

eTable 2. Demographic, clinical and radiological features of untreated relapsing remitting multiple sclerosis patients grouped according to disability worsening phenotypes.

Variables			vs Late worsening		vs Early Worsening		vs Rapid worsening	
			Effect size (95% CI) ^a	<i>p</i>	Effect size (95% CI) ^a	<i>p</i>	Effect size (95% CI) ^a	<i>p</i>
Age	Minimal worsening	Mean (SD) 31.8 (9.2)	-0.04 (-0.15, 0.07)	0.56	-0.30 (-0.55, -0.04)	0.02	-0.42 (-0.57, -0.27)	<0.001
	Late worsening	32.2 (9.9)			-0.26 (-0.50, -0.01)	0.03	-0.38 (-0.51, -0.26)	<0.001
	Early worsening	34.7 (9.3)					-0.13 (-0.39, 0.14)	0.55
	Rapid worsening	36.0 (10.8)						
Sex		Female/male	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>
	Minimal worsening	277/122	0.01 (-0.03, 0.06)	0.55	0.06 (-0.03, 0.15)	0.27	0.05 (-0.02, 0.13)	0.20
	Late worsening	1215/579			0.02 (-0.02, 0.07)	0.36	0.02 (-0.02, 0.07)	0.31
	Early worsening	42/26					0.02 (-0.08, 0.12)	0.76
	Rapid worsening	195/107						
		Median (IQR)	Effect size (95% CI) ^c	<i>p</i>	Effect size (95% CI) ^c	<i>p</i>	Effect size (95% CI) ^c	<i>p</i>

EDSS	Minimal worsening	2.0 (1.5, 3.0)	0.15 (0.11, 0.19)	<0.001	0.21 (0.12, 0.29)	<0.001	0.16 (0.08, 0.23)	<0.001
	Late worsening	1.5 (1.0, 2.0)			0.18 (0.14, 0.22)	<0.001	0.22 (0.17, 0.26)	<0.001
	Early worsening	2.5 (2.0, 3.5)					0.05 (0.00, 0.15)	0.27
	Rapid worsening	2.5 (1.5, 3.5)						
		Number (%)	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>
Onset brainstem (%)	Minimal worsening	99 (25%)	0.01 (-0.04, 0.05)	0.81	0.03 (-0.07, 0.12)	0.69	0.01 (-0.07, 0.08)	0.90
	Late worsening	458 (25%)			0.01 (-0.04, 0.06)	0.75	0.00 (-0.04, 0.04)	1.00
	Early worsening	19 (28%)					0.02 (-0.08, 0.12)	0.79
	Rapid worsening	77 (25%)						
		Number (%)	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>
Onset optic nerve (%)	Minimal worsening	89 (22%)	0.05 (0.01, 0.09)	0.03	0.07 (-0.02, 0.16)	0.20	0.02 (-0.06, 0.09)	0.71
	Late worsening	497 (28%)			0.05 (0.01, 0.10)	0.02	0.05 (0.01, 0.10)	0.01
	Early worsening	10 (15%)					0.06 (-0.04, 0.16)	0.33
	Rapid worsening	63 (21%)						
		Number (%)	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>
Onset spinal cord (%)	Minimal worsening	140 (35%)	0.06 (0.02, 0.11)	0.004	0.17 (0.08, 0.26)	<0.001	0.07 (0.00, 0.15)	0.06
	Late worsening	496 (28%)	12 (18%)		0.13 (0.08, 0.17)	<0.001	0.00 (-0.04, 0.05)	0.91

	Early worsening	40 (59%)					0.25 (0.15, 0.35)	<0.001
	Rapid worsening	85 (28%)						
		Number (%)	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>
Onset Hemispheric (%)	Minimal worsening	113 (28%)	0.02 (-0.02, 0.07)	0.30	0.09 (-0.01, 0.18)	0.09	0.12 (0.04, 0.19)	0.003
	Late worsening	558 (31%)			0.05 (0.01, 0.10)	0.03	0.06 (0.02, 0.11)	0.005
	Early worsening	12 (18%)					0.18 (0.08, 0.28)	0.001
	Rapid worsening	119 (39%)						
		Number (%)	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>
Brain T2 Lesions (1-2 3-8 ≥9)	Minimal worsening	67 (17%) 223 (56%) 109 (27%)	0.02 (-0.02, 0.07)	0.52	0.05 (-0.04, 0.14)	0.54	0.16 (0.08, 0.23)	<0.001
	Late worsening	344 (19%) 961 (54%) 489 (27%)			0.03 (-0.01, 0.08)	0.41	0.12 (0.08, 0.16)	<0.001
	Early worsening	10 (15%) 35 (51%) 23 (34%)					0.11 (0.01, 0.21)	0.01
	Rapid worsening	21 (7%) 174 (58%) 107 (35%)						
		Number (%)	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>

Brain Gd-lesion	Minimal worsening	194 (49%)	0.02 (-0.02, 0.06)	0.36	0.09 (0.00, 0.18)	0.05	0.08 (0.01, 0.15)	0.04
	Late worsening	825 (46%)			0.06 (0.01, 0.10)	0.01	0.07 (0.03, 0.12)	<0.001
	Early worsening	42 (62%)					0.04 (-0.06, 0.14)	0.52
	Rapid worsening	171 (57%)						
		Number (%)	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>
Spinal cord T2 lesions (0, 1-3, >3)	Minimal worsening	162 (41%) 211 (53%) 26 (7%)	0.01 (-0.04, 0.05)	0.96	0.23 (0.14, 0.31)	<0.001	0.19 (0.12, 0.26)	<0.001
	Late worsening	740 (41%) 935 (52%) 119 (7%)			0.13 (0.08, 0.17)	<0.001	0.13 (0.09, 0.18)	<0.001
	Early worsening	11 (16%) 43 (63%) 14 (21%)					0.12 (0.02, 0.22)	0.04
	Rapid worsening	70 (23%) 198 (66%) 34 (11%)						
		Number (%)	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>
Spinal cord Gd-lesion presence (%)	Minimal worsening	157 (39%)	0.04 (0.00, 0.08)	0.06	0.18 (0.09, 0.27)	<0.001	0.03 (-0.04, 0.11)	0.41
	Late worsening	617 (34%)			0.12 (0.07, 0.16)	<0.001	0.06 (0.02, 0.10)	0.006
	Early worsening	44 (65%)					0.17 (0.07, 0.27)	0.001

	Rapid worsening	129 (43%)						
		Number (%)	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>	Effect size (95% CI) ^b	<i>p</i>
OCB (%)	Minimal worsening		0.02 (-0.02, 0.06)	0.39	0.02 (-0.07, 0.11)	0.88	0.02 (-0.05, 0.09)	0.67
	Late worsening				0.00 (-0.04, 0.05)	1.00	0.00 (-0.04, 0.05)	0.94
	Early worsening						0.00 (-0.10, 0.10)	1.00
	Rapid worsening							

^a Cohen's d effect size

^b Cramer's V effect size

^c Cliff's delta effect size

Abbreviations: EDSS=Expanded Disability Status Scale; SD=standard deviation; CI=confidence interval; Gd-lesion=gadolinium enhancing lesions; OCB=oligoclonal bands.