased utilization of societal resources and, therefore, significantly increases the societal costs of MS. Therefore, the overall objective of the present analysis was to determine societal costs of patients achieving disease activity free status (DAF; no relapse, stable EDSS) and compare them with those having PIRA and RAW events within a 2-year real-world observational study.

### Methods

#### Study population

Patients with RRMS were recruited into PEARL (Prospective Pharmacoeconomic Cohort Evaluation) and PANGAEA (Post-authorization Non-interventional German Safety Study of Gilenya®) (sub-)studies, two prospective, non-interventional, multicentre studies conducted in Germany [15, 16]. In both studies, health economic and clinical data were collected with equal regularity. All patients provided written informed consent to participate in the study. The current analyses were limited to adult patients with a baseline EDSS score < 6.0 to ensure a sufficiently large population in each EDSS gradation. Regarding disease severity groups, we referred to the term mild for patients with EDSS scores < 4, while patients with scores ≥ 4 were considered as moderately affected.

#### Economic outcome measures

We used the MS-HRS to collect prospective longitudinal data on resource utilization [14]. The MS-HRS is an easy administrable tool for a holistic assessment of resource utilization from a societal perspective for patients with MS.

In accordance, we conducted all analyses from the societal perspective, which means that all costs were taken into account, regardless of who bears them [17]. Hence, cost data included direct medical costs (inpatient stays, outpatient stays, professional consultations, examinations, over-the-counter (OTC) medication, medical consumables and professional care), direct non-medical costs (informal care, investments/purchases) as well as indirect costs (MS-related productivity loss due to absenteeism and presenteeism). Resources were valued with societal opportunity costs or their best available approximation. Unit prices were taken from public sources and official statistics. Prices from different periods were adjusted to the 2011 price level using the consumer price index whenever necessary.

#### Clinical outcomes

Changes in disability were assessed at a regular basis using the EDSS every 6 months during clinical visits. CDP measured by EDSS was defined as: ≥ 1.5-point increase for a reference score of 0; ≥ 1-point increase for a reference score 1.0–5.0; and ≥ 0.5 point increase for a reference score greater than 5.5. Due to its higher sensitivity, we implemented a roving reference score instead of a fixed baseline reference score to detect CDP [12]. A roving EDSS score is independent of the baseline so that EDSS assessments at baseline, months 6 or 12 can be applied as reference. Increase in EDSS and confirmation of the increase can take place ≥ 6 and ≥ 12 months apart from the reference score, respectively. To have sufficient data to determine CDP and in accordance with earlier studies, patients with at least three EDSS assessments were included [18].

CDP events in which no relapse occurred between reference and confirmation assessment were declared as PIRA (Fig. 1). If a relapse occurred between reference and confirmation assessment, the event was classified as RAW (Fig. 1). Furthermore, we distinguished RAW from RWW applying to patients, who recover from relapses without having an increase in accumulated disability as defined by CDP. Patients achieving freedom of relapse activity and CDP were defined as DAF. Relapses were assessed from physicians every 3 months during routine clinical visits.
Mean and standard deviation (SD, ±) and percentage (%) were used to describe the population characteristics. We compared resource utilization-associated costs in socioeconomic- and disease-specific subgroups with Chi-squared, Kruskal–Wallis and Mann–Whitney U test. For model-based analysis, we applied a Generalized Linear Mixed Models (GLMM) with a negative binomial distribution and a log link function due to the right skewness of costs data. The influence of PIRA and RAW on (1) total costs excluding DMTs, (2) direct medical costs excluding DMTs, (3) direct non-medical costs and (4) indirect costs were reported through incidence rate ratios (IRR) and corresponding 95% confidence intervals (95% CI). For example, an IRR of 1.5 indicates that a specific group has a 50% higher quarterly resource consumption averaged over 2 years and compared to patients that were referred to as achieving DAF, while holding the other variables constant in the model. Patients achieving DAF served as the reference group for PIRA and RAW in the statistical models. Multivariate models were adjusted for sex, age, EDSS, data source and time, which indicated the sequence of assessments per patient. No imputations were made for missing information. Statistical analysis was performed using SPSS statistics for Windows Version 25.

Results

Patient characteristics

In total, 1959 patients had an EDSS score < 6 and were, therefore, included in the analysis. Patients were on average 41.62 ± 10.04 years of age and mostly female (72.82%). The mean disease duration of the total population was 7.30 ± 5.95 years with a baseline mean EDSS value of 2.26 ± 1.37. In terms of relapses in the year before baseline, patients were balanced between active (43.56%) and inactive (56.44%).

Of the total population, 985 patients (50.28%) were classified achieving DAF status after 2 years, 166 (8.47%) fell in the group PIRA, 150 (7.66%) into RAW and 407 (20.78%) had RWW (Table 1). Due to an insufficient number of EDSS assessments, 251 (12.81%) patients did not meet the definition of any aforementioned groups. For all subsequent analyses, these patients were summarized under the label “others”.

PIRA patients were older (44.48 ± 9.80 years of age) and longer affected by the disease (8.48 ± 7.13 years) compared to the other groups of interest. Furthermore, the rate of women was highest in patients with RAW (78.67%). In the year prior baseline, patients grouped in RAW and RWW were significantly more often relapse-active (51.68% and 57.18%, respectively) than patients with PIRA (30.91%) (p < 0.001).

Nearly two-third (62.17%) of all patients were employed at baseline with the lowest rate reported for PIRA patients (57.23%). RAW and RWW patients had a higher sick leave rate (17.33% and 17.44%, respectively) compared to PIRA (10.24%).

Costs

Total mean annual costs (inclusive of DMTs) were 27,958€ ± 10,139€ per patient, which corresponds to quarterly costs of 6929€ ± 2886€, averaged over a mean follow-up time of 20.68 ± 6.07 months. Excluding DMTs, overall
mean quarterly costs were 2029€ ± 2765€. Indirect costs accounted for 83.7% (1699€ ± 2444€) of resource utilization, followed by direct medical costs (14.59%; 296€ ± 888€) and direct non-medical costs (1.72%; 35€ ± 214€) (Table 2). The proportion of patients claiming resources in 2 years varied within cost categories: while 97.35% of the patients utilized at least once direct medical resources (without DMTs), 25.54% used resources leading to direct non-medical costs and 73.46% affirmed causing indirect costs.

Female patients utilized slightly more resources compared to males. Total societal costs increased with age from on average 984€ ± 1922€ for patients younger than 30 years of age.

Table 1 Baseline characteristics

| Baseline characteristics | Total (n = 1959) | DAF (n = 985) | PIRA (n = 166) | RAW (n = 150) | RWW (n = 407) | Others (n = 251) |
|--------------------------|-----------------|---------------|----------------|---------------|---------------|-----------------|
| Socio-demographic        |                 |               |                |               |               |                 |
| Female gender [n (%)]    | 1425 (72.82)    | 689 (70.02)   | 115 (69.28)    | 118 (78.67)   | 306 (75.18)   | 197 (78.80)     |
| Age [mean (SD)]          | 41.62 (10.04)   | 41.88 (9.93)  | 44.48 (9.80)   | 42.09 (10.17) | 40.24 (9.99)  | 40.66 (10.20)   |
| 18–29 years [n (%)]      | 271 (13.83)     | 125 (12.69)   | 13 (7.83)      | 22 (14.67)    | 71 (17.44)    | 40 (15.94)      |
| 30–49 years [n (%)]      | 1233 (62.94)    | 624 (63.35)   | 96 (57.83)     | 90 (60.00)    | 262 (64.37)   | 161 (64.14)     |
| 50 years and older [n (%)] | 455 (23.23)     | 236 (23.96)   | 57 (34.34)     | 38 (25.33)    | 74 (18.18)    | 50 (19.92)      |
| Patients in working age [n (%)] | 1920 (98.01) | 965 (97.97) | 162 (97.59) | 147 (98.00) | 403 (99.02) | 243 (96.81) |
| Employed [n (n (%))]     | 1218 (62.17)    | 624 (63.35)   | 95 (57.23)     | 92 (61.33)    | 248 (60.93)   | 159 (63.35)     |
| Employed at full time [n (n (%))] | 722 (36.86) | 385 (39.09) | 58 (34.94) | 54 (36.00) | 138 (33.91) | 87 (34.66) |
| Employed with sick leave (past 3 months) [n (n (%))] | 265 (13.53) | 101 (10.25) | 17 (10.24) | 26 (17.33) | 71 (17.44) | 50 (19.92) |
| Employed with disability pension [n (n (%))] | 289 (14.75) | 136 (13.81) | 28 (16.87) | 31 (20.67) | 64 (15.72) | 30 (11.95) |
| Not living alone [n (n (%))] | 1494 (81.42) | 746 (80.56) | 123 (79.87) | 109 (80.74) | 321 (82.95) | 195 (83.69) |
| Disease characteristics  |                 |               |                |               |               |                 |
| Disease duration [mean (SD)] | 7.30 (5.95) | 7.43 (5.94) | 8.48 (7.13) | 7.29 (5.42) | 6.66 (5.46) | 7.04 (6.09) |
| EDSS [mean (SD)]         | 2.26 (1.37)     | 2.15 (1.39)   | 2.16 (1.30)    | 2.17 (1.32)   | 2.48 (1.31)   | 2.46 (1.35)     |
| EDSS < 4 [n (%)]         | 1613 (82.34)    | 814 (82.64)   | 143 (86.14)    | 128 (85.33)   | 333 (81.82)   | 195 (77.69)     |
| EDSS ≥ 4 [n (%)]         | 346 (17.66)     | 171 (17.36)   | 23 (13.86)     | 22 (14.67)    | 74 (18.18)    | 56 (22.31)      |
| At least one relapse prior to baseline [n (%)] | 849 (43.56) | 352 (35.85) | 51 (30.91) | 77 (51.68) | 231 (57.18) | 138 (55.42) |

Table 2 Mean (SD) quarterly cost in Euro (€) within 2 years of study time (n = 1959)

| Total costs (excl. DMTs) | Direct medical costs | Direct non-medical costs | Indirect costs | DMT costs |
|-------------------------|----------------------|--------------------------|----------------|----------|
| Mean (SD)               | Mean (SD)            | Mean (SD)                | Mean (SD)      | Mean (SD) |
| Whole sample            | 2029 (2765)          | 296 (888)                | 35 (214)       | 1699 (2444) | 4900 (746) |
| Age                     |                      |                          |                |           |           |
| 18–29 years             | 984 (1922)           | 210 (655)                | 5 (41)         | 770 (1707) | 4939 (761) |
| 30–49 years             | 2059 (2790)          | 300 (924)                | 36 (216)       | 1723 (2453) | 4933 (763) |
| 50+ years               | 2520 (2933)          | 330 (897)                | 49 (258)       | 2140 (2618) | 4789 (678) |
| Gender                  |                      |                          |                |           |           |
| Male                    | 1984 (2811)          | 268 (829)                | 25 (146)       | 1691 (2509) | 4937 (753) |
| Female                  | 2046 (2746)          | 307 (910)                | 39 (236)       | 1701 (2417) | 4885 (742) |
| EDSS                    |                      |                          |                |           |           |
| < 4                     | 1707 (2556)          | 261 (816)                | 22 (171)       | 1423 (2248) | 4865 (731) |
| ≥ 4                     | 3566 (3254)          | 461 (1157)               | 95 (348)       | 3010 (2877) | 5064 (790) |
| Disability              |                      |                          |                |           |           |
| DAF                     | 1703 (2489)          | 201 (609)                | 26 (201)       | 1475 (2284) | 4916 (739) |
| RWW                     | 2316 (2837)          | 397 (1014)               | 31 (124)       | 1887 (2488) | 4877 (764) |
| PIRA                    | 2392 (2897)          | 329 (956)                | 55 (278)       | 2008 (2614) | 4773 (700) |
| RAW                     | 2812 (3426)          | 549 (1499)               | 76 (365)       | 2188 (2704) | 4861 (745) |
| Others                  | 2440 (3311)          | 421 (1217)               | 45 (181)       | 1978 (2883) | 5116 (764) |
to 2519€ ± 2933€ for patients older than 50 years significant (p<0.05), mainly due to higher expenditures for indirect and direct medical costs.

A significant monetary difference was also found in all cost categories between patients with mild (1707€ ± 2536€) and moderate disability (3556€ ± 3254€) (p<0.001). This is mainly due to indirect costs (3010€ ± 2877€ (EDSS < 4) vs. 1423€ ± 2248€ (EDSS ≥ 4)).

PIRA patients consistently incurred higher costs (2391€ ± 2897€) compared to stable patients achieving DAF (1703€ ± 2489€) (p<0.001). RAW status led to highest total resource utilization (2812€ ± 3426€) but did not statistically significant differ from PIRA.

**Multivariate associations between PIRA, RAW and costs**

After controlling for the effects of increased disability, age and female gender, multivariate GLMMs revealed that PIRA caused on average 29% higher total costs compared to patients achieving DAF status (IRR = 1.29, CI 1.08–1.53, p<0.05) (Fig. 2). The effect of PIRA was most striking in direct medical costs. These were factored by 1.48 (CI 1.13–1.95, p<0.01) compared to their stable counterparts. Indirect costs increased by 25% (CI 1.03–1.52, p<0.05).

In comparison to PIRA, the effect of RAW was stronger in all cost categories. Total costs increased by factor 1.56 (CI 1.30–1.87, p<0.001) in comparison to stable patients. Direct medical costs increased by factor 2.25 (CI 1.72–2.94, p<0.001) and indirect costs by factor 1.43 (CI 1.17–1.75, p<0.001) compared to patients achieving DAF.

For both, PIRA and RAW, the increases in direct medical costs were in particular due to higher rates of inpatient and outpatient hospitalizations (Fig. 3).

**Discussion**

Our research showed that CDP was highly associated with a substantial societal economic burden. In particular, 2-year real-world data revealed that not only RAW, but also PIRA were associated with a statistically significant increase in costs.

The economic burden of MS including its direct, indirect and intangible costs has been widely examined in cross-sectional analyses [19, 20]. However, to the best of our knowledge, no previous studies on health resource utilization used a longitudinal design comparable to ours. We generated robust quarterly cost estimates in a longitudinal format applying the recently validated MS-HRS on up to eight study visits. Additionally, we assigned patients to either clinical DAF, PIRA, RAW or RWW through up to five consecutive EDSS and eight relapse assessments. In line with our categorization, recent studies conducted research on PIRA and RAW in a clinical context, supporting the validity and importance of our approach [9, 12, 21].

Our study population represented typical patient characteristics for a clinical RRMS population: patients were on average 41.62 years old with a mean disease duration of 7.30 years. Furthermore, 72.82% of all patients were female. To ensure representativeness, we used data from two large observational studies in which patients were documented...
homogenously across Germany. Representativeness towards a real-world setting was further supported by the fact that no explicit exclusion criteria, except contraindications associated with current DMTs, had been stated for the (sub-)studies PEARL and PANGAEA.

In the present analyses, 985 patients neither showed disability progression nor relapses (herein defined as DAF), which corresponds to 50.28% of patients. This is in line with a comprehensive DAF analyses within a real-world cohort of 306 mild-to-moderately affected MS patients in Germany, in which DAF was achieved by 45% of patients after 2 years [22]. Although the analyzed population consisted exclusively of patients with RRMS, a substantial proportion of accumulated disability was due to a progressive clinical course: 8.47% of patients in our study had a PIRA event within 2 years which corresponds to findings from a recent study (7.00–9.66%) [9]. On the contrary, the incidence of RAW was slightly higher in our population (7.66% vs. 2.0–4.7%) which might be explained by differences in the methodology in the assessment of RAW events [9]. EDSS baseline scores were comparable between the subgroups.

Mean annualized economic burden including DMTs was 26,482€ ± 9107€ for patients with EDSS scores < 4. This finding is comparable to results of Flachenecker et al. [13] who found mean annual costs of 28,200€ (EDSS < 4) in a German substudy with self-assessed EDSS and a multinational survey by Karampampa et al. [23] in which mean annual costs of 25,270€ were reported for Germany [13, 23]. Furthermore, we found a cost ratio of 1.32 between EDSS strata (0–3.5 vs. 4–5.5), while Flachenecker et al. reported a cost ratio of 1.56 [13]. Taking into account that in Flachenecker, EDSS strata of 0–3.5 and 4.0–6.0 were compared, the ratios can be regarded as comparable. We also confirmed that a progressive clinical course increases societal economic costs [24]. Nevertheless, we found differences in the composition of total costs that depart from those reported in the literature [13]. Particularly noticeable are lower expenses for hospital stays, examinations and informal care in our analysis, which could be explained by the milder disease profile in our analysis.

Both, RAW and PIRA led to increased utilization of direct medical resources. Nevertheless, the monetary effect was stronger for RAW. The proportion of participants with inpatient hospitalizations was almost twice as high in RAW compared to PIRA within 2 years. However, the average number of inpatient days did not differ between the groups. In contrast, both the proportion of patients with outpatient admissions and the average days of outpatient stays in the RAW group were more than twofold compared to the PIRA population. Beyond disease activity, we observed further parameters influencing the economic burden of MS. Higher age was associated with increased costs. Higher age (≥ 50 years) was significantly more frequent in patients with PIRA compared to DAF and RAW, which could be explained by the underlying progressive course that preferentially occurs at later stages of the disease and thus, in older patients [11]. Increased mean disease duration for patients with PIRA supports this suggestion. Lastly, total costs were slightly higher in female patients compared to their counterparts. RAW status was associated with female gender. This observation can be attributed to predispositions of relapses in women [25]. Therefore, we adjusted the multivariate analysis for age, gender, EDSS to receive valid results.

In the present study, we used a novel longitudinal approach with up to eight relapse assessments to assess relapse-related costs over 2 years. We found an increase in costs of 613€ per quarter for patients with relapses compared
to those achieving DAF. Previous studies commonly assessed 3- or 6-month time-dependent, cross-sectional relapse costs [26]. As the relapse-related cost increases were averaged over a period of 2 years in our approach, costs are generally lower and not directly comparable with estimates from previous studies.

Limitations

Few limitations of the study should be mentioned. First, we excluded patients with baseline EDSS ≥ 6 to ensure a balanced mild-to-moderately affected study population. However, corresponding data on severely affected patients are yet not available but we are already conducting consecutive studies addressing a more severely affected population [14]. Second, we used patient-reported data on resource utilization, which may not be completely free of biases. To avoid potential conflicts, data were collected with the validated MS-HRS in a longitudinal format. Third, definitions of PIRA and RAW is solely based on EDSS which means that its limitation also applies for our analysis. Particularly noteworthy is the focus on functional mobility and insensitivity on MS-related impairments like cognition. To address this problem, novel composite measures additionally include Nine-Hole Peg Test and Timed 25-Foot Walk to detect composite PIRA and RAW events [9]. Nevertheless, as our definition is solely based on EDSS, it is less demanding and easier to implement in non-interventional studies.

During data collection phase, a small proportion of patients utilized direct non-medical resources with a high variability of costs, which might yield from the low disability level in the study population. In consequence, confidence intervals were conspicuously wide (Fig. 2). However, in former analyses, it has been shown that utilization of direct non-medical resources radically increase in more severely affected patients [13]. To better understand the effect of PIRA and RAW on direct non-medical costs, further analyses in more affected populations may be helpful.

Conclusion

Applying a standardized longitudinal model, we found significantly higher societal economic costs in patients with PIRA and RAW compared to those achieving DAF status. Accordingly, it is highly important from a societal perspective to delay or even prevent transition into progressive phase of MS, which is another argument for treating MS patients early with appropriate DMTs [27]. As our analysis implies an enormous societal economic burden of PIRA and RAW events, further studies on the incidence and prevalence of these events are demanded. Combining our results with epidemiological knowledge on PIRA and RAW could help assessing financial risks to health systems and optimizing health service planning in patients with MS.

Compliance with ethical standards

Conflicts of interest NHN has received funding for research from Novartis. DS has nothing to disclose. RH has received speaker fee from Sanofi and travel grants from Celgene. BE is an employee of Novartis. CC was an employee of Novartis at the time of this study, and now an employee of Siemens. TZ received personal compensation from Almirall, Biogen, Bayer, Celgene, Novartis, Roche, Sanofi, Teva for consulting and speaking services and he is the section editor for BMC Neurology. Additionally, he received financial support for research activities from BAT, Biogen Novartis, Teva and Sanofi.

Ethical standards Approval for PANGAEA and PEARL were obtained from independent, local competent ethics committees.

Informed consent All patients provided written informed consent for the collection of clinical and health economic information.

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