Harmonizing Definitions for Progression Independent of Relapse Activity (PIRA) in Multiple Sclerosis: A Systematic Review

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Key Points

- Question: What is the current evidence on progression independent of relapse activity (PIRA) in multiple sclerosis, and what definition and terminology is used in the literature?
- Findings: Recent evidence indicates that PIRA is the most common form of disability accumulation across all traditional MS phenotypes, including CIS and early RRMS. However, there is no uniform definition of PIRA in the literature.
- Meaning: Acknowledging the occurrence of PIRA may lead to a better understanding of the drivers of MS evolution and more targeted interventions in clinical trials and practice. Our harmonized definition could improve comparability of results in current and future studies.

Abstract

Importance: Emerging evidence suggests that progression independent of relapse activity (PIRA) is a substantial contributor to long-term disability accumulation in relapsing-remitting multiple sclerosis (RRMS).

Objective: To date, there is no uniform agreed definition of PIRA, limiting the comparability of published studies. Here, we (I) summarize the current evidence about PIRA based on a systematic review, (II) discuss the various terminologies used in the context of PIRA, and (III) propose a harmonized definition for PIRA for use in clinical practice and future trials.

Evidence Review: Following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)", we conducted a literature search using the search terms „multiple sclerosis", „PIRA" „progression independent of relapse activity", „silent progression", and „progression unrelated to relapses" in PubMed, Embase, Cochrane and Web of Science, published between 1990 and December 2022. Out of 119 identified single records, we identified 48 eligible studies.

Findings: PIRA was reported to occur in roughly 5% of all RRMS patients per anum, causing at least 50% of all disability accrual events in typical RRMS. The proportion of PIRA vs. relapse associated worsening increases with age, longer disease duration and - despite lower absolute event numbers - potent suppression of relapses by highly effective disease modifying therapy. However, different studies used various definitions of PIRA, rendering the comparability of studies difficult.

Conclusion and Relevance: PIRA is the most frequent manifestation of disability accumulation across the full spectrum of traditional MS phenotypes, including clinically isolated syndrome and early RRMS. Our suggested harmonized definition may improve the comparability of results in current and future cohorts and datasets.

Introduction

Traditionally, in relapsing Multiple Sclerosis (MS) the accrual of irreversible disability is attributed to incomplete recovery from relapses. Relapse-independent mechanisms have been considered the hallmark of the progressive forms of the disease.[1,2]

However, accumulating evidence suggests that progression unrelated to relapses is not restricted to patients diagnosed with progressive forms of MS. Already in the earliest phases of MS and in people classified as having a typical relapsing remitting disease (RRMS), a substantial proportion of disability accumulation occurs independent of relapse activity.[3-6] Clinical deterioration despite the lack of concomitant clinically-evident relapses has been termed *progression independent of relapse activity (PIRA)* or *silent progression,* in contrast to *relapse-associated disability worsening (RAW).*[3-6]

PIRA has been described in a number of observational studies[3,4,7-14] and in pooled data from randomized trials.[5,15,16] Based on these findings, it was proposed that a paradigm shift is needed for the classification of MS disease courses, moving away from the current clinical phenotypic classification to a classification that takes PIRA into account and includes biomarkers extending beyond clinical and imaging measures of acute inflammatory activity.[6,17-19]

However, to date, there is no uniform, agreed definition of PIRA, hereby hampering the comparability of current and future studies. Here, we (I) summarize the current knowledge on PIRA based on a systematic review of the literature, (II) discuss the terminology applied in the context of PIRA, and (III) propose a harmonized definition to use in clinical practice and future studies.

Search Strategy and Selection Criteria

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] We searched literature in PubMed, Embase, Cochrane and Web of Science for peer-reviewed records covering PIRA published between 01.01.1990 and

25.12.2022. The search terms „multiple sclerosis“, „PIRA“ „progression independent of relapse activity“, „silent progression“ and „progression unrelated to relapses“ were used.We excluded case reports/case series, interviews and study protocols of ongoing trials.

(I) Results of the Systematic Review

We identified 48 eligible studies out of 119 single records (see eFigure 1). Characteristics and methodologies are given in Table 1. Excluded articles and reason for ineligibility are provided in eTable 2.

Existence and Prevalence of PIRA

For decades, relapses have been considered the clinical hallmark of MS. However, in natural history studies and clinical trials, their association with long-term disability accumulation has been questioned.[6,21] This has been evidenced by a number of major studies over the last five years. In a retrospective analysis of 5,562 typical RRMS patients from the Tysabri Observational Program (TOP) with a median follow up of 5·5 years, approximately 50% of 24 week confirmed disability worsening (measured by the Expanded Disability Status Scale [EDSS]) occurred in absence of relapses (30 days prior to 12 weeks after disability increase).[3]

In a study of 480 participants (CIS n=88; RRMS n=392) from the EPIC-MS cohort, of which 372 were followed for over 10 years, disability accumulation was primarily driven by progression unrelated to relapses, there, termed *silent progression*.[4] Using a fixed baseline-EDSS and defining silent progression events as occurring without self-reported relapses in the preceding year, the authors observed an incidence rate of 2-5% for silent progression events. Furthermore, they found similar disability accumulation during annual intervals with and without relapses.

The pooled post-hoc analysis of the randomized phase 3 OPERA I and II trials included 1,656 RRMS patients and used a composite endpoint to detect PIRA:[5] A PIRA event was defined as ≥12 week confirmed worsening on either the EDSS, timed 25-Foot Walk Test (T25FWT), or 9-Hole

Peg Test (9HPT), each compared to a baseline reference. Over 96 weeks, 81% and 89% of disability accrual events in the interferon beta-1a and ocrelizumab group, respectively were classified as PIRA.

In the Novartis-Oxford MS (NO.MS) dataset comprising over 200,000 EDSS transitions from more than 27,000 MS patients Lublin *et al.* applied a more stringent definition of PIRA, namely a 3 or 6 month confirmed EDSS increase in patients with either no relapse prior to the EDSS increase, or an onset of more than 90 days after the last relapse. PIRA events in which the EDSS did not improve over the entire follow up were sub-classified as „sustained" PIRA. Even with this stricter definition, sustained PIRA accounted for the majority of confirmed disability accrual events (47·3% PIRA vs. 26·9% RAW).[16]

Accumulating evidence from a number of single-center and multi-center cohorts extends our knowledge about PIRA (see Table 1). In 224 RRMS patients with no evidence of disease activity-3 (NEDA-3, i.e. no relapse, disability worsening, or MRI activity) in the first two years of treatment with either glatiramer acetate or interferon beta, 26% had experienced disability accumulation after a median follow up of 12 years, hereof 53% within 3 months after a clinical relapse, and 47% unrelated to relapses.[22] Another cohort of 16,130 RRMS patients followed for 11·8 years found that PIRA was the main determinant of disability accrual, accounting for 72% of all disability accumulation events.[23] In patients with at least two episodes of confirmed disability worsening, 7% exclusively exhibited RAW, 50% exclusively PIRA, and 43% both RAW and PIRA.[23] In 5,169 patients with CIS or early RRMS (included within 1 year after first clinical event), 45% experienced disability accrual over a median follow-up of 11·5 years, of which roughly 40% were in temporal relation to, and 60% unrelated to relapses.[13] When analyzing „periods free of relapses" (time between two consecutive relapses, starting 3 months after a relapse) of 1,128 patients, 25% experienced PIRA at least once over a median follow up of 10·5 years, contributing to 66% of all confirmed disability worsening events (the remaining 34% being RAW).[14] Patients experiencing PIRA (n=277) had a

steeper annual increase of EDSS and an eight-fold greater risk of reaching EDSS 6·0 than non-PIRA patients, particularly if PIRA occurred within the first 5 years after the first demyelinating event (n=86, 31% of all PIRA patients), suggesting that PIRAs early occurrence implies a particularly unfavorable outcome.

Clinical risk factors of PIRA

Several studies have suggested age is a principal risk factor of PIRA,[13,14,22,24-26] although PIRA has been described as the major determinant of confirmed disability accrual in all age-groups.[27] In accordance with this finding, longer disease duration was associated with a higher risk of PIRA.[4,9,13]

Furthermore, in the OPERA studies,[5] PIRA was associated with male sex, higher baseline disability burden (as measured by the EDSS, 9HPT, Paced Auditory Serial Addition Test, or Multiple Sclerosis Functional Composite Score[28]), and lower perceived health-related quality of life (as measured by the 36-Item Short Form Survey). Data from the NO.MS database[16] confirmed that RRMS patients with sustained PIRA were older and had a higher baseline EDSS than those with RAW. Clinically, PIRA events were more often driven by EDSS functional scores such as bowel/bladder or cognitive symptoms (termed „hidden“ by the authors because they are challenging to quantify in clinical practice), compared to RAW events, that more frequently involved pyramidal or sensory EDSS functional scores.[29]

PIRA and fluid biomarkers

In 496 serum samples from 58 MS patients, serum neurofilament light chain (sNfL) levels at baseline were predictive of both RAW and PIRA after 48 weeks.[30] In the Swiss MS cohort (SMSC),the likelihood of future PIRA increased by 23·5% per 1 standard deviation increased baseline sNfL after adjusting for age, EDSS and treatment.[25] In contrast, in 3906 samples from 609 patients from the EPIC cohort, elevated sNfL at baseline was predictive of RAW (termed „progression associated with relapse activity, PARA“), but not PIRA.[31] Similarly, in 1468 serum samples from 685 MS patients of the Comprehensive Longitudinal Investigation of MS (CLIMB), serum glial fibrillary

acidic protein (sGFAP), but not sNfL was predictive of 6 month confirmed PIRA, over a median follow up of 8·3 years.[32] In the same cohort, in 257 MS patients with an EDSS score ≥ 3 (as a proxy for patients with a high risk of progressive pathology), sGFAP correlated with subsequent PIRA, while sNfL predicted RAW.[33] The combined elevation of both sGFAP and sNfL resulted in a 5-fold increased risk of PIRA (n=355, corrected for age, sex, and body mass index).[34]

PIRA and MRI

PIRA and MRI activity

Acute MRI disease activity (defined as contrast-enhancing lesions or new T2-lesions on brain or spinal cord MRI) was observed more frequently in RRMS patients experiencing RAW (90%) than PIRA (11%) or without disability accrual (33% of patients).[22] Similar results were seen in placebo treated patients from phase 3 randomized controlled trials of the NO.MS dataset.[16] Another observational study (46 RRMS patients followed for 18 months) showed that 30·8% of all PIRA events (n=26) were accompanied by MRI activity.[35]

„True PIRA", „pure PIRA", „progression independent of relapses and MRI activity"

For patients that were not only relapse-free, but also free of MRI activity (new/enlarging T2-lesions and/or gadolinium-enhancing T1-lesions) within 90 days before or 30 after the disability worsening event, the term „true PIRA" was introduced.[13] In 359 patients with a disability accumulation event, of whom all had brain and 217 (60·4%) also spinal MRI, PIRA accounted for 48% of all disability events when applying a purely clinical definition over a follow-up period of 11·5 (±5·5) years, but only for 25% when using the „true PIRA" definition. Similar results were observed in 727 CIS patients, of which only 20% were free of MRI defined inflammatory activity in the previous two years (termed „pure PIRA" by the authors).[36] Still, in 1,128 CIS patients from the same cohort, time to EDSS 6·0 was identical between „active-PIRA" (new T2-lesions on brain or spinal MRI in the two years before PIRA) and „non-active-PIRA" patients.[14] In another study, when adding the absence of

brain MRI activity (new or gadolinium-enhancing lesions) to the definition of PIRA (termed „progression independent of relapses and MRI activity, PIRMA“ by the authors), the proportion was only marginally lower than the proportion of patients with (purely clinically defined) PIRA (4·5% vs. 4·6%, in 5,339 RRMS patients, over an observation period of 24 months).[10]

Associations between PIRA and other MRI measures

In the OPERA trials, future PIRA was associated with higher T1- and T2-lesion load, lower whole brain and cortical grey matter volume, while RAW was only predicted by acute MRI lesion activity (gadolinium-enhancing T1-lesions).[5] Brain volume loss was higher in patients with PIRA (n=61) when compared to clinically stable patients (n=109) in a subgroup of the EPIC cohort, followed over 10 years.[4] In a propensity score based matched analysis of 46 patients with PIRA and clinically stable RRMS, PIRA patients exhibited increased total brain atrophy, mainly driven by cortical gray matter loss.[12] Using diffusion MRI in 53 PIRA patients, accelerated degeneration of large white matter tracts was observed, compared to 73 clinically stable RRMS patients.[37] Furthermore, PIRA patients (n=31) had higher cortical lesion numbers and volumes compared to those without PIRA (n=51) over a median follow up of 5 years.[38]

PIRA and spinal cord MRI

A study of 360 RRMS patients followed for 12 years showed that spinal cord atrophy (measured on cranial MRI at the C1 level) was markedly faster in patients with PIRA (there, termed „silent progression“) than stable patients.[39] C1 atrophy rate was the strongest predictor of disability accumulation of all studied brain and cord measures, particularly in patients who subsequently converted to SPMS.[39] Interestingly, spinal cord atrophy rates were higher in RRMS patients with PIRA than in patients with SPMS (as defined by the treating physician and ascertained by two investigators using the definition by Lorscheider *et al.*[40]). Besides spinal cord atrophy, also the presence of ≥1 focal spinal cord lesions on baseline MRI predicted PIRA in the following years.[22]

Relation of PIRA to other measures

Further studies looked at the relation of PIRA and optical coherence tomography,[7] PET of perilesional tissue,[41] cognitive function measured by SDMT,[7] or the socio-economic costs of PIRA.[8] Results of these studies are summarized in Table 1.

Treatment of PIRA

Although several recent observational studies support the beneficial effect of disease modifying therapy (DMT) on long-term disability accrual in RRMS,[42-45] a number of observational studies failed to confirm a beneficial effect of DMT on PIRA[7,9,10,22] though this may relate to small sample size and lack of measures to control indication bias. After correcting for the greater propensity of patients with a more severe MS to receive higher efficacy DMTs, fingolimod was superior in reducing the risk of PIRA compared to interferone beta-1a or glateramer acetate in 1,640 relapse-free RRMS patients.[11] In the large NO.MS dataset, DMT use was associated with a delay of disability milestones by several years in both patients experiencing RAW and PIRA.[16] In the post-hoc analysis of the OPERA I and II[5] and ASCLEPIOS I and II studies,[15] ocrelizumab and ofatumumab were superior to interferon beta-1a or teriflunomide, respectively, in preventing both RAW and PIRA. Similarly, in the post hoc analysis of the OPTIMUM phase 3 trial, ponesimod reduced the rate of composite PIRA by 24% over a follow up of 108 weeks.[46]

Importantly, most studies confirmed that PIRA accounted for a higher proportion of confirmed disability accruals in patients on DMT compared to those without or on placebo treatment.[7,13,16,18,47,48]

Discussion of Systematic Review

Observational and controlled clinical trials provide unequivocal evidence that PIRA is the most frequent manifestation of disability accumulation across the full spectrum of traditional MS phenotypes, including CIS and early RRMS, thus challenging the conceptual distinction between relapsing and progressive disease courses or stages. The reported proportion of patients experiencing PIRA varies depending on (I) the definition used, (EDSS vs. composite measures, fixed vs. roving

baseline), (II) population under study (randomized trials vs. observational data, CIS/early RRMS vs. late RRMS vs. progressive MS), and (III) length of follow up (Table 2). PIRA occurs in roughly 5% of all RRMS patients per anum, causing at least 50% of all disability accrual events in typical RRMS.[4,13,14] The proportion of PIRA vs. RAW increases with age, longer disease duration and - despite lower absolute event numbers - potent suppression of relapses by highly effective DMT.[13,16] The latter observation might be attributed to more effective suppression or complete abrogation of acute relapse activity by DMT, which reduces the „noise“ that may interfere with the detection of subtle signs of insidious progression, and also prolongs the duration of PIRA risk exposure due to the reduction of relapse rates, or both.[7,13,18] The structural correlates of PIRA are not yet fully defined, but it has been suggested that the same mechanisms that are responsible for the accrual of disability in progressive MS may also be responsible for PIRA.[12,49] This is supported by the fact that patients with RRMS, and even CIS, share qualitatively similar (but quantitatively different) pathology features as patients with progressive MS.[19] Patients with PIRA show increased brain, cortical and spinal cord atrophy as well as an increased proportion of paramagnetic rim lesions.[12,49] Additionally, leptomeningeal inflammation,[6,50] failure of compensatory mechanisms,[19] and focal spinal cord pathology[39] have been discussed to be potentially linked to PIRA.

Systematic follow-up and advancing control of acute inflammatory disease activity through effective disease modifying therapies helped to uncover the phenomenon of PIRA and bring it to the attention of researchers and clinicians. The failure to appreciate PIRA in early disease stages may also be facilitated by the fact that particularly younger MS patients with milder structural damage may compensate for the insidious, progressive accumulation of MS-related damage. Only after a certain time and continuous accumulation of damage, the „brain reserve“[51] may not be able to cope with the structural injury, explaining the correlation of PIRA with higher age and/or longer disease duration.[52] Still, PIRA may remain undetected due to the low granularity of our clinical measures, highlighting the importance of standardized, quantitated and structured assessment of MS patients

with sensitive and specific measures, allowing for more precise correlation studies with markers of progression and better targeted therapeutic interventions.[5-7,18,52,53]

(II) Terminology of PIRA

The identification of PIRA is complex and based on various determinants that have been used inconsistently in the literature. Therefore, in the following section, we aim to recapitulate, describe and discuss the terminology that has been used in the context of PIRA, before providing recommendations in the subsequent section.

Worsening, progression and accrual

In 2014, Lublin *et al.*[1] suggested the term „*disability worsening*" to describe an advancing disease due to relapses and/or incomplete relapse recovery in patients during the relapsing phase. „*Disability progression*" should be favored when reporting a persisting EDSS increase in the progressive phase of MS.[1] Later, „*worsening*" was proposed as a more general term for any increase of disability, while „*progression*" still described an accrual of disability in progressive MS.[54] While „*disability worsening*" and „*disability progression*" have been used in consideration of the clinical disease course, in context of PIRA (which may occur in patients with relapsing and progressive MS), some authors[3,5,9,14,24,47] used the more „neutral" term „*disability accrual*" to describe any clinical event reflected by an increase of disability, irrespective of the underlying clinical phenotype.

Measuring disability accrual

Typically, clinical trials quantify disability using the EDSS. An accrual of disability is usually determined on three consecutive assessments: (I) the *baseline/reference score*, usually the EDSS at study entry („A1" in Figure 1) or the last confirmed reference score if using a roving approach („A2" in Figure 1), (II) the *event score*, a measurable clinical deterioration reflected by a significant increase of the EDSS („B" in Figure 1), and (III) the *confirmation score*, usually the next assessment after the event score („C" in Figure 1), at a pre-specified period after the event. To identify

sustained disability accrual (see below), a fourth time point of observation is used, (IV) the *sustained score* („D“ in Figure 1), that is equivalent to the last on-study follow up, sensibly at least 12 or even 24 months apart from start of PIRA.

Given the nonlinearity of the EDSS (i.e. in the lower scores, a small clinical change is reflected by a large numerical increment, and the opposite in the higher scores), a *significant* increase of disability is typically calculated in a stepwise stratified manner, where the required amount of increase depends on the baseline EDSS: If the baseline/reference EDSS is 0, an increase of ≥1·5 points is required, if the baseline/reference EDSS is 1·0-5·5 (or in some studies 1.0-5·0), an increase of ≥1·0 points is needed, and if baseline/reference EDSS is >5·5 (or in some studies >5·0) an increase of ≥0·5 points is sufficient.[40]

Confirmation interval

To mitigate diagnostic noise and interrater variability, the EDSS increase should be confirmed at a subsequent visit. However, the confirmation interval varies considerably, with RCTs mostly using shorter (e.g. 12 weeks) and observational studies longer time intervals (e.g. 6 or 12 months). Although Portaccio *et al.*[13] showed that using a confirmation after 365 days vs. 90 days did not substantially alter the results, shorter confirmation times are generally supposed to increase sensitivity, whilst a longer confirmation time may increase specificity of PIRA detection.[40] Cree *et al.*[4] and Lublin *et al.*[16] introduced the term „sustained“ EDSS worsening, that describes a disability accrual that was not only confirmed, but remained above the criteria for a significant EDSS increase compared to baseline throughout the observation period (Figure 2·3 and 2·4).

Fixed and Roving Baseline, Re-baselining

Historically, most MS studies compared EDSS outcomes to fixed study entry baseline EDSS. A „re-baselining“ method was proposed to include multiple events of one patient during follow up, by resetting the EDSS to a new baseline/reference score, if a relapse caused residual disability that was eventually confirmed. Still, the term „re-baselining“ has been used inconsistently in the literature,

sometimes equivalently to the term “roving baseline”,[3] where a decrease of the EDSS confirmed at the following visit will set a new baseline to calculate future disability accrual (i.e. if a patient’s EDSS improved from 3·0 to 2·0, confirmed at the subsequent visit, 2·0 is set as new baseline). Applying this method on data from 5,562 patients in the TOP study detected 50% more events, with the proportion of PIRA events increasing from 50 to 70% suggesting that this approach is particularly sensitive to detect PIRA.[3]

Measuring disability accrual using composite scores

Using composite scores may improve the granularity and characterize clinical elements of disease progression more comprehensively.[5,6,55,56] Tests like the T25FWT or 9HPT have better test characteristics and less interrater variability than the EDSS.[57] In the OPERA I and II RCTs,[5] a composite endpoint was used to capture overall (EDSS), upper (9HPT) and lower (T25FWT) extremity function. Disability accrual was defined as an increase in one or more of those three measures, each compared to a fixed baseline. Bsteh *et al.*[7] used a composite outcome of EDSS and cognitive function quantified by SMDT. Broader acceptance of cognitive tests as part of composite outcomes was hampered by the strong learning effects typically observed with repeated cognitive testing, resulting in artificial improvement thus potentially masking true cognitive worsening.

Definition of relapses

Disability worsening events are categorized as either RAW or PIRA, depending on the temporal relation to clinical relapses. Thus, PIRA is defined „by exclusion“, i.e. by absence of relapses. Relapses are typically defined as acute/subacute onset episodes of new or exacerbating symptoms persisting for at least 24 hours, in absence of illness or fever, and occurring at least 30 days after a previous relapse.[21,58] RCTs usually use shorter periods of relapse absence (e.g. 30 days before and after the event) and observational studies rely on longer relapse free intervals around the occurrence of PIRA or request the complete absence of relapses between baseline/reference assessment and confirmation.

Challenges

In real-world cohort studies, patients are often enrolled after their first demyelinating event, making the first EDSS an event score (e.g. resulting in a baseline EDSS score of 3·0, Figure 2·2 and 2·3). Eventually patients may recover and their EDSS may decline so that a future EDSS increase (e.g. again to EDSS score 3·0) will not be recognized if only compared to the original baseline score. To address this issue the roving baseline approach has been proposed.[3] The downside of the roving approach is that the EDSS can start from a temporary/meaningless drop, e.g. caused by inter-rater variability, especially in the lower part of the EDSS, where measurements can fluctuate, falsely triggering a later disability accrual event.

Relapse associated worsening (RAW) and PIRA may - within a given time frame - occur in parallel as two different, more or less interleaved, pathologic processes. The clinical definition of PIRA that requires a temporal distance from a relapse serves the purpose of obtaining "pure progression" but does not allow the detection of PIRA if it occurs as a parallel or even a closely consecutive process to relapses and RAW. While this approach is fully justified to ensure an acceptable specificity of PIRA, it is important to acknowledge the inherent detection bias. Understanding this built-in detection bias is not only important conceptually but also when interpreting findings across patients treated with drugs of different efficacy. High efficacy drugs that suppress relapses widen the window for detection of PIRA. Detection bias becomes more pronounced as the required period of being relapse-free around PIRA gets longer and is also influenced by a decrease in the frequency of scheduled observations. The opposite effect (false positive PIRA events) may occur if an accurate reporting of relapses is compromised or if relapse definitions are too strict. The unequal EDSS assessment times of observational studies also have implications for an accurate PIRA definition. When the intervals between visits are larger than 6-12 months, it becomes challenging to define roving reference values, as well as confirmed disability accrual events. Therefore, estimation of

PIRA events should be limited to datasets with high quality and well defined standardized data collection.

(III) Proposal of harmonized definition of PIRA

As described above, the determinants of PIRA are used differently in the literature, complicating the comparability and interpretability of study results (see eTable 1). The elements constituting PIRA are summarized in Table 2. In order to harmonize these definitions, we compiled established descriptors related to progression in MS used in protocols of prospective controlled clinical trials and observational cohorts. These descriptors were further refined in several rounds by the author group representing clinical trial, imaging, and body fluid biomarker as well as biostatistical expertise. As a result, we recommend to use the following determinants for diagnosing PIRA both in RRMS and progressive MS (see Figure 3): *(I) Baseline/reference score:* A roving baseline should be applied, that sets a new reference score every time the EDSS or individual measure of the composite is lower than the previous measure and confirmed at the following visit.[3] The reference score should also be reset, if a relapse causes residual disability. *(II) Event score*: An increase of EDSS or composite measure should only be considered for classification to PIRA, if it is not determined within 30 days before and 90 days after the onset of an investigator reported relapse.[21,58] A clinically significant increase of EDSS should be defined in a stepwise stratified manner: EDSS $\geqslant$1·5 points from an EDSS of 0, $\geqslant$1·0 points from an EDSS of 1·0–5·0, or $\geqslant$0·5 point from an EDSS $\geqslant$5·5.[40] A composite measure is recommended and should include upper limb function (measured by 9HPT, threshold: >20% confirmed decline compared to previous visit), walking speed (measured by T25FWT, threshold: >20% decline compared to previous visit), and cognitive testing (information processing speed measured by SDMT, threshold: ≥4 points decline or >10% decline compared to the previous visit).[55] *(III) Confirmation score:* The confirmation visit should take place no earlier than 3 months, preferably 6, or 12 months after the initial disability increase and should

not happen 30 days before and 90 days after the onset of an investigator reported relapse. *(IV) Sustained score*: The EDSS score defining PIRA does not improve until the end of follow up, sensibly at least 12 or even 24 months apart from start of PIRA).

We propose to use the term *disability accrual* to describe any observed increase of disability within context of PIRA. The definition of PIRA represents a trade off of specificity and sensitivity. If a higher specificity for PIRA is desired in a study, we recommend that disability accrual events are only considered as PIRA events in the absence of relapses between baseline/reference score and confirmation score. To ensure reliable data, we recommend using datasets with regularly scheduled standardized clinical assessments with average intervals of 6 months and not exceeding 12 months.

For incorporating MRI data into the PIRA definition, new and/or enlarging T2-lesions and/or gadolinium-enhancing T1-lesions should be used as imaging signs of acute MRI activity, both on brain and spinal cord MRI. To be temporally associated to a clinical event, these signs must be detected in an MRI acquired within 90 days before or after the event. The terms „PIRMA“, „pure PIRA“ and „non-active PIRA“ can be used interchangeably, although the term „PIRMA" may be preferable, as it most accurately describes the situation. To be labeled as „PIRMA“, there should not be any signs of acute MRI activity on spinal and brain MRI within 90 days before the event date and a second spinal and brain MRI within 90 days after the confirmation date.

Remaining questions

The proposed harmonised definition may balance sensitivity and specificity and improve the comparability of results in current and future cohorts and datasets. However, a number of issues remain: (I) PIRA may frequently remain undetected due to the low granularity of our clinical measures. Therefore, in addition to the composite clinical determinants such as 9HPT, T25FWT, and SDMT, future studies should implement comprehensive digital measures including active tasks, passive monitoring, and patient reported outcomes.[59-62] (II) The relationship between PIRA and “true PIRA”, „pure PIRA“, or “PIRMA” should be further elucidated using conventional and advanced

imaging techniques of the brain and spinal cord to extend our understanding of the relation of subclinical (focal) inflammation and clinical PIRA. (III) A concept of progression independent of any disease activity (encompassing established and novel biomarkers) needs to be evaluated, to more precisely identify worsening that may be exclusively attributed to a neurodegenerative component, while accounting for the compensation and reorganization capacity of the CNS. (IV) Beyond traditional definitions advanced concepts based on multimodal characterization will allow more accurate prediction of both natural course and response to more targeted therapeutic options. The utility of diagnostic and treatment algorithms based on such multimodal classifications should be evaluated by combining the advantages of real-world evidence and randomized prospective trial design in pragmatic trials.

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Figure Legends

Figure 1, time points used to calculate disability accrual and define PIRA: Fixed baseline score (A1) or roving baseline score (A2), event score (B), confirmation score (C), sustained score (D). Note that the EDSS increase at visit 5 fulfills the criteria of a significant EDSS increase when using a roving baseline score (∂EDSS between A2 and B is 1·5), while it does not fulfill the criteria of a significant EDSS increase when using a fixed baseline (∂EDSS between A1 and B is 0·5). **Abbreviation:** EDSS Expanded Disability Status Scale, FU follow up.

Figure 2, temporal evolution of disease worsening: (1) EDSS increase at visit 4, not confirmed at visit 5; EDSS improvement at visit 7, not confirmed at visit 8. Such non-confirmed fluctuations may be classified as „noise"; (2) Relapse at visit 1 (indicated by asterisk), subsequent improvement at visit 2, confirmed at visit 3, significant EDSS increase at visit 4, confirmed at visit 5 (i.e. PIRA, indicated by yellow box). Subsequent improvement at visit 7 that goes below the significant EDSS increase compared to the reference at visit 2, hence the EDSS increase is not sustained. (3) Same trajectory as example 2, but the improvement at visit 7 remains above the criteria for a significant EDSS increase compared to the reference at visit 2, hence the EDSS increase is sustained. (4) EDSS increase at visit 3, confirmed at visit 4 (i.e. PIRA, indicated by yellow box), sustained until study end/last documented visit. **Abbreviation:** EDSS Expanded disability status scale, FU follow up.

Figure 3, trajectory of a single patient with disability accrual over time, with a relapse without residual disability (A), a relapse with confirmed disability accrual (relapse associated worsening, RAW; B) a PIRA event that is not sustained (C) and a PIRA event that is sustained (D). PIRA events are highlighted by the yellow boxes. **Abbreviation:** EDSS Expanded disability status scale, PIRA progression independent of relapse activity.

Table 1: Studies covering PIRA according to the systematic review, in chronological order.

Author	Year	Type of record	Methodology	Quality of Evidence§	Cohort	Patients	Main Focus	Primary endpoint	Time Frame	Main Message
Kappos L et al. [3]	2018	Full article	Retrospective analysis of data from observational program	2b	Tysabri observational Program (TOP)	5,562 RRMS on natalizumab	Detection of PIRA using different definitions	CDA, PIRA	Median time on natalizumab 108 weeks	Higher sensitivity using roving measurement
Cree BAC et al.[4]	2019	Full article	Single-center prospective observational cohort study	2b	Expression/genomics, proteomics, imaging, and clinical (EPIC-MS), USA	373 CIS and RRMS	Prevalence of PIRA, effect on MRI	EDSS, T25WT, SDMT, PASAT, 9HPT; brain volume loss	At year 5 and year 10	Long term disability accrual is not driven by relapses
Gil-Perotin S et al.	2019	Letter to the Editor	Letter to the Editor	5	n.a.	n.a.	Silent progression or bout onset PMS?	n.a.	n.a.	Is silent progression the same as BOPMS?
Cree BAC et al.	2019	Letter to the Editor	Letter to the Editor	5	n.a.	n.a.	Answer to question of Gil-Perotin	n.a.	n.a.	BOPMS refers to SPMS, PIRA to RRMS
Lorscheider J et al.[25]	2019	Conference abstract	Retrospective analysis of prospective longitudinal cohort	2b	Swiss MS Cohort Study (SMSC), Switzerland	917 RRMS	PIRA in Swiss MS Cohort	CDW, RAW, PIRA	Mean follow up 4·6 years	2/3 of CDW are PIRA, DMT prevents
Fillipi M and Rocca MA	2019	Comment	Comment	5	n.a.	n.a.	Classifying progression in RMS, discussing MS EPIC study	n.a.	n.a.	Paradigm shift, progression despite inflammatory control
Lorscheider J et al.	2019	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Swiss MS Cohort Study (SMSC), Switzerland	4,608 samples from 806 MS (715 RRMS, 43 SPMS, 48 PPMS)	sNfL and PIRA	sNfL, PIRA	Median follow up 4·7 years	NfL is higher at baseline in PIRA patients compared to clinically stable patients
Kappos L et al.[5]	2020	Full article	Retrospective analysis of RCT data	2b	Data from OPERA I and II trials	1,656 RRMS	Prevalence of PIRA	Composite CDA (EDSS, 25FW, 9HPT)	96 weeks	PIRA>RAW, ocrelizumab prevents

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Ness NH et al.[8]	2020	Full article	Retrospective analysis of prospective longitudinal cohort	2c	Prospective Pharmacoeconomic Cohort Evaluation (PEARL) and Post-Authorization Non-interventional German Safety Study of Gilenya (PANGEA), Germany	1,959 RRMS	Cost of PIRA and RAW	Direct and indirect medical costs of patients with CDW, PIRA and RAW	Mean follow up 21 months	Costs RAW≥PIRA>>stable
Sucksdorff M et al.[41]	2020	Full article	Longitudinal single center study	2b	MS Cohort, Turku, Finland	69 MS, 18 HCs	Perilesionial tissue in PET, and progression	TSPO-PET uptake in perilesional NAWM	Mean follow up 4·1 years	Higher TSPO binding in progressive MS
Bsteh G et al.[7]	2020	Full article	Prospective observational study	2b	Prospective Observational Study on OCT in RMS, Austria	171 RRMS	Retinal thickness in PIRA as marker of neurodegeneration	GCIPL, pRNFL, RAW, PIRA=CDW+SDMT	4 years	Rate of retinal thinning is faster in PIRA (EDSS+SDMT)
Rigoni E et al.[47]	2020	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Imperial College Healthcare Trust, UK	147 RRMS on alemtuzumab	PIRA among patients treated with alemtuzumab	CDA, PIRA, RAW	Mean follow up 3 years	Large proportion of CDW is PIRA in treated patients
Von Wyl V et al.[11]	2021	Full article	Retrospective analysis of prospective longitudinal cohort	2c	Swiss Confederation of Common Task of Health Insurances (SVK), Switzerland	1,640 relapse free RRMS on IFN/GA or fingolimod	PIRA in IFN/GA vs. fingolimod	CDW, RAW, PIRA	Median follow up time 5·0 (IFN/GA) and 3·9 (finglimod) years	Fingolimod>IFN/GA in preventing RAW and PIRA (after correction for indication bias)
Lorscheider J	2021	Transcript of educational Session	Comment, Abstract	5	n.a.	n.a.	When does progression start?	n.a.	n.a.	Paradigm shift, progression in early stages
Balasa R et al.	2021	Review	Review	3a	n.a.	n.a.	Blood brain barrier in progressive MS (amongst others)	n.a.	n.a.	PIRA as progression with intact blood brain barrier
Graf J et al.[9]	2021	Full article	Cross sectional retrospective analysis of longitudinal cohort	2b	Data from Heinrich Heine-University Düsseldorf and Ludwig-Maximilian University Munich, Germany	184 MS (140 RRMS) on natalizumab >24months	Prevalence of PIRA, PIRA as indicator of SPMS	CDA, PIRA, RAW	Median time to cPIRA 10 years	Natalizumab is more effective in preventing relapses than progression/PIRA

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Prosperini L et al.[22]	2021	Full article	Retrospective 2-center observational study	2b	Data from S. Camillo-Forlanini Hospital and S. Andreas Hospital, Rome, Italy	224 on IFNb or GA with NEDA3 >2 years after onset	PIRA in patients with NEDA-3, risk factors, spinal MRI	CDW, RAW, PIRA, CEL	Median follow up 12 years	PIRA also in patients who have NEDA-3. Drivers: Age and spinal cord lesions
Kapica-Topczewska K et al.[10]	2021	Full article	Retrospective analysis of observational multicenter study	2c	National Health Fund, Poland	5,339 RRMS	PIRA over first 2 years of treatment, PIRA and MRI	CDW, RAW, PIRA, PIRMA	Maximum follow up of 60 months (median not reported)	No effect of DMT, PIRA 4·6%, PIRMA 4·5%
Stampanoni-Bassi M et al.	2021	Full article	Cross sectional study	2b	Data from Neuromed Hospital, Pozzilli, Italy	266 RRMS	Age and CSF- and MEP-profiles	CSF, MEP	n.r.	Stratified age correlates with CSF and TMS-profile
Sandi D et al.	2021	Review	Review	2b	n.a.	n.a.	Silent progression and neuroprotective treatment	n.a.	n.a.	Neurodegeneration is pivotal in MS
Bellinvia A et al.[24]	2021	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Italian MS Registry, Italy	5,340 RRMS	RAW and PIRA in pediatric, adult and late onset MS	CDA, PIRA, RAW	Mean follow up 11·5 years	PIRA more in late>adult>pediatric
Tur C et al.[36]	2021	Conference abstract	Retrospective analysis of observational multicenter study	2b	Barcelona cohort, Spain	727 RRMS	Clinical and MRI features of patients with PIRA	CDA, RAW, PIRA, „true PIRA“, T2 PIRA	Median follow up 12 years	Small proportion of PIRA is „true PIRA“
Keenan A et al.[46]	2021	Conference abstract	Retrospective analysis of RCT data	2b	Data from OPTIMUM trial	1,133 RRMS	Efficacy of ponesimod on composite CDA, RAW and PIRA	Efficacy of ponesimod on composite CDA, composite RAW and composite PIRA	8 years	n.a.
Bischof A et al.[39]	2022	Full article	Retrospective analysis of longitudinal cohort study	2b	Expression/genomics, proteomics, imaging, and clinical (EPIC-MS), USA	360 RRMS, 47 SPMS, 80 HC	Spinal cord atrophy and progression in RRMS	Spinal cord atrophy on C1 level	Years of follow up 12 years	Spinal cord atrophy is pronounced in silent progression and SPMS
Giovannoni G et al.[6]	2022	Review	Review	2b	n.a.	n.a.	„Smouldering MS“	n.a.	n.a.	Smouldering MS as „real MS“, relapses as „side effect“

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Author	Year	Type of record	Methodology	Quality of Evidence§	Cohort	Patients	Main Focus	Primary endpoint	Time Frame	Main Message
Bittner S and Zipp F[50]	2022	Review	Review	2b	n.a.	n.a.	Progression in MS	n.a.	n.a.	Progression as a long term problem, NfL and PRL as biomarkers of progression
Filippi M et al.[52]	2022	Review	Review	2b	n.a.	n.a.	Early use of DMT	n.a.	n.a.	PIRA should be considered for therapeutic goals
Lublin FD et al.[16]	2022	Full article	Retrosspective analysis of RCTs and observational program	2b	Novartis-Oxford MS (NO.MS)	27,328 (3 sub-cohorts)	Contribution of PIRA and RAW to progression	3m/6m CDW, RAW, PIRA	Not reported, approx. 200,000 EDSS transitions	PIRA starts in RRMS, becomes main driver in PMS
Gärtner J et al.[15]	2022	Full article	Retrospective analysis of RCT data	2b	Data from ASCLEPIOS I and II trials	615 recently diagnosed, treatment-naive RR- and SPMS	Efficacy of ofatumumab, PIRA as study outcome	ARR, 6mCDW, 6mPIRA, (AE)	Median exposure to study treatment: 1·65 years	Ofatumumab prevents CDW, RAW and PIRA (but not in sensitivity analysis)
Portaccio E et al.[13]	2022	Full article	Retrospective analysis of longitudinal cohort study	2b	Italian MS Registry, Italy	5,269 CIS and early RRMS	PIRA in CIS and early MS patients	PIRA, RAW, „true PIRA“, „true RAW“	Mean follow up time 11·5 years	PIRA present in CIS/early MS, MRI reduces proportion of PIRA, DMT prevents both RAW and PIRA
Thebault S et al.[30]	2022	Full article	Retrospective analysis of prospective observational study	2b	Data from MEsenchymal StEm cells for Multiple Sclerosis (MESEMS), Canada and Italy	496 serum samples of 58 RRMS	Predictive value of sNfL and GFAP	sNfL, GFAP, composite CDA, RAW, PIRA	48 weeks	Baseline sNfL predictive of future cPIRA
Masanneck L et al.[35]	2022	Full article	Observational, longitudinal cohort study	2c	Data from two MS centers, Düsseldorf and Mainz, Germany	46 RRMS on first line DMT	PIRA and (loss of) NEDA-3	Composite CDA (EDSS, 25FW, 9HPT), (loss of) NEDA-3	Median follow up 68 months	cPIRA and NEDA-3 do not completely overlap
Cagol A et al.[12]	2022	Full article	Observational, longitudinal cohort study	2b	Swiss MS Cohort Study (SMSC), Switzerland	1,904 MRI scans from 516 RRMS	Brain atrophy and PIRA	Brain atrophy rates	Median follow up 3·2 years	Atrophy (specially GM) PIRA=RAW>>stable
Chen B et al.[26]	2022	Full article	Mediator analysis	2c	Data from Tongji Hospital, Huazhong, China	212 RRMS	Contribution of PIRA and RAW to progression	RAW, PIRA (although no clear definition reported)	n.r.	PIRA is the main contributor to disability accrual

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Author	Year	Type of record	Methodology	Quality of Evidence§	Cohort	Patients	Main Focus	Primary endpoint	Time Frame	Main Message
Tur C et al.[14]	2022	Full article	Retrospective analysis of observational multicenter study	2b	Barcelona cohort, Spain	1,128 CIS/RRMS after first demyelinating event	PIRA after first demyelinating event	CDA, RAW, PIRA, active/non-active PIRA, early/latePIRA	Median follow up 10·5 years	PIRA is associated with unfavorable outcomes especially early in the disease
Sedaghat N and Etemadifar M	2022	Full article	Correspondance	5	n.a.	n.a.	Commentary on IFN on RAW and PIRA	n.a.	n.a.	IFNs are not effective on PIRA
Portaccio E et al.[29]	2022	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Italian MS Registry, Italy	16,130 RRMS with FU >5 years	Affection of functional scores in PIRA and RAW	CDA, PIRA, RAW, functional scores	Median follow up 11·8 years	PIRA affects more bowel/bladder and cognition than RAW
Portaccio E et al.[23]	2022	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Italian MS Registry, Italy	16,130 RRMS with FU >5 years	Coexistence of PIRA and RAW in one patient	CDA, PIRA, RAW	Median follow up 11·8 years	PIRA main progression determinant, approx. 50% of patients have both PIRA and RAW
Zanghi A et al.[48]	2022	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Italian MS Registry, Italy	2,260 RRMS	PIRA/RAW and DMT (injectables vs. Orals)	CDA, PIRA, RAW	Mean follow up 39·5 months	Both PIRA and RAW occur more frequently in patients on injectables versus orals
Ocampo-Pineda M et al.[37]	2022	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Swiss MS Cohort Study (SMSC), Switzerland	126 RRMS	White matter tracts on MRI in PIRA/RAW	RAW, PIRA	Median follow up 4 years	Alterations of WM tracts associated with PIRA
Barro C et al.[32]	2022	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Comprehensive Longitudinal Investigation of MS at the Brigham and Women's Hospital (CLIMB), USA	685 MS	Predictive value of NfL and GFAP on CDW and PIRA, by age	CDW, PIRA	Median follow up 8·3 years	GFAP, not sNfL is predictive of PIRA
Polidoro F et al.	2022	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Imperial College Healthcare Trust, UK	406 MS	PIRA in patients with ocrelizumab and alemtuzumab	CDA, PIRA	Median follow up 3·7 years	Similar proportions of PIRA in both groups
Pisani AI et al.[38]	2022	Conference abstract	Longitudinal cohort study	2b	n.r.	82 RRMS	Cortical lesions and CSF profiles in patients with PIRA	CDA, PIRA, SDMT	Mean follow up 5 years	PIRA patients had larger number of CL and intrathecal inflammation

Table 1: Studies covering PIRA according to the systematic review, in chronological order.

Author	Year	Type of record	Methodology	Quality of Evidence§	Cohort	Patients	Main Focus	Primary endpoint	Time Frame	Main Message
Pawlitzki M et al.[56]	2022	Conference abstract	Observational, longitudinal cohort study	2b	Data from two MS centers, Düsseldorf and Mainz, Germany	301 RRMS	Comparison of composite measures for progression	CDA, NEDA, PIRA, RAW, NfL	Median follow up 67·2 months	Complementary use of measures increases sensitivity
Mancuso E et al.	2022	Conference abstract	Longitudinal cohort study	2b	n.r.	122 MS	Comparison of balance in PIRA, vs. HCs	Standing balance test, PIRA	Mean follow up of 12·7 months	Balance testing may detect silent progression
Ozakbas S et al.	2022	Conference abstract	Prospective cohort study	2b	ISA prospective Cohort, Turkey	276 RRMS on ocrelizumab	PIRA in patients on ocrelizumab, after >2 years	EDSS, T25WT, 9HPT	2 years	Protective effect of ocrelizumab lessens in the second year
Abdelhak A et al.[31]	2022	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Expression/genomics, proteomics, imaging, and clinical (EPIC-MS), USA	3,906 NfL samples of 609 MS	NfL in PIRA and PARA	PIRA, PARA	> 3 years follow up	Associations between EDSS and NfL are primarily driven by RAW/PARA, not PIRA
Iaffaldano P et al.[27]	2022	Conference abstract	Retrospective analysis of longitudinal cohort study	2b	Italian MS Registry, Italy	3,777 MS	Associations PIRA/RAW and age	CDA, PIRA, RAW	> 5 years follow up	PIRA is major determinant of CDA in all age groups

§ Level of evidence as by the Oxford Center for Evidence-Based Medicine: Levels of Medicine (March 2009). Abbreviations: BOPMS bout onset progressive multiple sclerosis; CDA confirmed disability accrual; CEL contrast enhancing lesion; CIS clinically isolated syndrome; CL cortical lesions; CSF cerebrospinal fluid; DMT disease modifying therapy; EDSS expanded disability status scale; FTY fingolimod; FU follow up; GA glatiramer acetate; GCIPL ganglion cell-inner plexiform layer; GFAP glial fibrillary acidic protein; GM gray matter; HCs healthy controls; IFN interferone; MEP motor evoked potentials; n.a. not applicable; n.r. not reported; NEDA no evidence of disease activity; NfL neurofilament light chains; NTZ natalizumab: MS multiple sclerosis; PARA progression associated with relapse activity; PASAT paced auditory serial addition test; PIRA progression independent of relapse activity; PIRMA progression independent of relapse and MRI activity; PRL paramagnetic rim lesions; PRNFL peripapillary rretinal nerrve fiber layer; RAW relapse associated worsening; RRMS relapsing remitting multiple sclerosis; SDMT symbol digit modalities test; SPMS secondary progressive multiple sclerosis; WM white matter; 9HPT 9-hole peg test; 25FWT 25-foot walk test.

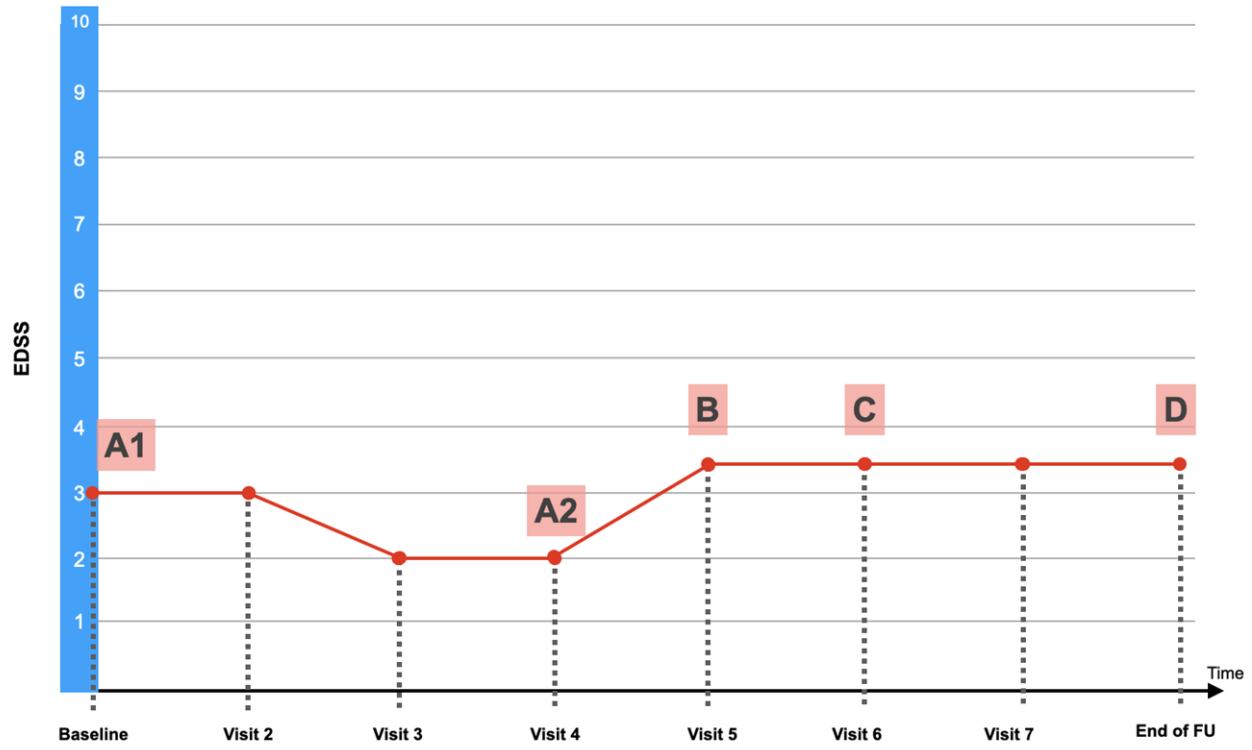


Figure 1, time points used to calculate disability accrual and define PIRA: Fixed baseline score (A1) or roving baseline score (A2), event score (B), confirmation score (C), sustained score (D). Note that the EDSS increase at visit 5 fulfills the criteria of a significant EDSS increase when using a roving baseline score (∂EDSS between A2 and B is 1·5), while it does not fulfill the criteria of a significant EDSS increase when using a fixed baseline (∂EDSS between A1 and B is 0·5). **Abbreviation:** EDSS Expanded Disability Status Scale, FU follow up.

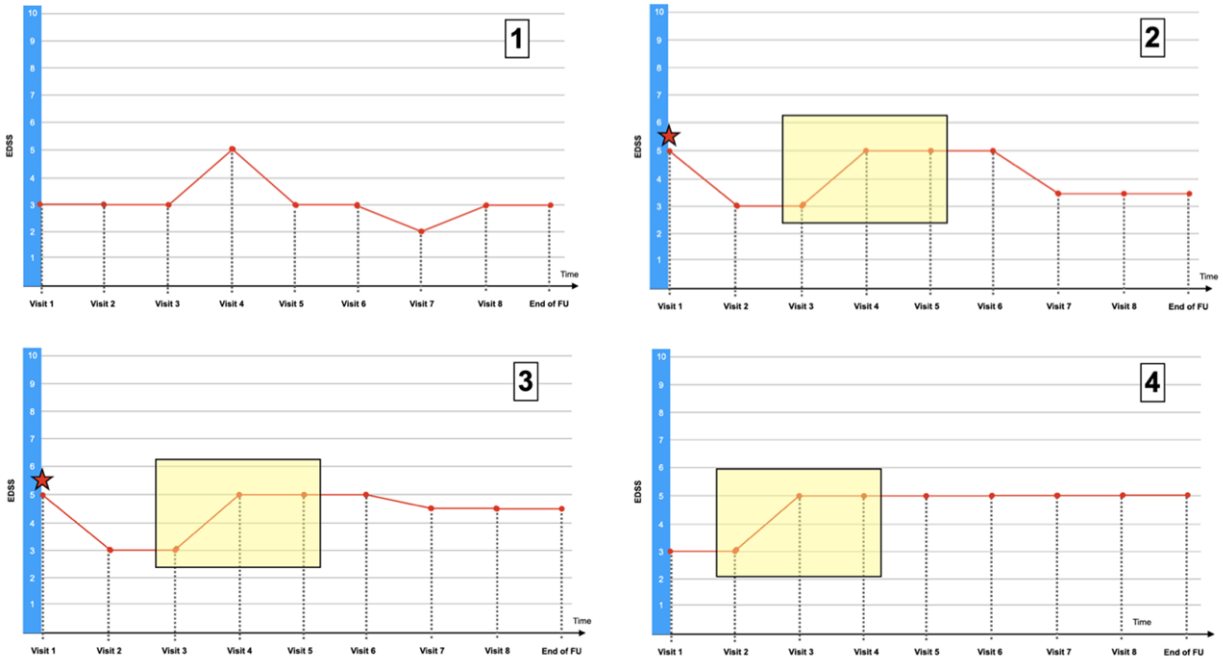


Figure 2, temporal evolution of disease worsening: (1) EDSS increase at visit 4, not confirmed at visit 5; EDSS improvement at visit 7, not confirmed at visit 8. Such non-confirmed fluctuations may be classified as „noise“; (2) Relapse at visit 1 (indicated by asterisk), subsequent improvement at visit 2, confirmed at visit 3, significant EDSS increase at visit 4, confirmed at visit 5 (i.e. PIRA, indicated by yellow box). Subsequent improvement at visit 7 that goes below the significant EDSS increase compared to the reference at visit 2, hence the EDSS increase is not sustained. (3) Same trajectory as example 2, but the improvement at visit 7 remains above the criteria for a significant EDSS increase compared to the reference at visit 2, hence the EDSS increase is sustained. (4) EDSS increase at visit 3, confirmed at visit 4 (i.e. PIRA, indicated by yellow box), sustained until study end/last documented visit. **Abbreviation:** EDSS Expanded disability status scale, FU follow up.

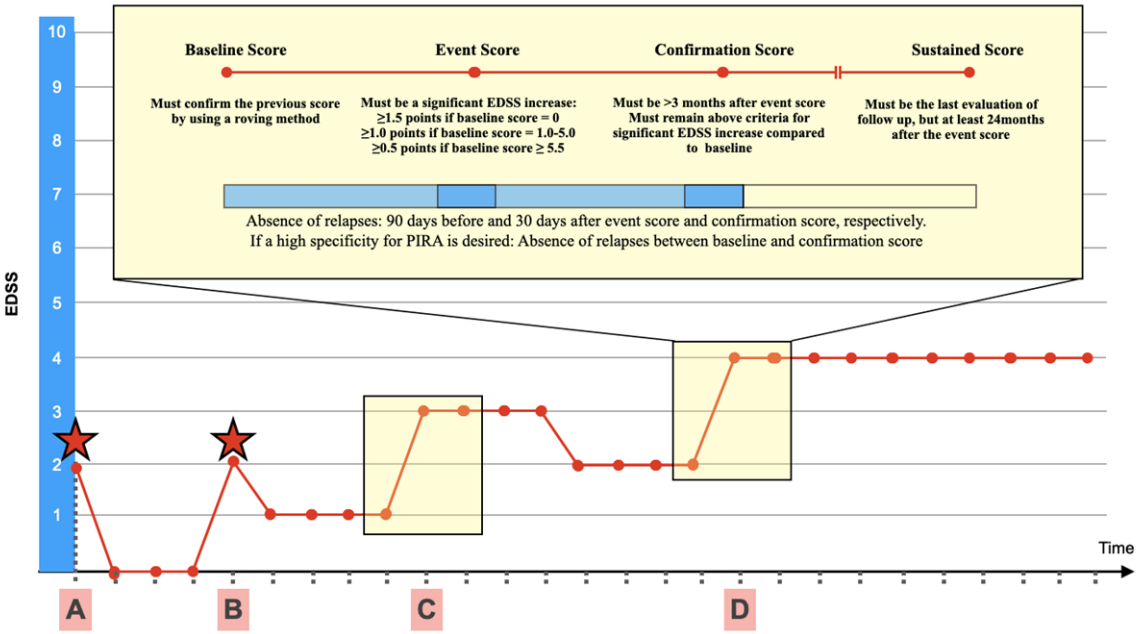


Figure 3, trajectory of a single patient with disability accrual over time, with a relapse without residual disability (A), a relapse with confirmed disability accrual (relapse associated worsening, RAW; B) a PIRA event that is not sustained (C) and a PIRA event that is sustained (D). PIRA events are highlighted by the yellow boxes. **Abbreviation:** EDSS Expanded disability status scale, PIRA progression independent of relapse activity.

Supplementary Material

Table of Content

1. Specification of the PRISMA Checklist, including PRISMA-Flowchart (eFigure 1) Pages 1-5

2. Search Strategy, Search Blocks and Search Results of Systematic Review Pages 6-9

3. eTable 1: Determinants of PIRA as applied in previous studies Pages 10-12

4. eTable 2: Excluded studies and reason for ineligibility Pages 13-15

1. Specification of the PRISMA Checklist

Title (PRISMA Checklist Item 1)

See title (manuscript page 1).

Abstract (PRISMA Checklist Item 2)

See abstract (manuscript page 3).

Introduction (PRISMA Checklist Items 3 and 4)

See introduction (manuscript page 4).

Eligibility Criteria (PRISMA Checklist Item 5)

Inclusion Criteria

- Peer reviewed manuscripts or peer reviewed abstracts
- 1990-25.12.2022
- Primary research focus of the article on progression independent of relapses in RRMS

Exclusion criteria

- Case reports/case series, interviews
- Study protocols of ongoing trails
- Articles not directly addressing PIRA in RRMS
- Conference abstracts, of which a publication with more data is available

Information Sources (PRISMA Checklist Item 6)

Pubmed, Embase, Cochrane, Web of Science

Search Strategy (PRISMA Checklist Item 7)

We searched literature in PubMed, Embase, Cochrane and Web of Science for peer-reviewed records covering PIRA published between 01.01.1990 and 25.12.2022. The search terms „multiple sclerosis“, „PIRA“ „progression independent of relapse activity“, „silent progression“, and „progression unrelated to relapses“ were used. The search blocks using Medical Subject Headings (MeSH-terms) and free text terms restricted to the title and abstract (tiab-terms) are provided below (supplementary material page 6-9).

Data collection and selection procedure (PRISMA Checklist Items 8 and 9)

JM screened the records, collected, and tabulated the data. The decision on whether to include a study in the review was based on a consensus judgement of JM, CG, and LK, and was confirmed by the other authors.

Data items (PRISMA Checklist Items 10a and b)

Predefined topics of interest were: definition and terminology applied for PIRA, reported prevalence/incidence, pathophysiology of PIRA, clinical, serologic and imaging risk factors and its potential treatment. To describe the different definitions of PIRA used in the literature, eight major parameters were identified, that affect the sensitivity and specificity of the PIRA definition: setting, term used for PIRA, clinical measure, clinically significant increase in disability, baseline, confirmation interval, reporting of relapses, and interval of relapse absence. Secondary data items collected for each study were the type of record (i.e., full article, conference abstract, letter to the editor, etc.), methodology (i.e., observational real-world evidence vs. randomized controlled trial data), cohort, main focus of the study, primary endpoint (clinical, imaging, laboratory), and time frame (i.e. length of follow up). No quantitative variables were sought or collected.

Study risk of bias assessment (PRISMA Checklist Item 11)

Given the design and aim of the study, which focused on summarizing the current definitions of PIRA reported and used in the literature, risk of reporting bias does not exist.

Effect measures (PRISMA Checklist Item 12)

Given the qualitative rather than quantitative analysis of the records, no effect measures were used.

Synthesis methods (PRISMA Checklist Items 13a-f)

Data items named in PRISMA Checklist item 10a and 10b were qualitatively extracted from the studies and tabulated in the excel files shown below.

Setting	Year	Type of data	Term used	Triggering Clinical Measure	Clinically significant increase of measure	Baseline	Confirmation Interval	Reporting of relapses	Interval of relapse absence	Other
1										
2										
3										

Number	Author	Year	Type of record	Methodology	Cohort	Patients	Main Focus	Primary endpoint	Time Frame	Main Message
1										
2										
3										

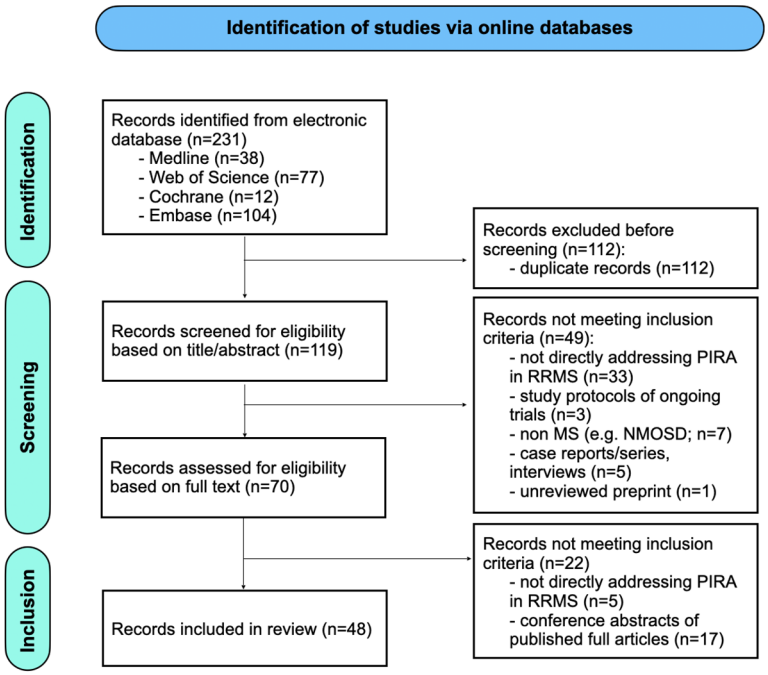
Reporting bias assessment (PRISMA Checklist Item 14)

Given the design and aim of the study, which focused on summarizing the current definitions of PIRA reported and used in the literature through a qualitative rather than quantitative analysis, the risk of reporting bias does not exist.

Certainty assessment (PRISMA Checklist Item 15)

Given the design and aim of the study, which focused on summarizing the current definitions of PIRA used in the literature through a qualitative rather than quantitative analysis, no assessments of certainty we applied.

Study selection (PRISMA Checklist item 16a and 16b)



eFigure 1, PRISMA-Flowchart. Abbreviations: NMOSD neuromyelitis optica spectrum disorder; PIRA progression independent of relapse activity; RRMS relapsing remitting multiple sclerosis

Study characteristics (PRISMA Checklist Item 17)

See Table 1.

Risk of bias in studies (PRISMA Checklist Item 18)

Given the design and aim of the study, which focused on summarizing the current definitions of PIRA used in the literature through a qualitative rather than quantitative analysis, the risk of reporting bias does not exist.

Results of individual studies (PRISMA Checklist Item 19)

Given the design and aim of the study, which focused on summarizing the current definitions of PIRA used in the literature through a qualitative rather than quantitative analysis, no summary statistics or effect estimates of individual studies were performed.

Results of syntheses (PRISMA Checklist Items 20a-d)

Given the design and aim of the study, which focused on summarizing the current definitions of PIRA used in the literature through a qualitative rather than quantitative analysis, no statistical syntheses were conducted.

Discussion (PRISMA Checklist Items 23a-d)

See discussion (manuscript page 11).

Registration and protocol (PRISMA Checklist Item 24a-c)

The review was not registered. Written requests for access to the review protocol will be considered by the corresponding author. There are no amendments to the protocol.

Support (PRISMA Checklist Item 25)

There was no project-specific funding, financial and/or non-financial support for this review.

Competing Interests (PRISMA Checklist Item 26)

The authors report no project-specific competing interests.

Availability of data, code and other material (PRISMA Checklist Item 27)

Other than the excel template provided under PRISMA Checklist Item 13a-f, no templates, codes or other materials were used for this review.

2. Search Strategy, Search Blocks and Search Results of Systematic Review

Systematic search performed on 25.12.2022, by Jannis Müller

Pubmed

#1 „Multiple Sclerosis“[Mesh] OR „Multiple Sclerosis, Relapsing-Remitting“[Mesh] OR „Multiple Sclerosis“[tiab] OR „Relapsing Remitting Multiple Sclerosis“[tiab]
#2 „PIRA“[tiab] OR „progression independent of relapse activity“[tiab] OR „silent progression“[tiab] OR „progression unrelated to relapses“[tiab]
#3 #1 AND #2

PubMedSearchHistory-3

Search number	Query	Search Details	Results	Time
3	#1 AND #2	("Multiple Sclerosis"[MeSH Terms] OR "multiple sclerosis, relapsing remitting"[MeSH Terms] OR "Multiple Sclerosis"[Title/Abstract] OR "Relapsing Remitting Multiple Sclerosis"[Title/Abstract]) AND ("PIRA"[Title/Abstract] OR "progression independent of relapse activity"[Title/Abstract] OR "silent progression"[Title/Abstract])	38	04:53:21
2	„PIRA"[tiab] OR „progression independent of relapse activity"[tiab] OR „silent progression"[tiab] OR „progression unrelated to relapses"[tiab]	"PIRA"[Title/Abstract] OR "progression independent of relapse activity"[Title/Abstract] OR "silent progression"[Title/Abstract]	306	04:53:11
1	„Multiple Sclerosis"[Mesh] OR „Multiple Sclerosis, Relapsing-Remitting"[Mesh] OR „Multiple Sclerosis"[tiab] OR „Relapsing Remitting Multiple Sclerosis"[tiab]	"Multiple Sclerosis"[MeSH Terms] OR "multiple sclerosis, relapsing remitting"[MeSH Terms] OR "Multiple Sclerosis"[Title/Abstract] OR "Relapsing Remitting Multiple Sclerosis"[Title/Abstract]	96,630	04:52:55

Web of Science

#1: ALL=(„multiple sclerosis")
#2: ALL=("PIRA" OR "progression independent of relapse activity" OR "silent progression" OR "progression unrelated to relapses“)

#3: #2 AND #1

#	Search Query	Entitlements	Results	Date Run
1	ALL=("multiple sclerosis")	- WOS.IC: 1993 to 2022 - WOS.CCR: 1985 to 2022 - WOS.SCI: 1900 to 2022 - WOS.AHCI: 1975 to 2022 - WOS.BHCI: 2005 to 2022 - WOS.BSCI: 2005 to 2022 - WOS.ESCI: 2017 to 2022 - WOS.ISTP: 1990 to 2022 - WOS.SSCI: 1900 to 2022 - WOS.ISSHP: 1990 to 2022	161410	Sun Dec 25 2022 14:36:39 GMT+0100 (Mitteleuropäische Normalzeit)
2	ALL=("PIRA" OR "progression independent of relapse activity" OR "silent progression" OR "progression unrelated to relapses")	- WOS.IC: 1993 to 2022 - WOS.CCR: 1985 to 2022 - WOS.SCI: 1900 to 2022 - WOS.AHCI: 1975 to 2022 - WOS.BHCI: 2005 to 2022 - WOS.BSCI: 2005 to 2022 - WOS.ESCI: 2017 to 2022 - WOS.ISTP: 1990 to 2022 - WOS.SSCI: 1900 to 2022 - WOS.ISSHP: 1990 to 2022	3638	Sun Dec 25 2022 14:37:50 GMT+0100 (Mitteleuropäische Normalzeit)
3	#2 AND #1	- WOS.IC: 1993 to 2022 - WOS.CCR: 1985 to 2022 - WOS.SCI: 1900 to 2022 - WOS.AHCI: 1975 to 2022 - WOS.BHCI: 2005 to 2022 - WOS.BSCI: 2005 to 2022 - WOS.ESCI: 2017 to 2022 - WOS.ISTP: 1990 to 2022 - WOS.SSCI: 1900 to 2022 - WOS.ISSHP: 1990 to 2022	77	Sun Dec 25 2022 14:38:00 GMT+0100 (Mitteleuropäische Normalzeit)

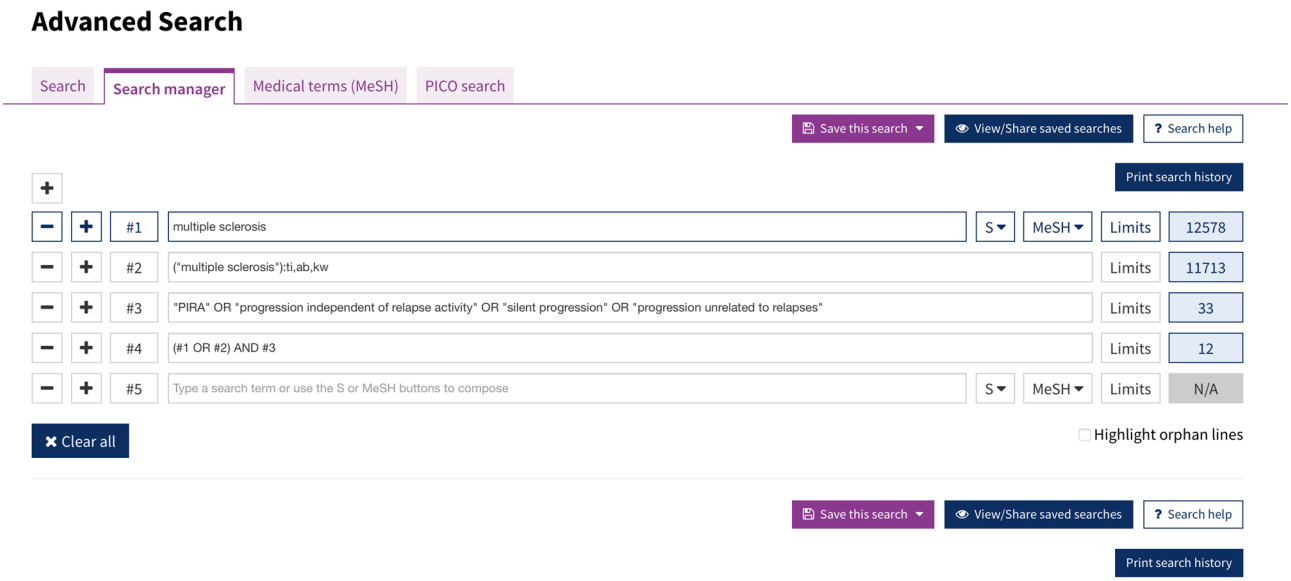
Cochrane

#1 multiple sclerosis

#2 („multiple sclerosis“):ti,ab,kw

#3 „PIRA“ OR „progression independent of relapse activity“ OR „silent progression“ OR „progression unrelated to relapses“

#4 (#1 OR #2) and #3



Embase

#1 multiple sclerosis'/exp OR 'multiple sclerosis’

#2 pira' OR 'progression independent of relapse activity' OR 'silent progression' OR 'progression unrelated to relapses’

#3 1 AND 2

No.	Query	Results
#3	#1 AND #2	104
#2	pira' OR 'progression independent of relapse activity' OR 'silent progression' OR 'progression unrelated to relapses'	1341
#1	multiple sclerosis'/exp OR 'multiple sclerosis'	175814

3. eTable 1: Determinants of PIRA as applied in previous studies

	Year	Type of data	Term used	Triggering Clinical Measure	Clinically significant increase of measure	Baseline	Confirmation Interval	Reporting of relapses	Interval of relapse absence
Kappos L et al. [3]	2018	Observational program	PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0)	Fixed baseline and roving baseline	24-weeks confirmed	Investigator	No relapse from the 30 days prior to the disability increase to either 30 days or 12 weeks after the disability increase
Cree BAC et al.[4]	2019	Observational	Silent progression	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Fixed baseline	„Confirmed“ (maintained for 2 consecutive annual visits), „long term“ (after 5 years), „sustained“ (after 10 years)	Patient	No relapse 12 months prior to disability increase
Lorscheider J et al.[25]	2019	Observational	PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0)	Roving baseline, re-baselining and fixed baseline	≥6-month confirmed	Treating neurologist	No relapse between baseline and confirmation
Lorscheider J et al.	2020	Observational	PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0)	Fixed baseline	≥6-month confirmed	Treating neurologist	No relapse during follow up
Kappos L et al.[5]	2020	RCT	PIRA	Composite (EDSS and/or 25FWT and/or 9HPT)	⩾1 points (from an EDSS of 0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0), or an increase of 20% or more in T25FW, or an increase of 20% or more in 9HPT	Fixed baseline, re-baselining after a relapse	≥12- or ≥24-weeks confirmed	Investigator	No relapse between reference and within 30 days after the disability increase and 30 days prior to and after the confirmation
Ness NH et al.[8]	2019	Observational	PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Roving baseline	6- or 12-month confirmed	Treating neurologist	No relapse between reference and confirmation
Von Wyl V et al.[11]	2020	Observational	PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Fixed baseline	12-months confirmed	Treating neurologist	No relapse over the entire observation period
Bsteh G et al.[7]	2020	Observational	PIRA	EDSS and/or SDMT	⩾1·0 points (from an EDSS of 0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0); or loss of 4 points or ≥10% in SDMT score	Fixed baseline	24-weeks confirmed	Treating neurologist	No relapse in the 30 days before or after disability increase
Sucksdorff M et al.[41]	2020	Observational	PIRA	EDSS	⩾1·0 points (from an EDSS of 0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0)	Fixed baseline	6-month confirmed	Treating neurologist	No relapse within 30 days of disability increase and confirmation
Rigoni E et al.[47]	2020	Observational	PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Fixed baseline	n.r.	n.r.	No relapse within 90 days of disability increase
Graf J et al.[9]	2021	Observational	PIRA	EDSS	⩾1·0 points (from an EDSS of 0–3), or ⩾0·5 point (from an EDSS ⩾3·5)	Roving baseline	≥12-week confirmed	Treating neurologist	„time interval without relapses for a minimum of 12 consecutive months“

	Year	Type of data	Term used	Triggering Clinical Measure	Clinically significant increase of measure	Baseline	Confirmation Interval	Reporting of relapses	Interval of relapse absence
Prosperini l et al.[22]	2021	Observational	PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Fixed baseline	6-month confirmed	n.r.	No relapse >3 months prior to disability increase
Kapica-Topczewska k et al.[10]	2021	Observational	PIRA, PIRMA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0)	Fixed baseline	12-months confirmed	Treating neurologist	n.r.
Bischof A et al.[39]	2021	Observational	Silent progression	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Fixed baseline	12-months confirmed	n.r.	n.r.
Bellinvia A et al.[24]	2021	Observational	PIRA	EDSS	n.r.	n.r.	6-months confirmed	n.r.	n.r.
Tur C et al.[36]	2021	Observational	PIRA, „pure PIRA“	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Fixed baseline, re-baselined after relapse	6-months confirmed	n.r.	No relapse within 3 months before disability increase (6 months if first relapse)
Keenan A et al.[46]	2021	RCT	PIRA	Composite (EDSS and/or 25FWT and/or 9HPT)	⩾1·0 points (from an EDSS of 0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0), or an increase of 20% or more in T25FW, or an increase of 20% or more in 9HPT	Fixed baseline	≥12- or ≥24-weeks confirmed	n.r.	n.r.
Lublin FD et al.[16]	2022	Observational, clinical trials and their extension studies	PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Fixed baseline	3- or 6-month confirmed	Investigator	No prior relapse or disability increase more than 90 days after a relapse
Gärtner J et al.[15]	2022	RCT	PIRA	Composite (EDSS and/or 25FWT and/or 9HPT)	⩾1·0 points (from an EDSS of 0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0), or an increase of 20% or more in T25FW, or an increase of 20% or more in 9HPT	Fixed baseline	3- or 6-month confirmed	Investigator	No relapse during onset of progression
Portaccio E et al.[13]	2022	Observational	PIRA, „true PIRA“	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0)	Fixed baseline	≥24-weeks confirmed	n.r.	No relapse >90 days before and >30 after disability increase
Thebault S et al.[30]	2022	RCT	PIRA	Composite (EDSS and/or 25FWT and/or 9HPT)	⩾1·0 points (from an EDSS of 0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0), or an increase of 20% or more in T25FW, or an increase of 20% or more in 9HPT	Fixed baseline	≥12-weeks confirmed	Investigator	n.r.

	Year	Type of data	Term used	Triggering Clinical Measure	Clinically significant increase of measure	Baseline	Confirmation Interval	Reporting of relapses	Interval of relapse absence
Masanneck L et al.[35]	2022	Observational	PIRA	Composite (EDSS and/or 25FWT and/or 9HPT)	⩾1·0 points (from an EDSS of 0–5·5), or ⩾0·5 point (from an EDSS ⩾6·0), or an increase of 20% or more in T25FW, or an increase of 20% or more in 9HPT	Fixed baseline, re-baselining after a relapse	Confirmed at next visit or at latest 6 months	Treating neurologist	No relapse between baseline and 30 days after disability increase
Cagol A et al.[12]	2022	Observational	PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Fixed baseline	>6-months confirmed	Treating neurologist	No relapse during 90 days before disability increase and during the 6-month period between disability increase and confirmation
Tur C et al.[14]	2022	Observational	PIRA, active/non-active PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Fixed baseline, re-baselined after relapse	n.r.	n.r.	Period between two relapses, >3 or >6 months after a relapse
Portaccio E et al.[23]	2022	Observational	PIRA	EDSS	n.r.	n.r.	6-month confirmed	n.r.	n.r.
Zanghi A et al.[48]	2022	Observational	PIRA	EDSS	n.r.	n.r.	n.r.	n.r.	n.r.
Ocampo-Pineda M et al.[37]	2022	Observational	PIRA	EDSS	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	Fixed baseline	>6-months confirmed	Treating neurologist	No relapses during entire follow up
Barro C et al.[32]	2022	Observational	PIRA	EDSS	n.r.	n.r.	6-months confirmed	n.r.	n.r.
Polidoro F et al.	2022	Observational	PIRA	EDSS	>1 point, not further specified	n.r.	n.r.	n.r.	No relapse within 90 days
Pisani AI et al.[38]	2022	Observational	PIRA	EDSS and/or SDMT	⩾1·5 points (from an EDSS of 0), ⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	n.r.	12-months confirmed	n.r.	n.r.
Mancuso E et al.	2022	Observational	PIRA	EDDS	⩾1·0 points (from an EDSS of 1·0–5·0), or ⩾0·5 point (from an EDSS ⩾5·5)	n.r.	n.r.	n.r.	n.r.
Ozakbas S et al.	2022	Prospective observational	PIRA	Composite (EDSS and/or 25FWT and/or 9HPT)	Increase of EDSS, increase >20% of 25FWT, increase >20% in 9HPT	Fixed baseline	3-months confirmed	n.r.	No relapse during 30 days before or after disability increase
Abdelhak A et al.[31]	2022	Observational	PIRA, „PARA“	EDSS	„EDSS increase“, not further specified	n.r.	12-months confirmed	n.r.	n.r.

No formal clinical definitions were provided in the records of: Gil-Perotin S et al. (2019), Cree BAC et al. (2019), Fillipi M and Rocca MA (2019), Filippi M et al. (2022), Giovannoni G et al. (2022), Bittner S and Zipp F (2022), Stampanoni-Bassi M et al. (2021), Balasa R at al. (2021), Chen B et al. (2022), Bellinvia A et al. (2021), Lorscheider J (2021), Sandi D et al. (2022), Pawlitzki M et al. (2022), Iaffaldano P et al. (2022), Sedaghat N and Etemadifar M (2022). **Abbreviations:** EDSS expanded disability status scale; n.r. not reported; PARA progression associated with relapse activity; PIRA progression independent of relapse activity; PIRMA progression independent of relapse and MRI activity; RCT randomized clinical trial; RAW relapse associated worsening; SDMT symbol digit modalities test; 9HPT 9-hole peg test; 25FWT 25-foot walk test.

4. eTable 2: Excluded studies and reason for ineligibility

	Author	Year	Type of Record	Exclusion	Reason for Ineligibility
49	**Cittadella R et al.**	2002	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
50	**Savettierei G et al.**	2003	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
51	**Savettierei G et al.**	2004	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
52	**Nicoletti A et al.**	2005	Full article	After title/abstract analysis	Case report/Case series
53	**Nocentini U et al.**	2006	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
54	**Patti F et al.**	2007	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
55	**Gergont A et al.**	2008	Full article	After title/abstract analysis	Non MS (pediatric)
56	**Pavone P et al.**	2010	Full article	After title/abstract analysis	Non MS
57	**Kappos L et al.**	2015	Conference abstract	After full text analysis	Same as Kappos et al. 2018
58	**Kappos L et al.**	2015	Conference abstract	After full text analysis	Same as Kappos et al. 2020
59	**Borroni B et al.**	2015	Full article	After title/abstract analysis	Non MS
60	**Steiner D et al.**	2016	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
61	**Sellebjerg F et al.**	2016	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
62	**Kappos L et al.**	2017	Conference abstract	After full text analysis	Same as Kappos et al. 2020
63	**Romania P et al.**	2017	Full article	After title/abstract analysis	Non MS
64	**Kapoor R et al.**	2018	Full article	After full text analysis	Addressing progression in SPMS
65	**Kappos L et al.**	2018	Conference abstract	After full text analysis	Same as Kappos et al. 2016
66	**Kappos L et al.**	2018	Conference abstract	After full text analysis	Same as Kappos et al. 2020
67	**Kappos L et al.**	2018	Conference abstract	After full text analysis	Same as Kappos et al. 2020
68	**Kim Y, Jung HN, Shin HJ and Kim SM**	2018	Full article	After title/abstract analysis	Case report/Case series
69	**Belachew S**	2018	Interview	After title/abstract analysis	Interview
70	**Cree BAC et al.**	2018	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
71	**Naismith RT et al.**	2019	Conference abstract	After full text analysis	Not directly addressing PIRA in RRMS
72	**Ness NH et al.**	2019	Conference abstract	After full text analysis	Same as Ness et al. 2019
73	**Von Wyl V et al.**	2019	Conference abstract	After full text analysis	Same as Von Wyl et al. 2020
74	**Ceglie G et al.**	2019	Full article	After title/abstract analysis	Case report/Case series
75	**Coyle D, Leahy T, Waldron E and Counihan T**	2019	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
76	**Cagol A et al.**	2020	Conference abstract	After full text analysis	Same as Cagol et al. 2022
77	**Kappos L et al.**	2020	Conference abstract	After full text analysis	Same as Gärtner et al. 2022
78	**Montalban X et al.**	2020	Conference abstract	After full text analysis	Same as Gärtner et al. 2022
79	**Kapica-Topczewska K et al.**	2020	Conference abstract	After full text analysis	Same as Kapica-Topczewska et al. 2021
80	**Grigorova A et al.**	2020	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS

81	**Masuda H et al.**	2020	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
82	**Piehl F et al.**	2020	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
83	**Bar-Or A et al.**	2020	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
84	**Tintoré M et al.**	2021	Conference abstract	After full text analysis	Not directly addressing PIRA in RRMS
85	**Cagol A et al.**	2021	Conference abstract	After full text analysis	Same as Cagol et al. 2022
86	**Kappos L et al.**	2021	Conference abstract	After full text analysis	Same as Gärtner et al. 2022
87	**Portaccio E et al.**	2021	Conference abstract	After full text analysis	Same as Portaccio et al. 2022
88	**Fonderico M et al.**	2021	Conference abstract	After full text analysis	Same as Portaccio et al. 2022
89	**Vécsei L et al.**	2021	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
90	**Laszlo V**	2021	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
91	**Akaishi T et al.**	2021	Full article	After title/abstract analysis	Non MS
92	**Tintoré M et al.**	2021	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
93	**Zipp F**	2021	Educational Session	After title/abstract analysis	Not directly addressing PIRA in RRMS
94	**Kister I**	2021	Educational Session	After title/abstract analysis	Not directly addressing PIRA in RRMS
95	**Schobel V and Stabb M**	2021	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
96	**EUCTR2020-005929-89-ES**	2021	Study protocol	After title/abstract analysis	Study protocol of ongoing trial
97	**EUCTR2020-00589936-ES2021**	2021	Study protocol	After title/abstract analysis	Study protocol of ongoing trial
98	**Bischof A et al.**	2022	Conference abstract	After full text analysis	Same as Bischof et al. 2021
99	**Gibbons E et al.**	2022	Full article	After title/abstract analysis	Case report/Case series
100	**Heibel M et al.**	2022	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
101	**Masuda H et al.**	2022	Full article	After title/abstract analysis	Non MS
102	**Bellinvia A et al.**	2022	Conference abstract	After title/abstract analysis	Non MS (pediatric)
103	**Hechenberger S et al.**	2022	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
104	**Sabsabi S et al.**	2022	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
105	**Mariottini A et al.**	2022	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
106	**Geladaris A, Torke S and Weber MS**	2022	Full article	After full text analysis	Not directly addressing PIRA in RRMS
107	**Shiroma K et al.**	2021	Conference abstract	After title/abstract analysis	not enough data on PIRA provided
108	**Kondo T**	2020	Full article	After title/abstract analysis	Not directly addressing PIRA in RRMS
109	**Nataf S, Guillen M and Pays L**	2022	Full article	After full text analysis	Not directly addressing PIRA in RRMS
110	**Van Lierop Z et al.**	2022	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
111	**Abdelhak A et al.**	2022	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
112	**Curcio-Rubertini A et al.**	2022	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS

113	**Zimianiti I et al.**	2022	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
114	**Leocanni L**	2022	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
115	**Arrambide G et al.**	2022	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS
116	**Geladaris A et al.**	2022	Conference abstract	After title/abstract analysis	Not directly addressing PIRA in RRMS in humans
117	**Martins E et al.**	2022	Conference abstract	After title/abstract analysis	not enough data on PIRA provided
118	**Ridley B et al.**	2022	Study protocol	After title/abstract analysis	Protocol of ongoing trail/planned meta analysis
119	**Kosa P et al.**	2022	Full article	After title/abstract analysis	Unreviewed preprint

eTable 2: Excluded studies of the systematic review and reason for ineligibility, continually numbered following the included studies from the review. Abbreviations: MS multiple sclerosis; PIRA progression independent of relapse activity; RRMS relapsing remitting multiple sclerosis; SPMS secondary progressive multiple sclerosis.