|  |  |  |  |
| --- | --- | --- | --- |
| **Demographics** | **Munich (n=124)** | **Berlin (n=77)** | ***p*-value** |
| Age, years | 31 (27 – 37) | 32 (26 – 36) | 0.74 |
| Sex female, No. (%) | 86 (69) | 51 (66) | 0.64 |
| Disease duration, months | 2.0 (1.0 – 3.0) | 4.0 (2.0 – 5.0) | **<0.0001** |
| EDSS | 1.0 (0 – 2.0) | 1.5 (1.0 – 2.0) | 0.05 |
| History of ON, No. (%) | 43 (35) | 27 (35) | >0.99 |
| Diagnosis, No. (%)* CIS
* RRMS
 | 7 (6)117 (94) | 21 (27)56 (73) | **0.02** |
| Disease modifying therapy, No. (%) | 17 (14) | 20 (26) | **0.04** |
| **MRI measures** |  |  |  |
| T2 lesion count  | 12 (9 – 19) | 9 (4 – 20) | **0.01** |
| Presence of infratentorial lesions, No. (%) | 73 (59) | 25 (32) | **0.0003** |
| **CSF measures** |  |  |  |
| Presence of oligoclonal bands, No. (%) | 114 (92) | 47 (70) # | 0.40 |
| **OCT measures** |  |  |  |
| pRNFL, µm | 103.1 ± 10.3 | 100.1 ± 9.9 | 0.09 |
| GCIP, µm | 71.8 ± 6.1 | 70.9 ± 6.1 | 0.32 |
| INL, µm | 35.0 ± 2.3 | 34.3 ± 2.2 | **0.02** |

**Supplementary table 1: Baseline characteristics at study baseline in both centers**

Expanded disability status scale (EDSS), optic neuritis (ON); clinically isolated syndrome (CIS), relapsing remitting multiple sclerosis (RRMS) according to the 2017 McDonald criteria; T2 lesion count and presence of infratentorial bands as measured by cerebral MRI; oligoclonal bands as measured in the cerebrospinal fluid; peripapillary retinal nerve fiber layer (pRNFL), common ganglion cell layer (GCIP) and inner nuclear layer (INL) as measured by optical coherence tomography; *p*-values marked in bold indicate significance; # CSF data was available in 54 of 77 patients.

|  |  |  |  |
| --- | --- | --- | --- |
| **Outcomes** | **Munich (n=124)** | **Berlin (n=77)** | ***p*-value** |
| Follow-up duration (months), median (IQR) | 60 (47 – 72) | 48 (33 – 69) | **0.03** |
| Clinical visits per patient and year, median (IQR) | 2.0 (1.4 – 2.7) | 1.5 (1.3 – 1.6) | **<0.0001** |
| MRI examinations per patient and year, median (IQR) | 1.6 (1.4 – 1.9) | 1.5 (1.3 – 1.6) | **0.0004** |
| DMT during follow-up, No. (%) | 99 (80) | 40 (52) | **<0.0001** |
| NEDA-3 criteria violation, No. (%) | 102 (82) | 63 (81) | >0.99 |
| Time to NEDA-3 criteria violation (months), median (IQR) | 12 (5 – 24) | 6 (2 – 18) | **0.0009** |
| EDSS worsening, No. (%) | 24 (19) | 15 (20) | >0.99 |
| Time to EDSS worsening (months), median (IQR) | 27 (14 – 54) | 10 (6 – 22) | **0.008** |
| Occurrence of relapse, No. (%) | 61 (49) | 28 (36) | 0.08 |
| Time to relapse (months),median (IQR) | 10 (3 – 29) | 8 (3 – 23) | 0.33 |
| Annualized relapse rate, median (IQR) | 0 (0 – 0.3) | 0 (0 – 0.2) | 0.11 |
| MRI disease activity, No. (%) | 90 (73) | 57 (74) | 0.87 |
| Time to MRI disease activity (months),median (IQR) | 12 (11 – 26) | 7 (2 – 19) | **0.0002** |

**Supplementary table 2: Outcomes during the study follow-up in both centers**

No evidence of disease activity (NEDA-3) defined as freedom from relapses, absence of sustained disability worsening and stable radiographic parameters (no change in T2 lesion load), Expanded disability status scale (EDSS), number (No.); 25%-75% interquartile range (IQR); p-values marked in bold indicate significance.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **NEDA-3 violation** | **Disability worsening** | **Relapse** | **MRI disease activity** |
|  | **Grouping** | **HR (CI)** | ***p*-value** | **HR (CI)** | ***p*-value** | **HR (CI)** | ***p*-value** | **HR (CI)** | ***p*-value** |
| **Age** | continuous1 | 0.98 (0.96-0.99) | **0.01** | 1.02 (0.98-1.06) | 0.33 | 0.97 (0.94-0.99) | **0.02** | 0.99 (0.96-1.02) | 0.43 |
| **Sex** | female | reference | - | reference | - | reference | - | reference | - |
| male | 1.10 (0.79-1.51) | 0.55 | 1.05 (0.52-2.01) | 0.88 | 1.06 (0.67-1.64) | 0.81 | 0.53 (0.27-0.96) | **0.05** |
| **Center** | Munich | reference | - | reference | - | reference | - | reference | - |
| Berlin | 1.56 (0.93-1.75) | 0.12 | 1.16 (0.59-2.19) | 0.66 | 0.78 (0.49-1.21) | 0.28 | 1.96 (1.08-3.48) | **0.02** |
| **Disease duration** | continuous2 | 1.02 (0.92-1.12) | 0.78 | 1.09 (0.89-1.33) | 0.41 | 1.06 (0.92-1.21) | 0.45 | 1.07 (0.87-1.30) | 0.51 |
| **EDSS** | continuous3 | 1.04 (0.87-1.23) | 0.67 | 0.81 (0.57-1.47) | 0.25 | 1.07 (0.85-1.33) | 0.58 | 1.07 (0.78-1.47) | 0.67 |
| **DMT** | no DMT | reference | - | reference | - | reference | - | reference | - |
| DMT | 1.52 (1.1-2.2) | **0.02** | 1.13 (0.57-2.42) | 0.75 | 2.46 (1.47-4.38) | **0.001** | 1.26 (0.89-1.82) | 0.21 |
| **pRNFL** | continuous4 | 1.02 (1.01-1.03) | **0.03** | 1.01 (0.97-1.03) | 0.88 | 0.99 (0.97-1.01) | 0.43 | 1.00 (0.97-1.03) | 0.83 |
| **GCIP** | continuous4 | 1.03 (1.01-1.05) | **0.04** | 1.05 (1.01-1.11) | **0.04** | 1.02 (0.98-1.05) | 0.30 | 1.02 (0.97-1.06) | 0.45 |
| **INL** | continuous4 | 1.04 (0.97-1.12) | 0.23 | 1.05 (0.92-1.22) | 0.45 | 1.06 (0.96-1.18) | 0.24 | 1.02 (0.95-1.10) | 0.60 |

**Supplementary table 3: Demographic factors and OCT measures associated with disease activity and disability**

Unadjusted Cox proportional hazard models for different predictors on violation of NEDA-3 criteria, disability worsening, occurrence of relapse and MRI disease activity. (1) increase per year, (2) increase per months, (3) increase per point on scale, (4) decrease per µm; unadjusted Hazard ratio (HR) with 95% confidence intervals (CI); *p*-values marked in bold indicate significance; Expanded disability status scale (EDSS), disease modifying therapy (DMT); peripapillary retinal nerve fiber layer (pRNFL), common ganglion cell layer (GCIP) and inner nuclear layer (INL) as measured by optical coherence tomography

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **NEDA-3 violation** | **Disability worsening** | **Relapse** | **MRI disease activity** |
|  | **Grouping** | **aHR (CI)** | ***p*-value** | **aHR (CI)** | ***p*-value** | **aHR (CI)** | ***p*-value** | **aHR (CI)** | ***p*-value** |
| **Diagnosis** | CIS | reference | - | reference | - | reference | - | reference | - |
| RRMS | 2.75 (1.59-5.14) | **0.0007** | 1.96 (0.66-8.43) | 0.29 | 1.70 (0.78-4.50) | 0.23 | 3.80 (2.08-7.67) | **<0.0001** |
| **Oligoclonal bands** | no | reference | - | reference | - | reference | - | reference | - |
| yes | 2.49 (1.28-5.49) | **0.01** | 1.43 (0.43-8.89) | 0.62 | 1.42 (0.67-3.68) | 0.41 | 1.87 (0.97-4.19) | 0.09 |
| **≥ 1 infratentorial lesion** | no | reference | - | reference | - | reference | - | reference | - |
| yes | 1.29 (0.94-1.78) | 0.11 | 0.93 (0.48-1.80) | 0.83 | 1.03 (0.67-1.59) | 0.91 | 1.44 (1.03-2.03) | **0.03** |
| **T2 lesion count** | ≤ 9 | reference | - | reference | - | reference | - | reference | - |
| > 9 | 2.36 (1.65-3.42) | **<0.0001** | 1.23 (0.61-2.63) | 0.57 | 1.22 (0.78-1.97) | 0.40 | 2.38 (1.61-3.57) | **<0.0001** |
| **GCIP thickness (cut-off 1)** | > 69 µm | reference | - | reference | - | reference | - | reference | - |
| ≤ 69 µm | 1.19 (0.85-1.64) | 0.30 | 2.23 (1.18-4.26) | **0.01** | 1.08 (0.68-1.69) | 0.73 | 1.18 (0.83-1.66) | 0.34 |
| **GCIP thickness (cut-off 2)** | > 77 µm | reference | - | reference | - | reference | - | reference | - |
| ≤ 77 µm | 1.66 (1.08-2.84) | **0.04** | 1.56 (0.65-4.61) | 0.65 | 1.09 (0.62-2.10) | 0.77 | 1.35 (0.86-2.21) | 0.21 |

**Supplementary table 4: Diagnosis, cerebrospinal fluid, cerebral MRI and OCT measures associated with disease activity**

Effect of diagnosis at study enrollment (as defined by the McDonald 2017 criteria), presence of oligoclonal bands within the cerebrospinal fluid (CSF), presence of at least one infratentorial lesion (≥ 1 infratentorial lesion) or T2 lesion count as measured by cerebral MRI at baseline, and thickness of the common ganglion cell and inner plexiform layer (GCIP) as measured by OCT at baseline on not meeting NEDA-3 criteria, EDSS worsening, occurrence of relapse, and increasing T2 lesion load during follow-up; adjusted multiple Cox proportional hazards regression models corrected for age, sex, center and disease modifying therapy; adjusted hazard ratio (aHR) with 95% confidence intervals (CI); *p*-values marked in bold indicate significance; clinically isolated syndrome (CIS), relapsing remitting multiple sclerosis (RRMS), no evidence of disease activity (NEDA-3), expanded disability status scale (EDSS).