**Supplemental Data**

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| **Title** | **Predicting aggressive multiple sclerosis using intrathecal IgM synthesis among patients with a clinically isolated syndrome.** |
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| **ESM Content:** | **Table e-1.** Type of treatments administered during MS evolution among patients with MS (n=165).**Table e-2.** Between-methods concordance analysis.**Figure e-1.** Forest plot for All Methods.**Table e-3.** Positive and negative predictive values of each method (including combinations between them) predicting EDSS 4 and 6 and development of SPMS.**Table e-4.** Unadjusted and multivariate Cox regression models for the risk of EDSS 4, EDSS 6 and development of SPMS among patients with clinically defined multiple sclerosis (CDMS) (n=149)**Table e-5.** Unadjusted and multivariate Cox regression models for the risk of EDSS 4, EDSS 6 and development of SPMS among patients with a 2017 McDonald RRMS (n=165)**Table e-6.** Unadjusted and multivariate Cox regression models for the risk of EDSS 4, EDSS 6 and development of SPMS among patients with at least 10 years of follow-up (n=120) |

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| **Table e-1. Type of treatments administered during MS evolution among patients with MS (n=165)** |
|  | **First lineb** | **Second linec** |
| **All patients (n=165), No. (%)a** | 141 (85.5) | 44 (26.7) |
| **OCMB, No. (%)** |
| Positive (n=70) | 60 (85.7) | 27 (38.6)d |
| Negative (n=95) | 81 (85.3) | 17 (17.9)d |
| **LS-OCMB, No. (%)** |
| Positive (n=52) | 47 (90.4) | 23 (44.2)d |
| Negative (n=113) | 94 (83.2) | 21 (18.6)d |
| **Reibergram (IF>0%), No. (%)** |
| Positive (n=27) | 24 (88.9) | 10 (37.0) |
| Negative (n=138) | 117 (84.8) | 34 (24.6) |
| **IgM Index, No. (%)** |
| ≥0.1 (n=69) | 58 (85.3) | 20 (29.0) |
| <0.1 (n=96) | 83 (85.6) | 24 (25.0) |

Abbreviation: MS: multiple sclerosis; LS-OCMB: lipid specific IgM oligoclonal bands; MS: multiple sclerosis; No: number; OCMB: IgM oligoclonal bands; RRMS: relapsing-remitting multiple sclerosis.

aPercentages reflect the proportion of patients ever treated with each type of DMT during their disease, so multiple types are frequently observed.

bFirst line: subcutaneous or intramuscular interferon-ß, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, azathioprine, methotrexate.

cSecond line: Natalizumab, Alemtuzumab, Ocrelizumab, Rituximab, Mitoxantrone, Cyclophosphamide.

d*P* value <0.05 (positive vs. negative results).

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| **Table e-2. Between methods concordance analysis.** |
| **Observed agreement (kappa index)** | **OCMB** | **LS-OCMB** | **Reibergram** |
| **LS-OCMB** | 90.2%(0.78) |  |  |
| **Reibergram** | 68.9%(0.25) | 76.7%(0.33) |  |
| **IgM Index (≥0.1)** | 69.4%(0.36) | 70.5%(0.36) | 73.6%(0.41) |

Abbreviation: LS-OCMB: lipid specific IgM oligoclonal bands; OCMB: IgM oligoclonal bands.

**Figure e-1. Forest plot for All Methods.**



Sensitivity and specificity of all methods (OCMB, LS-OCMB, Reibergram and IgM Index) assessing ITMS (including combinations between them) for predicting EDSS scores of 4 and 6 and conversion to SPMS. Abbreviature: EDSS, expanded disability status scale; ITMS, intrathecal IgM synthesis; LS-OCMB, lipid-specific IgM oligoclonal bands; OCMB, IgM oligoclonal bands.

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| **Table e-3. Positive and negative predictive values of each method (including combinations between them) predicting EDSS 4 and 6 and development of SPMS.** |
|  | **EDSS 4** | **EDSS 6** | **SPMS** |
|  | PPV(95% CI) | NPV(95% CI) | PPV(95% CI) | NPV(95% CI) | PPV(95% CI) | NPV(95% CI) |
| OCMB | 30.6 (20.2 – 42.5) | 84.3 (76.6 – 90.3) | 23.6 (14.4 – 35.1) | 90.1 (83.3 – 94.8) | 23.6 (14.4 – 35.1) | 87.6 (80.4 – 92.9) |
| LS-OCMB | 38.5 (25.3 – 53.0) | 85.1 (78.1 – 90.5) | 30.8 (18.7 – 45.1) | 90.8 (84.7 – 95.0) | 28.9 (17.1 – 43.1) | 87.9 (81.4 – 92.8) |
| IgM Reibergram | 31.3 (16.1 – 50.0) | 80.8 (73.8 – 86.5) | 21.9 (9.3 – 40.0) | 86.3 (80.0 – 91.2) | 25.0 (11.5 – 43.4) | 85.1 (78.6 – 90.2) |
| IgM Index (>0.1) | 22.2 (13.7 – 32.8) | 79.5 (70.8 – 86.5) | 16.1 (8.8 – 25.9) | 85.7 (77.8 – 91.6) | 16.1 (8.8 – 25.9) | 83.0 (74.8 – 89.5) |
| OCMB and Reibergram | 36.4 (17.2 – 59.3) | 80.7 (74.0 – 86.3) | 27.3 (10.7 – 50.2) | 86.6 (80.5 – 91.3) | 27.3 (10.7 – 50.2) | 84.8 (78.5 – 89.8) |
| LS-OCMB and Reibergram | 36.8 (16.3 – 61.6) | 80.5 (73.8 – 86.1) | 26.3 (9.1 – 51.2) | 86.2 (80.2 – 91.0) | 26.3 (9.2 – 51.2) | 84.5 (78.2 – 89.5) |

Abbreviature: CI: confidence interval; CIS: clinically isolated syndrome; EDSS: expanded disability status scale; HR: hazard ratio; IF: intrathecal fraction; LS-OCMB: lipid specific IgM oligoclonal bands; NPV: negative predictive value; OCMB: IgM oligoclonal bands; PPV: positive predictive value; SPMS: secondary progressive multiple sclerosis.

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| **Table e-4. Unadjusted and multivariate Cox regression models for the risk of EDSS 4, EDSS 6 and development of SPMS among patients with clinically defined multiple sclerosis (CDMS) (n=149)** |
|  | **Unadjusted** | **Multivariate modela** |
|  | **HR** | **95% CI** | ***P* Value** | **HRb** | **95% CI** | ***P* Value** |
| **EDSS 4** |  |  |  |  |  |  |
| OCMB | 2.04 | 1.05 – 3.97 | *0.036* | 1.88 | 0.95 – 3.69 | 0.068 |
| LS-OCMB | 2.99 | 1.55 – 5.77 | *0.001* | 3.55 | 1.75 – 7.22 | *<0.001* |
| Reibergram | 1.96 | 0.89 – 4.30 | 0.1 | 1.83 | 0.81 – 4.14 | 0.15 |
| IgM Index (>0.1) | 1.39 | 0.71 – 2.69 | 0.34 | 1.21 | 0.61 – 2.39 | 0.59 |
| **EDSS 6** |  |  |  |  |  |  |
| OCMB | 2.31 | 1.08 – 4.94 | *0.032* | 2.18 | 0.99 – 4.77 | 0.051 |
| LS-OCMB | 3.82 | 1.79 – 8.16 | *0.001* | 4.78 | 2.11 – 10.87 | *<0.001* |
| Reibergram | 2.32 | 0.98 – 5.49 | 0.055 | 2.34 | 0.96 – 5.69 | 0.061 |
| IgM Index (>0.1) | 1.46 | 0.69 – 3.10 | 0.32 | 1.34 | 0.62 – 2.89 | 0.46 |
| **SPMS** |  |  |  |  |  |  |
| OCMB | 1.84 | 0.89 – 3.80 | 0.10 | 1.61 | 0.76 – 3.44 | 0.22 |
| LS-OCMB | 2.50 | 1.22 – 5.13 | *0.01* | 2.50 | 1.14 – 5.47 | *0.02* |
| Reibergram | 2.26 | 0.96 – 5.29 | 0.06 | 2.19 | 0.91 – 5.28 | 0.08 |
| IgM Index (>0.1) | 1.16 | 0.55 – 2.43 | 0.71 | 1.04 | 0.48 – 2.28 | 0.92 |

Abbreviature: CI: confidence interval; CIS: clinically isolated syndrome; EDSS: expanded disability status scale; HR: hazard ratio; IF: intrathecal fraction; LS-OCMB: lipid specific IgM oligoclonal bands; OCMB: IgM oligoclonal bands; SPMS: secondary progressive multiple sclerosis.

aCox proportional hazard regression, adjusted by sex, age at CIS, topography of CIS, disease duration at the time of lumbar puncture and disease-modifying treatments as time-dependent covariates.

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| **Table e-5. Unadjusted and multivariate Cox regression models for the risk of EDSS scores of 4 and 6 and development of SPMS among patients with a 2017 McDonald MS (n=165)** |
|  | **Unadjusted** | **Multivariate modela** |
|  | **HR** | **95% CI** | ***P* Value** | **HRb** | **95% CI** | ***P* Value** |
| **EDSS 4** |  |  |  |  |  |  |
| OCMB | 1.75 | 0.95 – 3.24 | 0.07 | 1.53 | 0.82 – 2.86 | 0.182 |
| LS-OCMB | 2.59 | 1.40 – 4.77 | *0.002* | 2.74 | 1.43 – 5.25 | *0.002* |
| Reibergram | 2.10 | 1.02 – 4.29 | *0.04* | 1.89 | 0.90 – 3.99 | 0.09 |
| IgM Index (>0.1) | 1.55 | 0.83 – 2.88 | 0.17 | 1.39 | 0.74 – 2.60 | 0.31 |
| **EDSS 6** |  |  |  |  |  |  |
| OCMB | 2.32 | 1.06 – 4.69 | *0.03* | 2.19 | 1.03 – 4.66 | *0.04* |
| LS-OCMB | 3.64 | 1.73 – 7.64 | *0.001* | 4.71 | 2.13 – 10.41 | *<0.001* |
| Reibergram | 2.14 | 0.91 – 5.03 | 0.08 | 2.19 | 0.91 – 5.29 | 0.08 |
| IgM Index (>0.1) | 1.63 | 0.78 – 3.40 | 0.19 | 1.52 | 0.71 – 3.23 | 0.28 |
| **SPMS** |  |  |  |  |  |  |
| OCMB | 1.67 | 0.83 – 3.34 | 0.15 | 1.45 | 0.71 – 2.99 | 0.31 |
| LS-OCMB | 2.27 | 1.13 – 4.54 | *0.02* | 2.27 | 1.07 – 4.82 | *0.03* |
| Reibergram | 2.38 | 1.06 – 5.33 | *0.04* | 2.28 | 0.99 – 5.26 | 0.054 |
| IgM Index (>0.1) | 1.40 | 0.69 – 2.84 | 0.36 | 1.26 | 0.60 – 2.64 | 0.54 |

Abbreviature: CI: confidence interval; CIS: clinically isolated syndrome; EDSS: expanded disability status scale; HR: hazard ratio; IF: intrathecal fraction; LS-OCMB: lipid specific IgM oligoclonal bands; OCMB: IgM oligoclonal bands; SPMS: secondary progressive multiple sclerosis.

aCox proportional hazard regression, adjusted by sex, age at CIS, topography of CIS, disease duration at the time of lumbar puncture and disease-modifying treatments as time-dependent covariates.

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| **Table e-6. Unadjusted and multivariate Cox regression models for the risk of EDSS scores of 4 and 6 and development of SPMS among patients with at least 10 years of follow-up (n=120)** |
|  | **Unadjusted** | **Multivariate modela** |
|  | **HR** | **95% CI** | ***P* Value** | **HRb** | **95% CI** | ***P* Value** |
| **EDSS 4** |  |  |  |  |  |  |
| OCMB | 1.86 | 0.94 – 3.65 | 0.07 | 1.73 | 0.86 – 3.47 | 0.12 |
| LS-OCMB | 2.67 | 1.36 – 5.23 | *0.004* | 2.99 | 1.41 – 6.34 | *0.004* |
| Reibergram | 1.52 | 0.63 – 3.69 | 0.93 | 1.53 | 0.62 – 3.77 | 0.35 |
| IgM Index (>0.1) | 1.26 | 0.62 – 2.54 | 0.52 | 1.26 | 0.62 – 2.58 | 0.52 |
| **EDSS 6** |  |  |  |  |  |  |
| OCMB | 2.32 | 1.06 – 5.07 | *0.035* | 2.40 | 1.06 – 5.41 | *0.036* |
| LS-OCMB | 3.78 | 1.73 – 8.24 | *0.001* | 5.54 | 2.23 – 13.75 | *<0.001* |
| Reibergram | 2.20 | 0.88 – 5.52 | 0.09 | 2.26 | 0.88 – 5.80 | 0.09 |
| IgM Index (>0.1) | 1.44 | 0.65 – 3.17 | 0.37 | 1.50 | 0.67 – 3.35 | 0.32 |
| **SPMS** |  |  |  |  |  |  |
| OCMB | 1.70 | 0.80 – 3.63 | 0.17 | 1.47 | 0.66 – 3.27 | 0.34 |
| LS-OCMB | 2.24 | 1.05 – 4.77 | *0.037* | 2.22 | 0.95 – 5.20 | 0.067 |
| Reibergram | 1.80 | 0.68 – 4.77 | 0.24 | 1.69 | 0.62 – 4.59 | 0.31 |
| IgM Index (>0.1) | 0.98 | 0.43 – 2.25 | 0.97 | 0.93 | 0.40 – 2.17 | 0.86 |

Abbreviature: CI: confidence interval; CIS: clinically isolated syndrome; EDSS: expanded disability status scale; HR: hazard ratio; IF: intrathecal fraction; LS-OCMB: lipid specific IgM oligoclonal bands; OCMB: IgM oligoclonal bands; SPMS: secondary progressive multiple sclerosis.

aCox proportional hazard regression, adjusted by sex, age at CIS, topography of CIS, disease duration at the time of lumbar puncture and disease-modifying treatments as time-dependent covariates.