Supplementary Table 1: Multivariate regression analysis to explore the effect of age on adaptive and innate immune responses and on disability of M- and M+ patients.

Variable	M- patients (n=191)		M+ patients (n=72)	
	Coef	95% CI	Coef	95% CI
CSF leukocyte subsets (cells/ml)				
Total Mononuclear cells	-105.69	(-150.93 ;-60.46)	38.96	(-89.30 ;167.22)
Total Lymphocytes	-104.44	(-149.75 ;-59.13)	37.59	(-88.58 ;163.76)
CD4+ T cells	-70.26	(-103.38 ;-37.14)	39.02	(-49.70 ;127.73)
CD4+ IFN-gamma+	-23.69	(-38.31 ;-9.07)	29.81	(-10.25 ;69.87)
CD4+ TNF-alpha+	-51.31	(-79.49 ;-23.14)	66.79	(-16.75 ;150.34)
CD4+ IL-17+	-4.05	(-8.31 ;0.21)	-3.78	(-8.85 ;1.28)
CD4+ GM-CSF+	-37.92	(-63.91 ;-11.94)	-8.30	(-22.79 ;6.18)
CD8+ T cells	-16.88	(-26.14 ;-7.62)	6.14	(-18.52 ;30.80)
CD8+ IFN-gamma+	-9.70	(-15.30 ;-4.11)	10.59	(-7.14 ;28.33)
CD8+ TNF-alpha+	-10.00	(-15.98 ;-4.01)	20.01	(-5.03 ;45.04)
CD8+ IL-17+	-1.05	(-2.46 ;0.35)	-1.77	(-3.64 ;0.10)
CD8+ GM-CSF+	-5.89	(-9.85 ;-1.92)	-1.09	(-3.82 ;1.63)
CD19+ B Cells	-5.77	(-8.48 ;-3.06)	1.76	(-8.41 ;11.94)
CD19+ TNF-alpha+	-5.55	(-9.54 ;-1.56)	-2.49	(-6.56 ;1.59)
CD19+ GM-CSF+	-0.63	(-1.26 ;-0.00)	-0.38	(-1.29 ;0.52)
Total NK cells (cells/ml)	-5.16	(-10.21 ; -0.12)	-1.40	(-16.33; 13.54)
Soluble factors				
PD-L1 (pg/ml)	0.33	(0.13 ;0.53)	0.52	(0.18 ;0.87)
TIM- 3 (pg/ml)	5.80	(-5.80 ;17.40)	27.13	(8.91 ;45.35)

Serum IgG anti-CMV (IV)	0.50	(0.21 ;0.79)	0.22	(-0.24 ;0.69)
CHI3L1 (ng/ml)	4.02	(2.25 ;5.79)	3.44	(-3.96 ;10.84)
Activin A (pg/ml)	2.86	(1.22 ;4.49)	3.57	(1.93 ;5.20)
Disability scores				
EDSS	0.05	(0.03 ;0.06)	0.04	(0.006 ;0.08)
MSSS	0.08	(0.04 ;0.11)	0.07	(0.006 ; 0.14)

Footnote: CHI3L1: Chitinase 3-like 1; Coef: Coefficient; CI: Confidence Interval; CMV: Cytomegalovirus; CSF: cerebrospinal fluid; EDSS: Expanded Disability Status Scale; IFN: Interferon; IL: Interleukin; IV: Index Value; GM-CSF: Granulocyte/macrophage-colony stimulating factor; NK: Natural Killer. M+ patients: Those showing lipid-specific oligoclonal IgM bands; M- patients: Those lacking lipid-specific oligoclonal IgM bands; MSSS: Multiple Sclerosis Severity Score; PD-L1: Programmed Death-ligand 1; TIM-3: T-cell immunoglobulin and mucin domain-3; TNF: Tumor necrosis factor. All soluble factors were quantified in CSF with the exception of IgG anti-CMV, quantified in serum. All Coefficients and Confidence Intervals were adjusted by disease duration.