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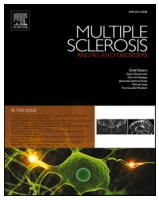

Multiple sclerosis relapse incomplete recovery and associated factors – a systematic review and meta-analysis

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ABSTRACT

Objectives: We conducted a meta-analysis to assess the frequency of incomplete recovery from multiple sclerosis (MS) relapses and a systematic review to evaluate the influence of six factors on incomplete recovery: relapse severity, age, sex, disease duration, disease-modifying treatment use, and the presence of contrast-enhancing lesions at relapse.
Methods: We searched Scientific databases to identify suitable publications. Our outcome was MS relapse incomplete recovery, defined as a post-relapse EDSS measured at least 6 months after the event higher than the pre-relapse EDSS. We synthesized the rate of incomplete recovery using meta-analysis (random effect model). and summarized the effect estimates (or HR) for demographic and clinical factors.
Results: We included 13 studies (with a total of 19,920 patients and 27672 relapses having at least six month of follow up) . The pooled rate of incomplete recovery was 0.42 (95 % confidence interval 0.31 to 0.54). The subgroup systematic review identified that relapse severity was the most consistent and strongest predictor of incomplete recovery, with odds ratios ranging from 2.4 to 17.2. Other factors were less consistently associated with relapse recovery.
Conclusion: This systematic review indicates that relapse recovery is often incomplete, with relapse severity being the strongest and most consistent predictor of incomplete recovery

1. Introduction

Multiple sclerosis (MS) is a major cause of neurological disability in young adults (Jakimovski et al., 2024). Relapse-associated disability (RAW) and progression independent of relapse activity (PIRA) both contribute to disability accumulation (Kappos et al., 2020). Currently available disease-modifying treatments (DMT) are highly efficacious in preventing relapses, but their impact on disability progression is modest (Gonzalez-Lorenzo et al., 2024) with an unknown effect on each of the drivers of disability progression, namely RAW and PIRA.

It is essential to gain a deeper understanding of the RAW components of MS, specifically the risk factors and biomarkers associated with incomplete recovery following relapse. An enhanced comprehension of relapse recovery might help to identify patients at risk of incomplete recovery to propose them to more effective treatment and contribute to the design of future trials testing remyelinating and/or neuroprotective drugs.

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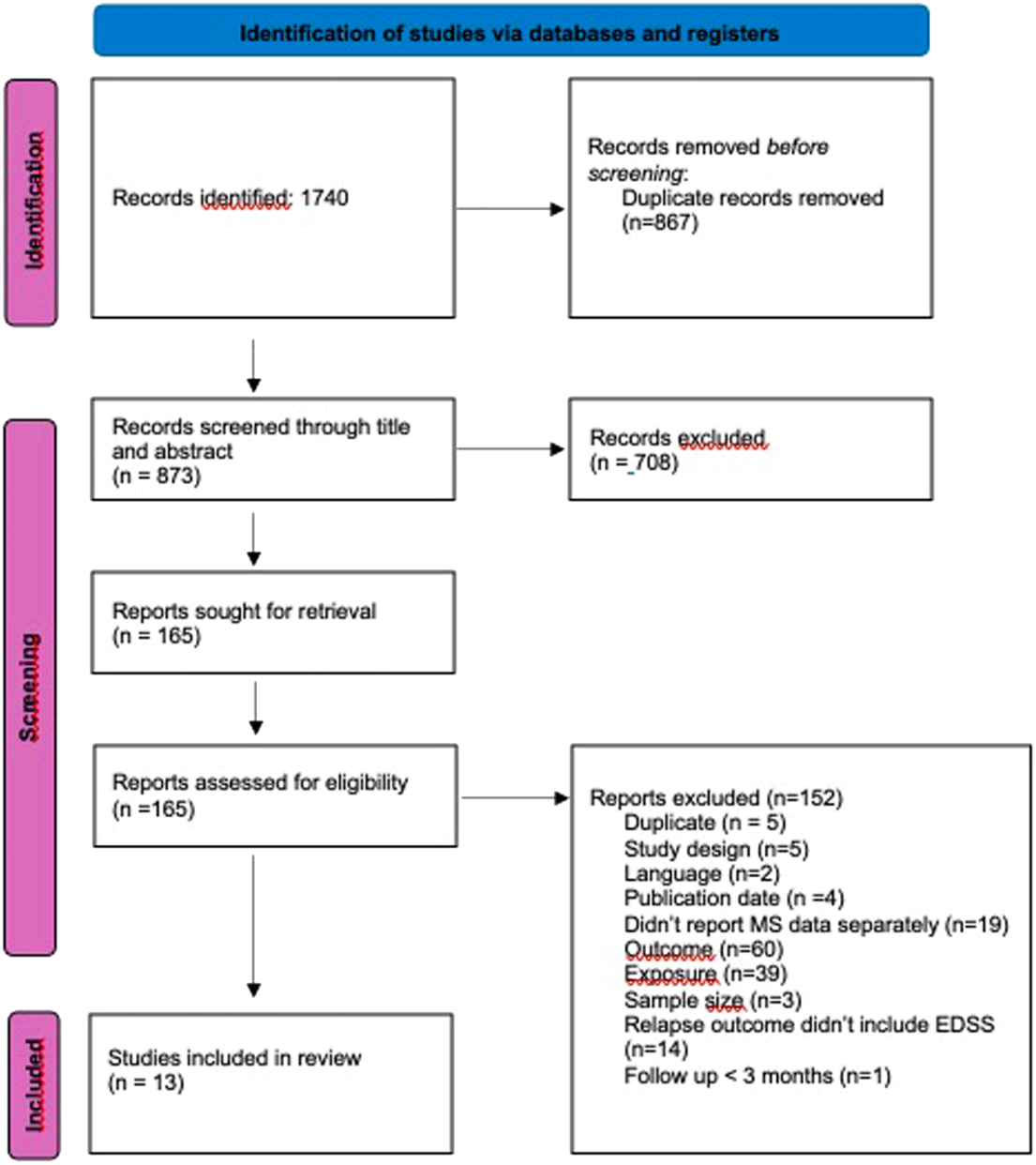

Fig. 1. PRISMA flowchart of the search strategy.

2. Objectives

We performed a meta-analysis to evaluate the rate of incomplete recovery following MS relapse, and a systematic review to evaluate whether the following six factors were associated with incomplete relapse recovery: relapse severity, age, sex, disease duration, disease-modifying treatment use, and the presence of contrast-enhancing lesions at the time of relapse.

3. Methods

3.1. Study design and registration

Our review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA guidelines). (Page et al., 2021)

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42024623911)

3.2. Search strategy

A comprehensive search of the Literature in MEDLINE through PubMed, Scopus, and Web of Science electronic databases was performed on February 1, 2024. The search only included published manuscripts. The search terms were set to ("multiple sclerosis") AND ("relapse recovery"); ("multiple sclerosis") AND ("relapse associated worsening"); ("multiple sclerosis") AND ("RAW"). Studies were selected according to the following PICO criteria:

Study design: Randomized controlled trials, observational studies, and cohort studies with a minimum of 25 patients and at least one follow-up visit for relapse recovery assessment were included. MS relapses were defined according to previous guidelines for MS: new or worsening of existing neurological symptoms, lasting for >24 hours, in the absence of fever, infection or any other cause, after a stable period of at least one month (McDonald et al., 2001; Recommendations, 2024 Mar 30). Stricter definitions of relapse were also included as long as they fulfilled the previous criteria. Follow-up assessments had to be

Table 1
Summary of the main characteristics of included studies.

Source	Patients, n	Female, n	Mean age (SD/ range)	MS type		Relapse definition		Type of relapses included	Severe relapse definition	Relapses, n	Relapses on DMT, n (%)
				CIS/ RRMS, n	Progressive MS	Duration	EDSS/FS increased				
Achiron 2019	720	NA	NA	720	0	≥ 48 hours	Required	SR, any topography	≥ 2 EDSS points	720	720 (100 %)
Cossburn 2011	1424	1018	31.6 (±9.6)	1424	0	≥ 24 hours	Not required	IDE, any topography	NA	1424	0 (0 %)
Hirst 2012	144	116	38.6 (17–65)	122	22	≥ 24 hours	Not required	SR, any topography	≥ 2 EDSS points	82	NA
Kalincik 2014	14,969	10,434	37 (±11)	13,666	1303	≥ 24 hours	Not required	IDE and SR, any topography	subjective	22,276	NA
Koch 2023	240	175	36 (28–44)	240	0	≥ 24 hours	Required	SR, any topography	≥ 1 EDSS points	240	240 (100 %)
Leone 2008	72	38	31.5 (±9.9)	72	0	≥ 24 hours	Not required	IDE and SR, any topography	≥ 2 points in 1 FS or ≥ 1 point in 2 FS	209	NA
Lublin 2014	283	248	NA	283	0	≥ 24 hours	Not required	SR, any topography	stratified ≥ 0,5 and ≥ 1 EDSS points	283	183 (60.0 %)
Malik 2014	253	201	34.7 (±9.6)	253	0	≥ 24 hours	Not required	IDE, ON only	decrease is VA ≤20/200	253	0 (0 %)
Mowry 2009	330	224	34.7 (±12)	330	0	≥ 48 hours	Not required	IDE, any topography	≥ 2 points in ≥ 3 FS or ≥ 1 point in 2 FSdecrease is VA ≤20/200	322	0 (0 %)
Sotiropoulos 2021	360	265	36.7 (±9.1)	360	0	≥ 24 hours	Not required	IDE and SR, any topography	subjective	736	232 (31.5 %)
Vercellino 2009	174	99	35.6 (10.3)	174	0	≥ 24 hours	Not required	SR, any topography	≥ 2 EDSS points	174	124 (71.3 %)
West 2006	186	127	34 (10)	186	0	≥ 24 hours	Not required	IDE and SR any topography	≥ 2 EDSS points	186	124 (66.6 %)
Zhangi 2023	767	536	35.5 (11.2)	767	0	≥ 24 hours	Not required	SR, any topography	NA	767	767 (100 %)

Abbreviations: DMT: disease-modifying treatments; EDSS: Expanded Disability Status Scale; IDE: initial demyelinating event; NA: Not available; OD: optic neuritis; SD: standard deviation: SR: subsequent relapse.

performed at least six months after symptom onset and must have included the Expanded Disability Status Scale (EDSS) scores. The publication date was restricted to studies published in January 2004 or later, since this was the year when Neuromyelitis Optica Spectrum Disorder (NMOSD) was recognized as a separate syndrome. Non-English studies, case reports, protocols, reviews, and commentaries were also excluded.

Participants: Adult MS patients (aged 18 years or older). Studies addressing both adults and children were included if adult data were reported separately. NMOSD and Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) studies were included if the MS data were reported separately.

Exposures/comparison: the effect on relapse recovery of the following factors was assessed: relapse severity, age, sex, DMT, disease duration, and presence of CEL on MRI at baseline. Steroid treatment was not included as an exposure since previous publications have already assessed its effect on relapse recovery (Lattanzi et al., 2017; Sellebjerg et al., 2005; Costello et al., 2019)

Outcomes: The primary outcome was incomplete MS relapse recovery based on EDSS change. We defined incomplete recovery as a post-relapse EDSS measured at least 6 months after relapse higher than the pre-relapse EDSS.

3.3. Search strategy

Between February and March 2024, five neurologists (F.L., A.C., I.G., P.F., and M.S.) independently screened titles and abstracts after duplicate exclusion. Eppi-reviewer, an Internet-based platform, was used to assist with abstract allocation and selection. Two neurologists (F.L. and A.C.) assessed the full text and selected the final articles according to the PICO criteria, and disagreement was resolved through discussion.

3.4. Risk of bias assessment

Bias assessment was performed with the Newcastle-Ottawa scale (NOS) for quality assessment of observational studies by 2 investigators (F.L. and M.R.). A good, fair, and poor quality was assigned to a ⩾7, 4–6, and < 4 stars score, respectively. We included good- and fair-quality studies in the final analysis.

3.5. Data extraction

Two authors (F.L., A.C.) independently extracted the following data from the selected manuscripts: study characteristics (first author, publication year, design), patient data (number of participants, mean/median age, sex, disease duration, clinical course defined as clinically isolated syndrome and relapsing remitting MS (*CIS*/RRMS) and primary and secondary progressive MS (PPMS/SPMS), relapse data (number of relapses, relapse definition, relapse type defined as initial demyelinating event (IDE) or subsequent relapse (SR), relapse topography, relapse severity, number of relapses with incomplete recovery during follow-up, exposure factors assessed as predictors of incomplete recovery, odds ratio (OR) or hazard ratio (HR) of relapse incomplete recovery for all exposures of interest – relapse severity, age, sex, disease duration, disease-modifying treatment use, and the presence of CEL at the time of relapse). We contacted the corresponding authors of the included studies via email in case of missing data (see the Acknowledgements section).

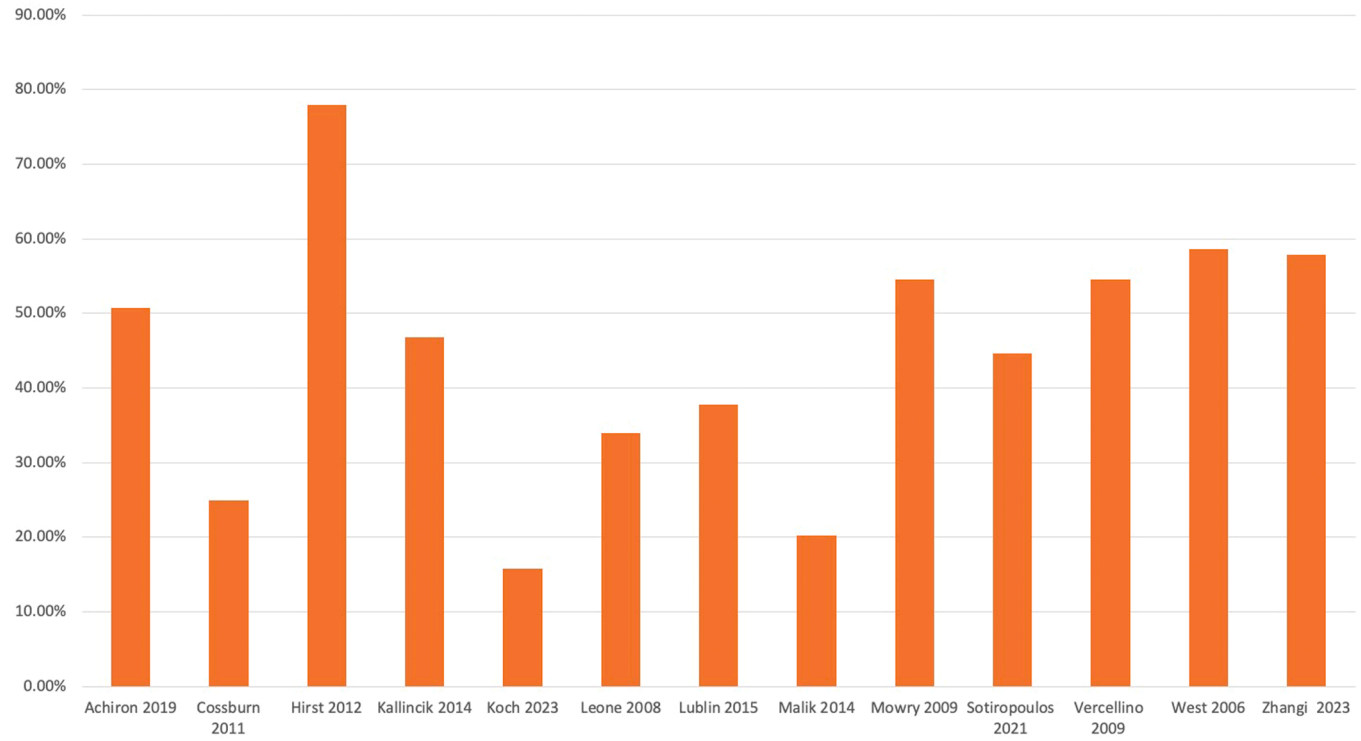

Fig. 2. Proportion of patients experiencing MS relapse incomplete recovery across different cohorts.

3.6. Statistical analysis

A meta-analysis evaluating the pooled effect size and 95 % confidence intervals of incomplete recovery from MS relapse was performed using a random-effects model. Heterogeneity and inconsistencies were assessed using Cochran's Q-value and I^2 statistics, respectively. Publication bias was visually screened using funnel plots to detect any asymmetry.

A subgroup systematic review without meta-analysis was performed to evaluate whether incomplete MS relapse recovery was linked to relapse severity, age, sex, disease duration, disease-modifying treatment use, and the presence of CEL at the time of relapse. We grouped the studies according to exposure and summarized the range and distribution of effect estimates.

4. Results

4.1. Included studies

The search identified 1740 records (Fig. 1). After removing duplicate, 873 references were screened using the titles and abstracts. This process yielded 165 eligible studies that were fully reviewed. Among these, 152 studies were excluded for the following reasons: 5 due to duplicate data, 5 due to study design (four reviews and one cross-sectional), 2 due to language, 4 due to publication date, 19 did not report MS data separately, 60 did not study incomplete recovery as the relapse outcome, 39 did not study any of the exposures of interest, 3 included <25 patients, 14 did not include EDSS measurements in the follow-up assessment, and 1 due to a follow-up assessment inferior to 3 months. Thus, 13 studies were included (Fig. 1).

The quality assessment of included studies by NOS presented an overall inter-rater reliability at first evaluation of 87.5 % between raters, and for each category of bias assessment the Cohen's kappa or weighted Cohen's kappa ranged between 0.26 and 1.0. Disagreements were resolved through consensus. All studies were classified as fair or good quality and were therefore included (Supplementary Table 1).

4.2. Study characteristics

There was a lack of standardization in relapse definitions between the included studies regarding minimal symptom duration and the requirement of EDSS increase; however, all studies satisfied the broad definition of relapse defined in our inclusion criteria (Table 1). The relapse outcome was also heterogeneous in terms of the designation used, but the concept was consistent between the included studies, reflecting an increase in post-relapse EDSS vs. pre-relapse. Terms such as post-relapse residual disability, relapse with sequelae, incomplete relapse recovery or poor and/or fair recovery were used. Additionally, some studies assessed it as a dichotomous outcome, while others included more than two categories; however, in the latter, it was possible to aggregate the groups into two categories corresponding to complete/incomplete return to pre-relapse EDSS. In the present study, we adopted the terminology of incomplete relapse recovery, reflecting any increase in post-relapse vs. pre-relapse EDSS, and considered it a binary variable (incomplete/complete).

Of the 13 studies included in the analysis,1 was performed in Israel (Achiron et al., 2019), six in the United States of America (Koch et al., 2023; Lublin et al., 2014; Malik et al., 2014; Mowry et al., 2009; Sotiropoulos et al., 2021; West et al., 2006), two in the United Kingdom [17, 18] three in Italy (Leone et al., 2008; Vercellino et al., 2009; Zanghì et al., 2023) and one used data from the MS Base International Registry (Kalincik et al., 2014)

The majority (n = 11, 84.6 %) were cohort studies including prospective follow-up data (Achiron et al., 2019; Malik et al., 2014; Mowry et al., 2009; Sotiropoulos et al., 2021; West et al., 2006; Hirst et al., 2012; Cossburn et al., 2012; Leone et al., 2008; Vercellino et al., 2009; Zanghì et al., 2023; Kalincik et al., 2014), and 2 (15.4 %) were post-hoc analyses of randomized controlled trials (Koch et al., 2023; Lublin et al., 2014)

In eight studies (61.5 %), a single relapse per patient was analyzed (Achiron et al., 2019; Koch et al., 2023; Lublin et al., 2014; Malik et al., 2014; West et al., 2006; Cossburn et al., 2012; Vercellino et al., 2009; Zanghì et al., 2023) while in the remaining studies more than a relapse

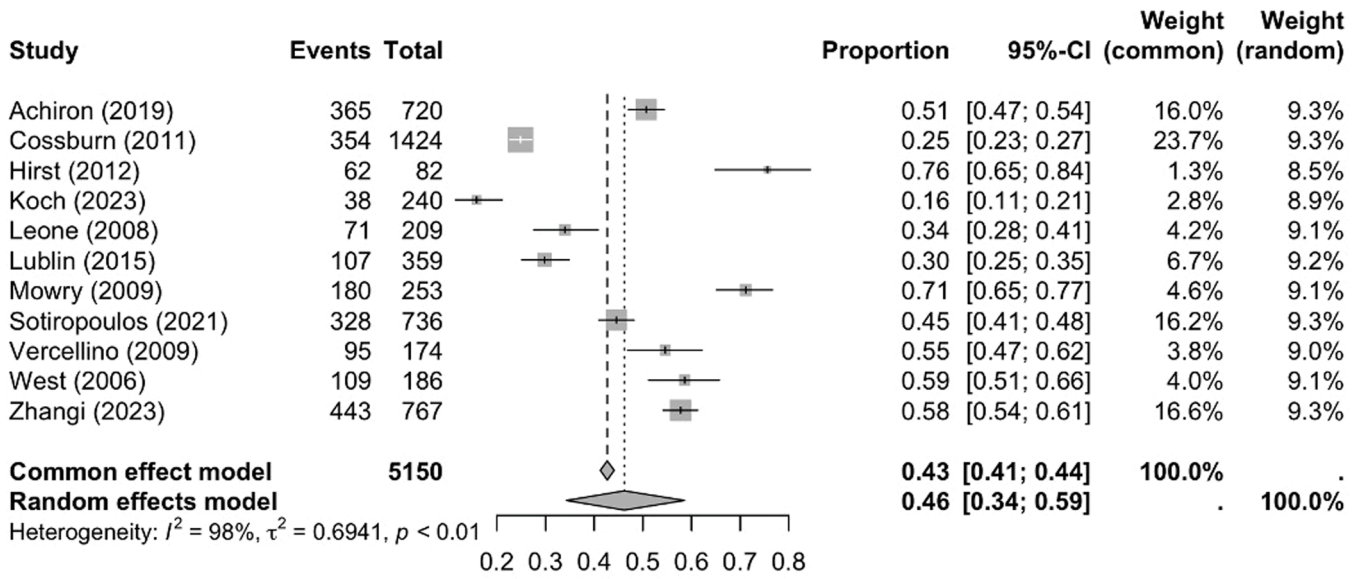

Fig. 3. Forest plot of the results of the meta-analysis on incomplete relapse recovery.

Table 2
Effect of severe relapses on relapse recovery.

Source	Sample size		Relapse incomplete recovery		OR/HR (95 %CI) of incomplete recovery	Covariates	Overall conclusion: Relapse severity association with incomplete recovery
	Total	severe	Total	severe			
Hirst 2012[17]	82	24	64	NA	Adjusted OR 4.802 (95 %CI 1.615–14.275)	Age Sex DMT MS type Early recovery	Yes
Leone 2008[19]	209	69	71	37	Mild, moderate or severe relapses vs very mild adjusted OR 17.2, (95 %CI 2.2–136.4)	Relapse duration Age Number of symptoms	Yes
Malik 2014 (Malik et al., 2014)	253	122	51	NA	Adjusted OR 5.24 (95 %CI NA)	Sex Steroid-treatment	Yes
Koch 2023 (Koch et al., 2023)	240	91	38	NA	NA (adjusted HR reported for complete recovery)		Yes
Morwy 2009 (Mowry et al., 2009)	330	57	172	NA	Adjusted OR for moderate vs mild severity 2.38 (95 %CI 1.38–4.07) Adjusted OR for severe vs mild 5.08 (95 % CI 2.42–10.69)	Age Race Relapse topography and severity	Yes
Sotiropoulos 2021 (Sotiropoulos et al., 2021)	736	NA	328	NA	NA (adjusted HR reported for complete recovery)		No
Vercellino 2009 (Vercellino et al., 2009)	174	78	95	NA	Adjusted OR for severe relapse OR 9.594 (95 %CI 1.346–68.390)	Sex Age Disease duration DMT treatment OCBs Polysymptomatic relapse Recovery at 1st month	Yes
West 2006 (West et al., 2006)	186	26	109	20	NA (reported for complete recovery)		Yes

Abbreviations: EDSS: Expanded Disability Expanded Scale; NA: not available; OCB's: oligoclonal bands; OR: odds-ratio; HR: hazard-ratio; DMT: disease-modifying treatment.

per patient was studied.

Regarding the patients' baseline characteristics, most patients were women (52.8 %−80.2 %); in 11 studies, the only MS type included was RRMS (Achiron et al., 2019; Koch et al., 2023; Lublin et al., 2014; Malik et al., 2014; Mowry et al., 2009; Sotiropoulos et al., 2021; West et al., 2006; Cossburn et al., 2012; Leone et al., 2008; Vercellino et al., 2009; Zanghì et al., 2023), while 2 also included progressive MS (Hirst et al., 2012; Kalincik et al., 2014).

The type of relapse varied, with 11 studies including any relapse topography (Achiron et al., 2019; Koch et al., 2023; Lublin et al., 2014; Mowry et al., 2009; Sotiropoulos et al., 2021; West et al., 2006; Hirst et al., 2012; Cossburn et al., 2012; Leone et al., 2008; Vercellino et al., 2009; Zanghì et al., 2023; Kalincik et al., 2014), while one study included only optic neuritis (Malik et al., 2014), three studied only the initial demyelinating event (IDE) (Malik et al., 2014; Mowry et al., 2009; Cossburn et al., 2012), and the remaining studies included either the

Table 3
Effect of age (as continuous variable) on relapse recovery.

Age as continuous variable						
Source	Mean age			Relapse incomplete recovery according to age		Overall conclusion: Increase age association with incomplete recovery
	Total sample	Incomplete recovery	Complete recovery	OR/HR, (95 %CI), p-value	Covariates	
Achiron 2019 (Achiron et al., 2019)	NA	NA	NA	NA	Sex Age Disease duration DMT use Relapse severity EDSS pre relapse	No
Cossburn 2011 (Cossburn et al., 2012)	31.6	33.1	29.6	NA (adjusted OR reported for complete recovery)	Sex Relapse topography	Yes
Hirst 2012 (Hirst et al., 2012)	38.6	NA	NA	Adjusted OR 1.068 (95 %CI 1.068–1.101)	Relapse severity Sex DMT MS type Early recovery	Yes
Kalincik 2014 (Kalincik et al., 2014)	NA	NA	NA	Adjusted OR =1.93 (95 %CI NA)	Age Sex Relapse symptoms MS type Disease duration Number of previous relapses	Yes
Koch 2023 (Koch et al., 2023)	NA	NA	NA	NA (adjusted HR Reported for complete recovery)		No
Malik 2014 (Malik et al., 2014)	34.7	NA	NA	Unadjusted OR 1.9 (95 %CI NA)		No
Morwy 2009 (Mowry et al., 2009)	34	NA	NA	Adjusted OR 1.18 (95 %CI 0.95–1.46)	Race Relapse topography and severity	No
Vercellino 2009 (Vercellino et al., 2009)	35.6	NA	NA	Adjusted OR 1.035 (0.933–1.148)	Sex Disease duration DMT treatment OCB's Relapse severity Polysymptomatic relapse Recovery at 1 month	No
Zhangi 2022 (Zanghì et al., 2023)	35.5	NA	NA	Ajusted OR 1.02 (95 %CI 1.01–1.04)	Relapse phenotype	Yes

Abbreviations: EDSS: Expanded Disability Expanded Scale; NA: not available; OR: odds-ratio; HR: hazard-ratio; DMT: disease-modifying treatment.

Table 4
Effect of age (as categorical variable) on relapse recovery.

Age as categorial variable							
Source	Sample size		Relapse incomplete recovery		OR (95 %CI) of incomplete recovery	Covariates	Overall conclusion: Increase age association with incomplete recovery
Leone 2008 (Leone et al., 2008)	Total 209	⩾30 123	total 71	⩾30 51	Adjusted OR 2.9 (95 %CI 1.5–5.7)	Relapse severity Relapse duration Number of symptoms	Yes
West 2006 (West et al., 2006)	Total 186	⩾30 128	total 109	⩾30 71	NA (adjusted OR reported for complete recovery)		No

Abbreviations: EDSS: Expanded Disability Expanded Scale; NA: not available; OR: odds-ratio; HR: hazard-ratio; DMT: disease-modifying treatment.

first or subsequent relapses .

Finally, the exposure definitions were heterogeneous, namely the relapse severity categories applied in different studies.

4.3. Incomplete relapse recovery rate meta-analysis

Across the 13 studies, a total of 19920 patients experienced one or more relapses, with 27672 of these cases having at least six months of follow-up. The proportion of patients experiencing incomplete relapse recovery varied between studies (Fig. 2). The summary estimate from 13 studies for the frequency of incomplete recovery was 0.42 (95 % CI, 0.31–0.54). When the analysis was restricted to the 11 studies with moderate risk of bias, the frequency of incomplete recovery was 0.46 (95 % CI, 0.34–0.59) (Fig. 3).

4.4. Systematic review on factors associated with incomplete recovery

The association between relapse severity and recovery was assessed in 8 studies (Table 2). There was an association between relapse severity and recovery outcomes in 87.5 % (7/8) of the studies; however, in two

Table 5
effect of male sex on relapse recovery.

Source	Sample size		Relapse incomplete recovery		OR (95 %CI) of incomplete recovery	Covariates	Overall conclusion: Male sex association with incomplete recovery
	Total	Male	Total	Male			
Cossburn 2011 (Cossburn et al., 2012)	1424	406	354	112	NA (Reported for complete recovery)	Age Relapse topography	Yes
Hirst 2012 (Hirst et al., 2012)	82	NA	64	NA	Adjusted OR 1.364 (95 %CI 0.454–4.095)	Relapse severity Age DMT MS type Early recovery	Yes
Kalincik 2014 (Kalincik et al., 2014)	22,276	NA	10,415	NA	Adjusted OR 1.04 (95 % CI NA)	Age Sex Relapse symptoms MS type Disease duration Number of previous relapses	Yes
Malik 2014 (Malik et al., 2014)	253	53	51	NA	Adjusted OR 2.28 (95 %CI NA)	Severity Steroid-treatment	Yes
Koch 2023 (Koch et al., 2023)	240	65	38	NA	NA (adjusted HR Reported for complete recovery)		No
Sotiropoulos 2021 (Sotiropoulos et al., 2021)	736	NA	328	NA	NA (adjusted HR reported for complete recovery)		No
Vercellino 2009 (Vercellino et al., 2009)	174	75	95	NA	Adjusted OR 0.49 (95 %CI NA)	Age Disease duration DMT use Recovery at 1 month OCB Relapse Symptoms Relapse severity	No
West 2006 (West et al., 2006)	186	59	109	37	Unadjusted OR 0.76 (95 %CI NA)		No
Zhangi 2022 (Zanghì et al., 2023)	767	231	443	NA	Unadjusted OR 0.95 (95 % CI 0.62–1.45)		No

Abbreviations: EDSS: Expanded Disability Expanded Scale; NA: not available; OCB's: oligoclonal bands; OR: odds-ratio; HR: hazard-ratio; DMT: disease-modifying treatment.

Table 6
Effect of Disease-modifying treatment use on relapse recovery.

Source	Sample size		Relapse incomplete recovery		OR (95 %CI) of incomplete recovery	Covariates	Overall conclusion: DMT treatment association with incomplete recovery
	Total	DMT	Total	DMT			
Hirst 2012 (Hirst et al., 2012)	86	NA	64	NA	Adjusted OR 2.246 (0.642–7.858)	Relapse severity Age Sex MS type Early recovery	No
Lublin 2014 (Lublin et al., 2014)	359	176	107	NA	NA (adjusted HR reported for complete recovery)		Yes
Sotiropoulos 2021 (Sotiropoulos et al., 2021)	736	232	328	67	NA (unadjusted HR reported for complete recovery)		Yes
Vercellino 2009 (Vercellino et al., 2009)	174	124	95	NA	Adjusted OR 2.708 (95 %CI 0.449–16.350)	Sex Age Disease duration OCB's Relapse severity Polysymptomatic relapse Recovery at 1 month	No

Abbreviations: EDSS: Expanded Disability Expanded Scale; NA: not available; OR: odds-ratio; HR: hazard-ratio.

studies, the effect size was reported for complete recovery. In the remaining, an adjusted OR of 2.38 - 17.2 of incomplete recovery in severe relapses was reported, suggesting that severe relapses have an increased odd of incomplete recovery.

The relationship between the age at relapse and recovery was assessed in 11 studies (Tables 3 and 4). In the majority (81.8 %), age was assessed as a continuous variable, and in two studies, it was assessed as a 2-level variable: </ ⩾30 years. The majority (54.4 %) of the studies did not find an association between age and recovery outcomes; when an association was found, increased age presented a higher odd of incomplete recovery, with an adjusted OR of 1.02–2.9.

The effect of sex and recovery was studied in 9 of the 13 included studies (Table 5). Most studies (54.4 %) did not find an association between sex and recovery outcomes; when an association was found, the

Table 7
Effect of disease duration on relapse recovery.

Source	Mean disease duration			Relapse incomplete recovery according to disease duration		Overall conclusion: Increased disease duration association with incomplete recovery
	Total sample	Incomplete recovery	Complete recovery	OR (95 %CI)	Covariates	
Achiron 2019 (Achiron et al., 2019)	NA	NA	NA	NA (adjusted HR reported for severe relapses only)	Sex Age Disease duration DMT use Relapse severity EDSS pre relapse	No
Kock 2023 (Koch et al., 2023)	NA	NA	NA	NA (adjusted HR reported for complete recovery)		No
Sotiropoulos 2021 (Sotiropoulos et al., 2021)	NA	NA	NA	NA (adjusted HR reported for complete recovery)		Yes
Vercellino 2009 (Vercellino et al., 2009)	6.43	NA	NA	Adjusted OR 0.963 (95 %CI 0.834–1.112)	Sex Age DMT treatment OCB's Relapse severity Polysymptomatic relapse Recovery at 1 month	No
Zanghi 2022 (Zanghì et al., 2023)	NA	NA	NA	Unadjusted OR 1.00 (0.99–1.004)		No

Abbreviations: EDSS: Expanded Disability Expanded Scale; NA: not available; OR: odds-ratio; HR: hazard-ratio; DMT: disease-modifying treatment.

Table 8
Effect of contrast-enhancing lesions on relapse MRI and relapse recovery.

Source	Sample size		Relapse incomplete recovery		OR (95 %CI) of incomplete recovery	Covariates	Overall conclusion: CEL presence association with incomplete recovery
	Total	CEL	Total	CEL			
Leone 2008 (Leone et al., 2008)	125	86	44	11	NA		No
Koch 2023 (Koch et al., 2023)	240	NA	13	NA	Unadjusted HR 1.30 (0.78–2.17)		No

Abbreviations: NA: not available; OR: odds-ratio; HR: hazard-ratio; DMT: disease-modifying treatment.

adjusted male OR for incomplete recovery was 1.04–2.28.

The association between DMT use at the time of relapse and relapse recovery was analyzed in four of the 13 included studies (Table 6). No study identified a relation between incomplete recovery and DMT use, and in two an association with complete recovery was observed.

The influence of disease duration on recovery was assessed in 5 studies (Table 7). Only one study found an association between longer disease duration and complete recovery.

The relationship between the presence of CEL on MRI and recovery was assessed in only 2 studies (Table 8). None of the studies found an association between the presence of CEL and relapse outcome.

5. Discussion

Disability progression prevention is an unmet need in multiple sclerosis. This systematic review including 13 studies, and and 27672 relapses followed at least for 6 months suggests that relapse recovery is incomplete in more than one-third-of patients.

Incomplete recovery from relapses might be due to the extension of the initial injury and associated axonal damage or to impairment of the repair process. The identification of factors associated with recovery can be relevant for selecting patients for neuroprotective or remyelinating agents, more effective DMT or intensive rehabilitation programs. Relapse severity was the factor more consistently associated with incomplete recovery across studies, and with a larger effect in studies reporting OR for incomplete recovery. For the remaining factors evaluated –sex, age, DMT use, disease duration, and presence of CEL on MRI – the association was less consistent, and the effect was weaker.

There was heterogeneity between studies included. The definition of relapses was heterogeneous, and higher rates of incomplete recovery were reported in studies that required an EDSS increment in their relapse definition, as expected. The follow-up time was also variable because some studies censored patients at the time of a new relapse. However, included relapses presented a follow-up of at least 6 months, when most recovery events take place[11]. Relapse topography/symptoms were not evaluated since their categorization between studies was highly variable and they are to some extent associated with severity. Finally, most patients were not under DMT at the time of relapse, which might limit extrapolation for patients already under treatment, and might not reflect most of the MS patients followed in contemporary MS centers

Designations of relapse outcomes widely varied among studies, although in the included studies they referred to the same concept: an increase in post-relapse disability compared to pre-relapse. In the future, uniformization of relapse outcomes would be useful to simplify comparisons between studies and to determine the actual contribution of relapses to disability accumulation. Also, standardization of relapse severity categories will be relevant when assessing predictors of relapse-associated disability.

In conclusion, this study indicates that incomplete MS relapse recovery is frequent, occurring in more than one-third-of patients at 6 months post relapse. There appears to be an association between relapse

severity and relapse recovery, while other predictors were less consistent between studies. Future research on relapse recovery, ensuring harmonization and consistency in relapses outcomes and exposures, and evaluating other predictors such as serum biomarkers or neurological reserve might help to better identify patients at increased risk of incomplete relapse recovery.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article or its supplementary materials.

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CRediT authorship contribution statement

Filipa Ladeira: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Mafalda Soares:** Writing – review & editing, Investigation. **Patrícia Faustino:** Writing – review & editing, Investigation. **Miguel Leal Rato:** Writing – review & editing, Investigation. **Inês Gomes:** Writing – review & editing, Investigation. **André Caetano:** Writing – review & editing, Investigation. **Ricardo Taipa:** Writing – review & editing, Supervision. **Maria José Sá:** Writing – review & editing, Supervision.

Declaration of competing interest

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Supplementary materials

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