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Contribution of Polygenic Scores to Progression Independent of Relapse Activity in Multiple Sclerosis

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ABSTRACT

Background: Despite effective therapeutic control of relapses, many patients with multiple sclerosis (MS) experience, from the earliest phases of disease, disability accrual, which mostly occurs as progression independent of relapse activity (PIRA). In this observational study, we aimed at evaluating the genetic contribution to PIRA, using polygenic risk scores (PRS) in a cohort of 1162 Italian patients.

Methods: PRS were derived from the largest multi-centric genome-wide association study on MS severity, conducted on more than 20,000 patients. The scores were computed at 5 *p*-value thresholds after a clumping procedure. Association with the rate of PIRA events was tested by fitting negative binomial regression models.

Results: Analyses revealed a trend for association of PRS with the rate of PIRA events, which were significant in the subset of patients with age at onset ≤ 50 years (Rate Ratio = 1.148, 95% CI: 1.01 to 1.304, $p = 0.0328$). An interaction effect was identified between PRS and AAO, indicating a significant mild antagonistic effect ($RR_{int} = 0.98$, 95% CI: 0.96 to 1.0, $p = 0.033$).

Conclusions: Our results suggest an influence of severity-related genetic load on the rate of PIRA events, especially in subjects with disease onset before the age of 50 years, characterized by a less prominent effect of aging processes on disability accumulation. This finding supports previous observations from other studies of an age-dependent influence of genetic risk scores on complex traits.

1 | Introduction

Multiple Sclerosis (MS) is a disease of the central nervous system characterized by chronic inflammation, demyelination, and axonal loss. The disease is highly heterogeneous, with genetic and environmental factors contributing to susceptibility and clinical expression [1].

Despite multiple drugs are successful in controlling disease activity, MS patients often report irreversible worsening in physical and cognitive disability. Accumulation of disability can stem from incomplete recovery after relapses (relapse-associated worsening, RAW) or as silent accrual independently of them (progression independent of relapse activity, PIRA).

Both RAW and PIRA events are identifiable during the relapsing phase of the disease: indeed, a multi-centric investigation conducted on more than 5000 patients from the Italian multiple sclerosis register [2] revealed that PIRA worsening was detectable from the very first year after disease onset, overcoming

RAW events since the second year. Further, in a pooled analysis of two randomized clinical trials [3], the authors found that PIRA events accounted for disability accumulation in more than 80% of RRMS patients. In these studies, older age emerged as the most important predictor of higher risk of PIRA.

To date, genetic determinants of PIRA have yet to be elucidated. In the context of complex traits, pooling individual genetic variants into a single additive risk score (polygenic risk score, PRS) has emerged as a valuable tool for quantifying genetic contribution [4].

In this study, starting from a cohort of Italian MS patients, we sought to determine whether there was an effect of severity-based PRS, which estimates individual cumulative genetic propensity to long-term severity, on the rate of PIRA events.

The PRS were computed by harnessing the large genome-wide association study [5] conducted by the International Multiple Sclerosis Genetic Consortium (IMSGC) and MultipleMS Consortium, a study that was pivotal for elucidating the genetic architecture of MS severity.

2 | Patients and Methods

2.1 | Study Population

We included patients with longitudinal clinical records extracted from the Italian multiple sclerosis register (August 2024), followed at Ospedale San Raffaele (OSR). Patients with the following characteristics were excluded: (i) primary or secondary progressive course at first neurological evaluation; (ii) clinically isolated syndrome; (iii) less than 3 visits with expanded disability status scale (EDSS) evaluation; (iv) follow-up < 5 years; and (v) participation to the above mentioned IMSGC study on MS severity.

The study was approved by the local ethics board; all patients provided written informed consent.

PIRA events were defined based on confirmed EDSS worsening. More precisely, a disability worsening event was declared if an increase of EDSS score of 1.5, 1.0 or 0.5 was observed with respect to a baseline score of, respectively, 0, 1.0 to 5.0, greater than 5.0, and confirmed at least at 6 months. A roving baseline scheme was applied, where the reference value was initially set as the first valid outcome value, then updated after each confirmed progression or after an improvement event [6]. A confirmed EDSS progression was labeled as PIRA if no relapses occurred in the interval from 90 days before the event to 30 days after the event. PIRA events were identified by means of the *msprog* R package [7].

2.2 | PRS Calculation

Genotyping and standard per-sample and per-SNP quality control were conducted as previously described [8]: imputation was performed against Haplotype Reference Consortium v1.1 European panel on GRCh37/hg19 genome, only retaining variants with minor allele frequency > 1% and good imputation quality (Rsq > 0.6).

We leveraged summary statistics from the largest multi-centric study on MS severity [5]. This study, conducted on a cohort of 12,584 patients with replication in an independent cohort of 9805 cases, performed a genome-wide screen of association with cross-sectional long-term severity.

Approximately independent signals were identified from IMSGC statistics upon application of clumping procedure, with $r^2 > 0.1$ and a maximum distance of 250 kb, which generated a set of 319,525 independent SNPs out of 7,716,790.

PRS was calculated as the sum of effect alleles, weighted by the reported beta coefficient, using *R* v4.2 environment and PLINK1.9 [9] allele scoring function, with a clumping and thresholding (C + T) strategy. Five *p* value thresholds were considered: $p < 5*10^{-6}$ (*PRS_P5E_06*, $N = 10$), $p < 5*10^{-4}$ (*PRS_P5E_04*, $N = 723$), $p < 0.05$ (*PRS_P0.05*, $N = 39{,}738$), $p < 0.1$ (*PRS_P0.1*, $N = 68{,}819$), $p < 0.2$ (*PRS_P0.2*, $N = 119{,}666$). The scores were transformed on a standardized scale with a mean of 0 and a standard deviation of 1.

2.3 | Statistical Analysis

We fitted negative binomial regression models [10] to test the association between severity PRS and the number of PIRA events during follow-up. The models were adjusted for gender, age at first EDSS assessment, EDSS at first visit, year of onset (to account for different epochs that are proxies for different availability of treatments), with the addition of the logarithm of the duration of follow-up as an offset variable. The first five eigenvectors from principal component analysis were additionally incorporated into the models to account for population genetic substructure. Secondary pre-specified analysis was conducted in the cohort without patients with late-onset MS, that is, those with age at onset (AAO) > 50 years. Since loci in the HLA region might impact AAO, we conducted a sensitivity analysis, also testing the association of PRS with PIRA events upon exclusion of variants in the HLA region.

Given the exploratory nature of the study, associations were declared significant at a nominal level $p < 0.05$. Models were fitted using the *MASS* R package.

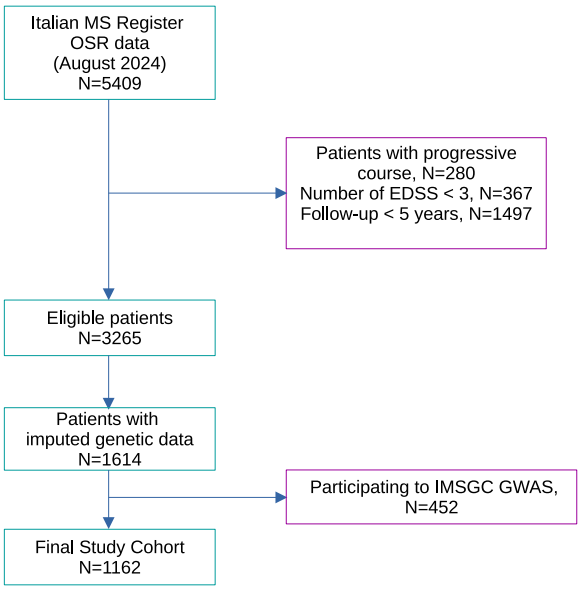
3 | Results

Upon application of exclusion criteria and quality control, the final study cohort was composed of 1162 patients (Figure 1A). Clinical and demographic characteristics are shown in Figure 1B. At the first neurological evaluation, patients had a mean age of 35.8 years and a disease duration of 6.7 years; a minority of patients were free of PIRA ($N = 533$, 45.9%), with events ranging from 1 to 7 over a median follow-up of 15.8 years.

The five PRS were not associated with the rate of PIRA events at the nominal level of significance, although a trend was observed in the expected direction for all scores, i.e., a rate ratio (RR) > 1

Study cohort

A)



B)

	N = 1162
Sex	
Females	778 (67%)
Males	384 (33%)
Follow up, years, median (IQR)	15.82 (10.1)
Course at end follow-up	
RRMS	721 (62%)
SPMS	439 (37.8%)
missing	2 (0.2%)
EDSS 1st visit, median (IQR)	2 (1.5)
Age 1st visit, years, mean (sd)	35.8 (10.4)
Disease duration 1st visit, years, mean (sd)	6.7 (7.4)
Age at onset, years, mean (sd)	29.2 (9.4)
Number of PIRA events	
0	533 (45.9%)
1	302 (25.9%)
2	167 (14.4%)
3	96 (8.2%)
4	46 (3.9%)
5	15 (1.3 %)
6	2 (0.17%)
7	1 (0.08%)

FIGURE 1 | Inclusion criteria and characteristics of study cohort. (A) Flow diagram showing the process of patient selection; (B) Clinico-demographic features for the final study cohort. The table shows mean values (with standard deviaton), median values (with interquartile range, IQR), or raw numbers (with percentages), as appropriate.

TABLE 1 | Association statistics of PRS with the rate of PIRA events.

	PRS	RR	p^a	95% CI
Overall cohort ($N = 1162$)	*PRS_P5E_06*	1.0266	0.4353	[0.9603, 1.0976]
	PRS_P5E_04	1.0555	0.1507	[0.9802, 1.1367]
	PRS_P0.05	1.1075	0.0958	[0.9811, 1.2502]
	PRS_P0.1	1.1219	0.0779	[0.9860, 1.2763]
	PRS_P0.2	1.1288	0.0759	[0.9865, 1.2913]
Age at onset < 50 years ($N = 1127$)	*PRS_P5E_06*	1.0512	0.1558	[0.9799, 1.1277]
	PRS_P5E_04	1.0716	0.0779	[0.9918, 1.1578]
	PRS_P0.05	1.1482	**0.0328**	[1.0106, 1.3044]
	PRS_P0.1	1.1385	0.0592	[0.9940, 1.3037]
	PRS_P0.2	1.0512	0.0717	[0.9881, 1.3112]
Age at onset < 40 years ($N = 1005$)	*PRS_P5E_06*	1.0585	0.1200	[0.9841, 1.1391]
	PRS_P5E_04	1.0989	**0.0224**	[1.0128, 1.1922]
	PRS_P0.05	1.1800	**0.0140**	[1.0335, 1.3474]
	PRS_P0.1	1.1566	**0.0410**	[1.0050, 1.3305]
	PRS_P0.2	1.1613	**0.0459**	[1.0024, 1.3450]

Note: Association statistics for each of the five calculated PRS are reported for the overall cohort study, for the subset of patients with age at onset ≤ 50 years and for the subset of patients with age at onset ≤ 40 years. Associations significant at level $\alpha = 0.05$ are reported in bold.
Abbreviations: PRS, polygenic risk score; RR, rate ratio.
[a]*p* value, RR and 95% CI were computed from negative binomial regression models.

for increasing values of the severity scores (Table 1). However, in the secondary analysis, discarding patients with late onset MS (AAO ≤ 50 years, $N = 1127$), we observed an association of the *PRS_P0.05* with the rate of PIRA events (RR = 1.148, 95% CI: 1.01 to 1.304, $p = 0.0328$, Table S1). When categorizing *PRS_P0.05* in quintiles, patients in the upper quintile were estimated to have a 27% higher rate of PIRA events compared to patients having genetic scores in the lowest one (RR = 1.27, 95% CI: 1.01 to 1.61, $p = 0.038$, Figure S1).

The association became increasingly apparent when further limiting analysis to patients with earlier onset (AAO ≤ 40 years), despite the reduction in sample size ($N = 1005$): again, the *PRS_P0.05* was the score showing the most significant level of association (RR = 1.18, 95% CI: 1.033 to 1.347, $p = 0.014$, Table 1).

Indeed, when investigating the overall cohort for an interaction between *PRS_0.05* and AAO, we detected a significant mild antagonistic effect ($RR_{int} = 0.98$, 95% CI: 0.96 to 1.0, $p = 0.033$), indicating a less pronounced genetic contribution to the rate of PIRA events with increasing values of AAO.

When excluding loci in the HLA region, we still detected the same AAO-dependent pattern of association of the PRS with PIRA events, as reported in Table S2.

4 | Discussion

Older age at baseline has been consistently reported as the most relevant determinant of the risk of PIRA [2, 11], pointing to the role of aging processes in the accumulation of permanent disability in MS. This pattern was observed also in the present study (Table S1). Beyond the effect of age, our results suggest that an increased cumulative genetic load carried by PRS correlates with a higher rate of PIRA events at medium and long term (follow-up > 5 years). Specifically, we found that associations were significant in the cohort of patients with AAO ≤ 50 years, and even more in the smaller set with earlier AAO (≤ 40 years). This pattern of association was confirmed after removal of variants in the HLA region, thus corroborating the robustness of our findings.

We can hypothesize that the effect of genetic factors on PIRA would generally be lower in magnitude in patients with late onset, because of the extended window during which risk might be influenced also by aging effects, as well as by concomitant pathologies, and because such individuals might have had more time to be exposed to environmental factors that influence risk for disability accumulation: in other complex traits it has already been found evidence of an age-varying genetic risk score prediction [12, 13].

It is also notable that a pattern of results emerged only when PRS aggregated effects across many loci, indicating that the additive genetic risk is actually spread across many variants [14].

A strength of our investigation is that analyses were carried out on a well-characterized Italian population, with a study cohort that was completely independent of IMSGC data, allowing an unbiased estimate of the impact of PRS on the rate of PIRA events.

On the other hand, a limitation of our study is that further alternative algorithms are available for the calculation of PRS [15].

Overall, the present study suggests that cumulative genetic load implicated in long-term disease severity influences the rate of PIRA events, especially in subjects with earlier AAO.

Author Contributions

Ferdinando Clarelli: writing – original draft, conceptualization, methodology, formal analysis, data curation, software, investigation, visualization, writing – review and editing. **Melissa Sorosina:** data curation, investigation, writing – review and editing, visualization. **Antonino Giordano:** data curation, investigation, visualization, writing – review and editing. **Elisabetta Mascia:** data curation, writing – review and editing. **Giulia Visentin:** data curation, writing – review and editing. **Matteo Missaglia:** data curation, writing – review and editing. **Lucia Moiola:** data curation, writing – review and editing. **Maria A. Rocca:** writing – review and editing, supervision, data curation. **Massimo Filippi:** supervision, writing – review and editing, resources. **Federica Esposito:** conceptualization, writing – review and editing, supervision, investigation, resources.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.