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# Original Article Progression independent of relapse activity and relapse-associated worsening in adult patients with secondary progressive multiple sclerosis

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# ABSTRACT

**Background:** In multiple sclerosis (MS), disability may accumulate in the form of deterioration linked to relapses, known as Relapse-Associated Worsening (RAW), or through a continuous progression unaffected by relapse activity, termed Progressive Independent of Relapse Activity (PIRA).

**Objectives:** To investigate PIRA's baseline predictors at the time of MS diagnosis and the contributions of PIRA versus RAW to the long-term clinical outcomes in secondary progressive MS (SPMS) patients.

**Methodology:** A retrospective cohort study was conducted at Nasser institute hospital on 150 patients with SPMS. Baseline and clinical data were collected during MS diagnosis, progression data during the disease course, and further outcome data. Also, different disability scores associated with PIRA and RAW were performed.

**Results:** Of 150 SPMS patients, 90 had PIRA, and 60 had RAW. Only age and type of relapses before starting disease modifying drugs (DMDs) showed significant differences between the groups. Patients with PIRA had higher mean age  $(40.1 \pm 5.1 \text{ vs}. 38.3 \pm 5.43, \text{ p} = 0.04)$  and fewer vision relapses than patients with RAW (34.4% vs. 51.7%, respectively p = 0.036). Moreover, no differences were found in magnetic resonance imaging (MRI) findings, including lesions and oligoclonal bands. There were significant associations between PIRA and poor long-term outcomes indicated by expanded disability status scale (EDSS), simple digit modalities test (SDMT), and 25-foot timed walk test (25FWT).

**Conclusion:** After the initial diagnosis of PIRA manifesting multiple sclerosis is prevalent among patients who develop secondary progression and indicates an unfavorable long-term prognosis. However, the prediction of PIRA is challenging, and further prospective research is warranted.

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**Keywords:** Expanded disability status scale (EDSS ), multiple sclerosis (MS), relapse-associated worsening (RAW), secondary progressive MS (SPMS), progression independent of relapse activity (PIRA)

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# **INTRODUCTION**

Multiple sclerosis (MS) can cause irreversible impairment accumulation at any stage of the disease mostly via two major mechanisms, including relapseassociated worsening (RAW) and progression independent of relapse activity (PIRA) <sup>[1,2]</sup>. Nonetheless, even in individuals without a confirmed secondary progressive MS (SPMS) diagnosis, PIRA, linked to a robust underlying neurodegenerative component, seems to be the major relevant mechanism <sup>[3]</sup>. PIRA is a novel and potentially revolutionary concept in MS that has evolved in recent years. Regardless of relapses, in the context of early stage relapsing multiple sclerosis, a discernible signal of disability progression is detected. The concept aims to measure the fraction of disability deterioration caused by neurodegenerative processes independent of inflammatory factors. PIRA appears similar to "smouldering MS" or "silent progression" at first appearance. However, the three concepts are pretty different. Smouldering inflammation or demyelination is a term used to describe persistent active and slowly growing Magnetic Resonance Imaging (MRI) lesions<sup>[4]</sup>. The term "silent progression" refers to handicap deterioration that occurs irrespective of relapses or white-matter lesions and appears to be associated with brain atrophy<sup>[5]</sup>. PIRA, on the other hand, does not consider MRI activity. The phrase arose from examining data from the Tysabri Observational Program (TOP) of patients taking natalizumab for a median of two years<sup>[6]</sup>.

While patients have the potential for full recovery from a relapse, their symptoms may progressively worsen in some circumstances. This partial recovery is known as RAW. RAW could be defined as confirmed disability accumulation (CDA) episodes that occur when the initial elevation in disability follows the occurrence of a protocol-defined relapse within the preceding 90 days<sup>[7]</sup>.

PIRA was investigated in individuals with particularly early-stage MS, including those with an initial central nervous system demyelinating assault<sup>[8]</sup> and people with documented MS<sup>[9]</sup>. However, to our knowledge, the predictors of PIRA, including clinical and radiological, compared to RAW during the initial demyelinating event among patients with SPMS, have not yet been examined. Furthermore, the outcomes of long-term disability of patients with PIRA compared to RAW are still mostly unclear. Considering that PIRA may be assumed as the first clinical indicator of progression in a relapsing-remitting context. It is crucial to identify whether patients with their first PIRA event early in the disease cycle have a particularly poor prognosis. Additionally, it is unknown how PIRA and brain inflammation activity are related<sup>[9]</sup>. We attempted to determine the likelihood of PIRA after the beginning of symptoms and to assess any possible radiological and clinical predictors at the time of such initial occurrence in this retrospective longitudinal investigation of a cohort of patients with an SPMS. We also aimed to estimate the long-term evolution of PIRA patients and recognize if there was a link between the PIRA episode and long-term impairment outcomes.

## **PATIENT AND METHODS**

This retrospective cohort study was conducted at Nasser Institute Hospital's MS clinic for research and treatment. The ethical committee waived written informed consent due to the observational nature of the study. All cases admitted during the period between November 2020 and May 2022 and met the inclusion criteria were chosen. The inclusion criteria included patients who have MS diagnosed according to McDonald criteria 2017 [1], being over the age of 18, and being clinically diagnosed with SPMS. Patients with other autoimmune diseases were excluded. The study was approved by the institutional review board (IRB), AZHAR university at 20 December 2020

Sociodemographic data, comorbidities, onset age and the time of diagnosis, first relapse history, relapses before starting any disease-modifying drugs (DMDs), data concerning PIRA and RAW diagnosis, and laboratory and radiological data at the time of MS diagnosis were collected from medical records. Comorbidities include diabetes mellitus (DM), hypertension, hypo- and hyperthyroidism, epilepsy, and deep venous thrombosis (DVT). Clinical evaluations comprised a neurological examination, progression assessment, 25-foot timed walk test (25FWT), and simple digit modalities test (SDMT). For any missing data, patients and their families were contacted.

The concept of CDA (confirmed disability established to measure the accumulation) was progression of impairment in individuals participating in this study. This progression was assessed using the EDSS(expanded disability status scale ), with an increase of 1.0 points if the baseline EDSS score was 5.5 points or a 0.5-point increase if the baseline EDSS score was below 5.5 points. Alternatively, a confirmed increase of 20% or more in the T25FW after 12 or more weeks or 24 weeks was also considered evidence of CDA. The events classified as RAW events are a specific subset of the broader category of composite CDA events. In cases classified as RAW, the observed rise in impairment from the study's starting point took place within 90 days or fewer following the initiation of a relapse as determined by the study's protocol. PIRA was established when the baseline assessment, consisting of EDSS or T25FW values, was re-baselined after 30 days or longer following the onset of each relapse. The first available assessment of each scale was conducted 30 days after the commencement of the relapse. The reassessed disability evaluation should not be lower than the initial baseline rating. During the baseline reference assessment and within 30 days before and after the initial increase in disability confirmation, it is expected that no relapse described by the protocol should take place<sup>[10]</sup>.

#### Statistical analysis

All quantitative data variables were normally distributed and expressed as mean  $\pm$  standard deviation (SD), except the diagnosis time, IgG, and OCB that are expressed as median and interquartile range (IQR), as demonstrated visually and statistically using Kolmogorov-Smirnov test. The independent samples ttest and/or Mann-Whitney U test was used to compare continuous data between two groups. The chi-square test, was employed to assess the disparities in categorical data among different groups, as deemed appropriate. The statistical analyses were conducted using SPSS version 28. All statistical tests conducted in this study were two-tailed and were carried out with a predetermined significance threshold of 0.05.

## RESULTS

In the present study, 150 SPMS patients were included, of them 90 had PIRA, and 60 had RAW. The mean age was higher among PIRA patients than those with RAW. However, the differences between SPMS patients with PIRA and RAW regarding sex, onset age, and diagnosis time were insignificant. Additionally, comorbidities were insignificantly more frequent among patients with PIRA than those with RAW (27.8 vs. 15%, p = 0.07).

Concerning the relapse history, the first relapse type, including brainstem, cerebellar, cerebral, paroxysmal,

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spinal, and vision, did not differ significantly between the two groups (p = 0.21). Moreover, the first relapse recovery with partial or full recovery with or without solumedrol treatment did not show a significant difference between the groups (p=0.72). On the other hand, the type of relapse before starting and DMDs did not show significant differences in brainstem, cerebellar, cerebral, paroxysmal, and spinal involvement. However, vision involvement was more frequent significantly among patients with RAW (p = 0.036). Additionally, the mean number of relapses before stating any DMD (disease modifying drug) did not differ significantly between the groups  $(3.2 \pm 2.12)$ vs.  $2.18 \pm 0.28$ , respectively), as shown in table (1).

Regarding radiological and laboratory data, no significant differences were found between the two groups in all MRI-based radiological findings at the time of progression, including several lesions, periventricular (PV) site, juxta-cortical (JC) site, infratentorial (IT) site, spinal lesion number, visual affection, presence of atrophy, presence of black halls, and mean oligoclonal bands (OCB). Additionally, mean immunoglobulin G (IgG) did not show a significant difference between the groups  $(1.09 \pm 0.50 \text{ vs.} 1.16 \pm 0.58$ , respectively) as shown in table (2).

MS's prognosis was assessed at two points: at EDSS of 3 and the current state using SDMT, 25FWT, and EDSS instruments. Current SDMT was lower among patients with PIRA than those with RAW (mean  $\pm$  SD of 18.97  $\pm$  6.98 vs. 22.12  $\pm$  8.09). Additionally, current EDSS was higher among patients with PIRA than those with RAW (mean  $\pm$  SD of 5.37  $\pm$  0.95 vs. 4.88  $\pm$  0.92). However, the current 25FWT did not differ between the groups. On the other hand, at the time of EDSS of 3, 25FWT was higher among patients with PIRA compared to those with RAW (mean  $\pm$  SD of 15.46  $\pm$  3.67 vs. 14.14  $\pm$  3.58). However, SDMT at EDSS of 3 did not show a significant difference between the groups (p = 0.053) as shown in table (3).

Table(1): Demogra	phic data and	l relapse history	among the studie	d groups

rable(1): Demographic data an		RAW	PIRA		
Variables		(n =60)	(n = 90)	Stat. test	p- value
		No. (%)	No. (%)		value
Gender	Female	43 (71.7%)	68 (75.6%)	$X^2 - 0.28$	0.59
Gender	Male	17 (28.3%)	22 (24.4%)	(n = 90)Stat. testNo. (%) $3(75.6\%)$ $X^2 = 0.28$ $3(75.6\%)$ $X^2 = 0.28$ $2(24.4\%)$ $X^2 = 3.35$ $5(72.2\%)$ $10 \pm 5.10$ $t = 2.06$ $10 \pm 5.10$ $t = 2.06$ $88 \pm 5.22$ $t = 1.07$ $(8 - 14)$ MW=1.28 $(10.1\%)$ $(22.2\%)$ $(12.2\%)$ $X^2 = 7.144$ $2(22.2\%)$ $(14.4\%)$ $2(28.9\%)$ $X^2 = 1.34$ $2(28.9\%)$ $X^2 = 0.47$ $3(4.4\%)$ $X^2 = 0.36$ $2(23.3\%)$ $X^2 = 0.83$	0.59
Comorbidities	Yes	9 (15%)	25 (27.8%)	$X^2 - 3.35$	0.07
Comorbiantes	No	51 (85%)	65 (72.2%)	A -5.55	
Age years, mean ± SD		$38.3 \pm 5.43$	$40.10 \pm 5.10$	t =2.06	0.04*
Onset age years, mean ± SD		$27.92 \pm 5.57$	$28.88 \pm 5.22$	t=1.07	0.28
Diagnosis time (years), media	n (IQR)	10.5 (6 - 14.75)	11 (8 – 14)	MW=1.28	0.2
	Brainstem	5 (8.3%)	9 (10.1%)		0.21
1 <sup>st</sup> relapse type	Cerebellar	7 (11.7%)	20 (22.2%)		
	Cerebral	13 (21.7%)	11 (12.2%)	$x^2 - 7.144$	
	Paroxysmal	5 (8.3%)	8 (8.9%)	$\Lambda = 7.144$	
	Spinal	15 (25%)	29 (32.2%)		
	Vision	15 (25%)	13 (14.4%)		
1 <sup>st</sup> relapse recovery	Full, no treatment	17 (28.3%)	26 (28.9%)		0.72
	Full, soulmedrol	15 (25.1%)	16 (17.8%)	$v^2 - 1.24$	
	Partial, no treatment	11 (18.3%)	17 (18.9%)	A =1.54	
	Partial, soulmedrol	17 (28.3%)	31 (34.4%)		
Type of relapses before any DMDs	Brainstem	10 16.7%)	19 (21.1%)	$X^2 = 0.47$	0.500
	Cerebellar	27 (45.0%)	45 (50.0%)		0.548
	Cerebral	18 (30.0%)	21 (23.3%)	$X^2 = 0.83$	0.362
	Paroxysmal	5 (8.3%)	7 (7.8%)	$X^2 = 0.015$	0.902
	Spinal	35 (58.3%)	63 (70.0%)	$X^2 = 2.16$	0.141
	Vision	31 (51.7%)	31 (34.4%)	$X^2 = 4.4$	0.036*
Relapses no. before any DMD	s, mean ± SD	$3.02 \pm 2.18$	$3.2 \pm 2.12$	t=0.54	0.59

Diagnosis period/years were calculated as a year difference between the time of diagnosis and 2022. Onset years were calculated as a difference between onset age and current age, IQR: Interquartile range, PIRA: Progression independent of relapse activity, RAW: Relapse-associated worsening, SD: Standard deviation. X<sup>2</sup>: Chi-square test was used comparison of qualitative data, and T: independent t-test and/or MW: Mann-Whitney test was used for comparison of quantitative data, \* Significant p-value (<0.05)

Table (2): Differences of Ma	gnetic resonance imagin	g findings betweer	the studied groups
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Table (2): Differences of M	agnetic resonance	RAW	PIRA	Jups	
Item		(n =60)	(n = 90)	Stat. test	p-value
		No. (%)	No. (%)		
Number of lesions	1 – 5	1 (1.7%)	7 (7.8%)		0.26
	6 – 10	23 (38.3%)	31 (34.4%)	$X^2 = 2.7$	
	> 10	36 (60%)	52 (57.8%)		
Site of lesion PV	Yes	60 (100%)	90 (100%)		
	No	0 (0%)	0 (0%)		NA
Site of lesion JC	Yes	42 (70.0%)	67 74.4%)	$X^2 = 0.36$	0.550
Site of resion JC	No	18 (30.0%)	23 (25.6%)	Λ =0.50	
Site of lesion IT	Yes	53 (88.3%)	76 (84.4%)	$X^2 = 0.45$	0.500
Site of lesion 11	No	7 (11.7%)	14 (15.6)	$\Lambda = 0.45$	
Spinal	1	12 (20.3%)	11 (12.4%)		0.710
	2	17 (28.8%)	29 (32.6%)		
	3	18 (30.5%)	26 (29.2%)	$X^2 = 2.135$	
	4	9 (15.3%)	18 (20.2%)		
	5	3 (5.1%)	5 (5.6%)		
Visual	ND	31 (51.7%)	38 (42.2%)		0.521
	Normal	5 (8.3%)	9 (10.0%)	$X^2 = 1.29$	
	Prolonged	24 (40.0%)	43 (47.8%)		
A twomber	Yes	37 (61.7%)	65 (72.2%)	$X^2 = 1.84$	0.175
Atrophy	No	23 (38.3%)	25 (27.8%)	A =1.64	
Black holes	<3	14 (23.3%)	15 (16.7%)		0.290
	>5	17 (28.3%)	36 (40.0%)	$X^2 = 3.67$	
	3 – 5	22 (36.7%)	24 (26.7) %	A =3.07	
	no	7 (11.7%)	14 (15.6%)		
IgG index, median (IQR)		1 (0.8 – 1.36)	0.95 (0.78 – 1.23)	MW=0.73	0.467
OCB, median (IQR)		2 (1 – 10)	2 (0 – 10)	MW= 0.26	0.793

IT: Infra-tentorial, IQR: Interquartile range, JC: Juxta-cortical, OCB: oligoclonal bands, PV: Periventricular, PIRA: Progression independent of relapse activity, RAW: Relapse-associated worsening, ND: Not done, IgG: Immunoglobulin G,  $X^2$ : Chi-square test, MW: Mann-Whitney test, \*: Significant p-value (<0.05)

#### Table (3): Multiple sclerosis outcomes among the studied groups

Item	RAW (n =60)	PIRA (n = 90)	Stat. test	p-value
SDMT (Current EDSS)	$22.12 \pm 8.09$	$18.97\pm6.98$	t=2.54	0.012*
SDMT (at EDSS =3)	$27.10 \pm 5.87$	$25.21 \pm 5.74$	t=1.95	0.053
25FWT (Current EDSS)	$24.81 \pm 19.39$	$26.83 \pm 14.93$	t=0.69	0.49
25FWT (at EDSS =3)	$14.14 \pm 3.58$	$15.46 \pm 3.67$	t=2.17	0.03*
EDSS	$4.88\pm0.92$	$5.37\pm0.95$	t=3.19	0.002*

PIRA: Progression independent of relapse activity, RAW:R-associated worsening, SDMT: Simple digit modalities test, 25FWT: 25-Foot timed walk test, EDSS: Expanded disability status scale, t: Independent t-test, \*: Significant p-value (<0.05)

### **DISCUSSION**

Based on the current results, this retrospective cohort study showed that about two-thirds of the SPMS patients experienced early PIRA during the disease progression course, while the other third experienced early RAW in their course. Moreover, older age was associated with a greater risk of PIRA. However, sex, disease onset age, and comorbidities were not associated with the PIRA mechanism of the MS progression. Relapses, either at the first time or as a cumulative before starting DMDs, were also not associated with the PIRA mechanism. However, vision-involved relapses were associated with the RAW mechanism. Additionally, MRI-based lesion characteristics obtained with the MS diagnosis were not associated with the PIRA pathway of the MS progression. Further, results suggest that PIRA was associated with unfavorable long-term outcomes indicated by EDSS, 25FWT, and SDMT. Our findings are consistent with Portaccio et al. in their study on PIRA in early MS<sup>[11]</sup>. As a result, many MS patients may experience progression in the absence of relapses relatively early in the disease course <sup>[12]</sup>.

Despite being SPMS traditionally linked with a low level of disability, it appears that a subset of relapse MS patients can progress early in the disease course <sup>[13]</sup>. Patients with PIRA were older, more likely to have comorbidities, and more likely to have vision involvement in their early relapses before starting DMDs than those without PIRA. However, MRI findings found no differences between PIRA and RAW groups. Despite these distinctions, predicting which individuals would eventually develop PIRA based solely on baseline features was difficult. In accordance with previous research<sup>[14]</sup>, PIRA was associated with more brain lesions and oligoclonal bands than patients without PIRA in the univariate analysis. However, the sole predictor of PIRA at the time of the first demyelinating episode among MS patients was older age at the time of the first attack using a multivariate survival model.

The study conducted by Portaccio et al. <sup>[11]</sup> suggested that the occurrence of progressive isolated relapsing activity (PIRA) might potentially be anticipated based on certain factors, including the presence of a relapsing-remitting illness course, a more protracted duration of the disease, and a reduced frequency of relapses before the onset of PIRA. In addition to older age at the study baseline. However, except for greater age, none of these predictors were associated with PIRA risk, as the present study focused on SPMS patients.

Notably, patients with PIRA performed quite differently throughout the time than those with RAW: patients with PIRA had substantially higher EDSS rise rates than those without PIRA. Additionally, patients with PIRA had somewhat lower SDMT than patients with RAW at the time of secondary progression diagnosis. This decrease became significantly greater at the current time compared to RAW patients. Additionally, a much higher 25FWT score was reported at the time of secondary progression diagnosis among patients with PIRA than those with RAW. However, these differences became less significant in the current state. In agreement with our findings, TUR et al. <sup>[15]</sup> found that patients with PIRA had substantially faster EDSS increase rates than those without PIRA, and they were about 8-fold more likely to achieve EDSS 6.0 from the first demyelinating episode. Similarly, a pooled Analysis of two randomized clinical trials reported PIRA-associated worsening to overall disability accumulation among patients with relapsing MS<sup>[7]</sup>.

These data suggested that early identification of individuals developing PIRA may be critical for regulating patients' expectations and, possibly, identifying the most effective treatment approaches. Moreover, further research is needed to discover all people who will acquire PIRA as soon as possible and to understand the mechanisms that lead to PIRA, particularly the link between age and early PIRA.

This study had some limitation that deserve to be mentioned; the retrospective diagnosis of PIRA and RAW could be affected by different disability assessments over time. Another factor to consider is the potential impacts of medications. It was overcome by taking clinical and radiological data before any DMDs were started. Additionally, some individuals might have an MRI evaluation somewhat later after the onset of the symptoms.

# CONCLUSION

According to the findings of this retrospective study, PIRA is essentially a major nonreversible mechanism of MS progression associated with unfavorable longterm impairment outcomes. We can identify all individuals who will develop PIRA as soon as feasible after the initial MS diagnosis, which may lead to improved treatment options and, as a result, superior long-term outcomes.

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الملخص العربي

التقدم المستقل عن نشاط الانتكاس والتفاقم المرتبط بالانتكاس لدى المرضى البالغين المصابين بالتصلب المتعدد التقدمى الثانوي منار احمد شوقي 1، طارق ابراهيم منيسي<sup>2</sup>، ايمان محمد سيف الدين<sup>3</sup>، محمد حامد رشاد<sup>2</sup> وحدة التصلب المتعدد، قسم طب الاعصاب، مستشفيي معهد ناصر للبحوث والعلاج، القاهرة، جمهورية مصر العربية <sup>2</sup> قسم طب الاعصاب، كلية طب البنين، القاهرة، جامعة الازهر، جمهورية مصر العربية <sup>3</sup> قسم طب الاعصاب، كلية طب البنات، القاهرة، جامعة الازهر، جمهورية مصر العربية <sup>4</sup> قسم طب الاعصاب، كلية طب البنات، القاهرة، جامعة الازهر، جمهورية مصر العربية

ملخص البحث :

**الخلفية:** مرض التصلب المتعدد يتميز بتراكم الإعاقة إما فى شكل تدهور مرتبط بالانتكاسات، المعروف باسم التفاقم المصاحب للانتكاس، أو من خلال التقدم المستمر غير المتأثر بنشاط الانتكاس، والذي يسمى التقدم المستقل عن نشاط الانتكاس

**الهدف:** تهدف هذه الدراسة الي تحديد السمات الاكلينيكية الموضحة لكلا من مجموعتين مرض التصلب المتعدد الثانوي المتقدم سواء مجموعة المرضي التي تميزت بتراكم الاعاقة من دون هجمات او مجموعة المرضي التي تميزت بتراكم الاعاقة بعد تعرضها للهجمات

**الطرق:** هذه دراسة أتراب بأثر رجعى أجريت على 150 مريض بوحدة معهد ناصر للتصلب المتعدد من واقع سجلات قاعدة البيانات للمرضي في الوحدة و قد تم جمع البيانات الأساسية والسريرية أثناء تشخيص مرض التصلب العصبي المتعدد، وبيانات التقدم خلال مسار المرض، وأيضا تم تسجيل درجات الاعاقة المختلفة والعوامل المؤثرة عليها

النتائج : شملت الدراسة 150 مريضا من مرضي التصلب المتعدد التقدمي الثانوي ( 90 مريض منهم يمكن تنصيف الاعاقة الخاصة بهم الي اعاقة تقدمية بدون هجمات و60 مريض منهم يمكن تصنيف سبب الاعاقة الخاصة بهم الي الهجمات السابقة) وقد أظهر فقط العمر ونوع الانتكاسات قبل البدء بالأدوية المعدلة للمرض اختلافات كبيرة بين المجموعتين حيث كان لدى المرضى الذين يعانون من PIRA متوسط عمر أعلى وانتكاسات رؤية أقل من المرضى الذين يعانون من RAW (34.4% مقابل 51.7%، على التوالي). علاوة على ذلك، لم يتم العثور على اختلافات في نتائج التصوير بالرنين المغناطيسي. كما كان هناك ارتباطات كبيرة بين PIRA والنتائج على المدى الطويل التي أشار إليها مقياس حالة الإعاقة الموسع.

الاستنتاجات :اظهر البحث أن وجود المرضي الذين تطورت لديهم اعاقة في عدم وجود هجمات هو السائد بين مرضي التصلب المتعدد من النوع التقدمي الثانوي ويشير ذلك إلى توقع غير مستحسن على المدى الطويل. ومع ذلك، فإن التنبؤ بـ PIRA يمثل تحديًا، وهو ما يبرر إجراء المزيد من البحوث المستقبلية

**الكلمات المفتاحية:** التصلب المتعدد، مقياس اتساع مدي الاعاقة، تصلب متعدد تقدمي ثانوي، تراكم الاعاقة بدون هجمات

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