# Supplementary Online Content

Januel E, Hajage D, Labauge P, et al. Association between anti-CD20 therapies and COVID-19 severity among patients with relapsing-remitting and progressive multiple sclerosis. *JAMA Netw Open*. 2023;6(6):e2319766. doi:10.1001/jamanetworkopen.2023.19766



This supplementary material has been provided by the authors to give readers additional information about their work.

E-Method 1: **Detail of included data**

For all patients were recorded: age, gender, date of MS diagnosis, type of MS (RR-MS or P-MS), EDSS score (15) before COVID-19, current MS DMT, comorbidities (cardiovascular disease, pulmonary disease, diabetes, obesity [BMI > 30 kg/m2], active tobacco smoking), exposure to high dose methylprednisolone during the last month before COVID-19 (methylprednisolone ≥ 500 mg / J ≥ 1 day), vaccination before COVID-19 (defined as an infection occurring at least 7 days after the second dose of COVID-19 vaccine). Regarding COVID-19, were collected: date of symptoms onset, type and date of COVID-19 confirmatory testing positivity (PCR, antigen test), treatment with COVID-19 monoclonal antibody in the 5 days after symptoms onset. COVID-19 severity was defined at the nadir state, according to an ordinal scale ranging from 1 to 7: 1.No limitations on activities; 2.Not hospitalized, limitation on activities; 3.Hospitalized, not requiring supplemental oxygen; 4. Hospitalized, requiring supplemental oxygen; 5.Hospitalized, on non-invasive ventilation or high flow oxygen devices; 6.Hospitalized, on invasive mechanical ventilation; 7.Death. COVID-19 variant was approximated at the date of infection (symptoms onset or if not available date of confirmatory testing positivity) from the weekly French COVID-19 variant surveillance: the proxy for the variant was the one considered dominant at the date of infection, i.e. representing more than 50% of the positive samples in the week of interest: “Original-Alpha” before 30/06/2021, “Delta”: 30/06/2021-27/12/2021, and “Omicron”: after 27/12/2021. For anti-CD20 treated patients, number of anti-CD20 infusions, lymphocyte count and immunoglobulin G, were also recorded. Data were recorded by the treating neurologist at the subsequent consultation following COVID-19 resolution, or at the time of COVID-19-related-hospitalization for the most severe patients.

## E-Method 2: Description of multiple imputation method

### 1) Multiple imputation for analysis of the impact of anti-CD20 therapies on COVID-19 severity:

Multiple imputation with the chained equations (MICE) technique was used to replace missing values when appropriate, assuming that missing data were missing at random:

For RR-MS patients on the one hand and P-MS patients in the other, ten copies of the datasets were created separately in anti-CD20 treated and non-treated groups, with the missing values replaced by imputed values.

### Variables used in the imputation phase

The following variables were used in the imputation phase:

- age, gender, time from MS diagnosis, EDSS score before COVID-19, presence of cardiovascular disease, pulmonary disease, diabetes, obesity, active tobacco smoking), exposure to high dose methylprednisolone during the last month before COVID-19, post vaccine COVID-19, date of COVID-19 symptoms onset, type and date of COVID-19 confirmatory testing positivity (PCR, antigen test), treatment with COVID-19 monoclonal antibody in the 5 days after symptoms onset. COVID-19 severity at the nadir state, COVID-19 variant

### Procedures chosen and software used

Multiple-imputation analyses using chained equations procedure, with linear imputation for continuous variables, proportional odds regression for ordinal variables, and logistic or multinomial regression for categorical variables were used. Analyses were performed using the R software and the mice package.

Number of imputations: 10

Pooling procedures for analysis :

Results from each imputed dataset were pooled using Rubin's rules to obtain overall estimates and their standard errors.

2) Multiple imputation for the analysis of the risk factors for COVID-19 severity among anti-CD20 treated patients

Some variables were recorded only for anti-CD20 treated patients, such as immunoglobulin G level, lymphocytes count level, number of cycles of antiCD20 treatment, delay between last anti-CD20 cycle and COVID-19. For all anti-CD20 treated patients, ten copies of the datasets were imputed with the missing values replaced by imputed values.

Variables used in the imputation phase

The following variables were used in the imputation phase: age, gender, time from MS diagnosis, EDSS score before COVID-19, presence of cardiovascular disease, pulmonary disease, diabetes, obesity, active tobacco smoking), exposure to high dose methylprednisolone during the last month before COVID-19, post vaccine COVID-19, date of COVID-19 symptoms onset, type and date of COVID-19 confirmatory testing positivity (PCR, antigen test), treatment with COVID-19 monoclonal antibody in the 5 days after symptoms onset. COVID-19 severity at the nadir state, COVID-19 variant, lymphocytes count level, immunoglobulin G level, number of cycles of antiCD20 treatment, delay between last anti-CD20 cycle and COVID-19

Procedures chosen and software used

Multiple-imputation analyses using chained equations procedure, with linear imputation for continuous variables, proportional odds regression for ordinal variables, and logistic or multinomial regression for categorical variables were used. Analyses were performed using the R software and the mice package.

Number of imputations: 10

Pooling procedures for analysis

Results from each imputed dataset were pooled using Rubin's rules to obtain overall estimates and their standard errors.

**e-Table 1: Demographic, clinical characteristics and outcomes of ocrelizumab and rituximab treated recurrent-remittent and progressive MS patients**

| | Anti-CD20 treated Relapsing Remitting Multiple Sclerosis Patients | | | |
|---|---|---|---|---|
| | Overall | RR-MS treated with ocrelizumab | RR-MS treated with rituximab | p |
| N | 418 | 350 (83.7) | 68 (16.3) | |
| Gender | | | | 0.59 |
| - Males | 91 (21.8) (1) | 74 (21.2) (1) | 17 ( 25.0) (0) | |
| - Female | 326 (78.2) (1) | 275 (78.8) (1) | 51 (75.0) (0) | |
| Age, years | 39.15 [31.22, 45.81] (3) | 38.67 [31.09, 45.43] (3) | 42.46 [34.30, 48.55] (0) | 0.05 |
| EDSS | 2.00 [1.00, 4.00] (26) | 2.00 [1.00, 4.00] (25) | 3.00 [1.50, 4.25] (1) | 0.02 |
| Delay from MS onset, years | 8.96 [4.70, 14.78] (11) | 8.61 [4.27, 14.19] (7) | 10.94 [7.26, 15.96] (4) | 0.02 |
| Comorbidities | | | | |
| - Cardiovascular disease | 11 (2.6) | 11 (3.1) | 0 (0.0) | 0.22 |
| - Diabetes | 7 (1.7) | 5 (1.4) | 2 (2.9) | 0.32 |
| - Obesity | 19 (4.5) | 13 (3.7) | 6 (8.8) | 0.13 |
| - Pulmonary disease | 12 (2.9) | 8 (2.3) | 4 (5.9) | 0.11 |
| - Smoking | 42 (10.0) | 36 (10.3) | 6 (8.8) | 0.88 |
| Number of cycles of antiCD20 treatment | 4.00 [2.00, 5.00] (61) | 3.00 [2.00, 5.00] (49) | 5.00 [4.00, 8.00] (12) | <0.001 |
| Delay between last anti-CD20 cycle and COVID-19, months | 3.35 [1.54, 5.03] (30) | 3.29 [1.48, 4.77] (22) | 4.90 [2.07, 10.85] (8) | 0.001 |
| High dose methylprednisolone during the month before COVID-19 | 4 (1.0) (1) | 4 (1.1) (1) | 0 (0.0) (0) | 1.00 |
| Vaccinated against COVID-19 | 169 (40.4) | 144 (41.1) | 25 (36.8) | 0.59 |
| Sars-COV-2 variant | | | | 0.04 |
| - Original-alpha | 211 (50.5) | 167 (47.7) | 44 (64.7) | |
| - delta | 70 (16.7) | 61 (17.4) | 9 (13.2) | |
| - omicron | 137 (32.8) | 122 (34.9) | 15 (22.1) | |
| Anti-COVID-19 Monoclonal antibody treatment | 17 (4.1) | 16 (4.6) | 1 (1.5) | 0.33 |
| Lymphocyte count/mm3 | 1500 [1150, 1955] (132) | 1495 [1123, 1896] (114) | 1516 [1230, 2105] (18) | 0.36 |
| Immunoglobulin G, mg/dL, mean (SD) (NA) | 930 (244) (142) | 951 (242) (114) | 837 (2.30) (16) | 0.002 |
| Outcome | | | | |

| | | | | |
|---|---|---|---|---|
| - Hospitalization or higher severity | 61 (15.2) | 44 (13.0) | 17 (27.0) | 0.008 |
| - Hospitalization with oxygen or higher severity | 51 (12.7) | 36 (10.7) | 15 (23.8) | 0.008 |
| - Non-invasive or invasive ventilation or higher severity | 19 (4.7) | 12 (3.6) | 7 (11.1) | 0.02 |
| - Death | 2 (0.5) | 1 (0.3) | 1 (1.6) | 0.72 |
| - NA | (17) | (12) | (5) | |

Anti-CD20 treated Progressive Multiple Sclerosis Patients

| | Overall | P-MS treated with ocrelizumab | P-MS treated with rituximab | p |
|---|---|---|---|---|
| N | 226 | 104 (46.0) | 122 (54.0) | |
| Gender | | | | 0.15 |
| - Males | 102 (45.1) | 41 (39.4) | 61 (50.0) | |
| - Female | 124 (54.9) | 63 (60.6) | 61 (50.0) | |
| Age, years | 53.16 [46.84, 58.62] | 52.98 [46.45, 59.41] | 53.34 [47.75, 57.41] | 0.82 |
| EDSS | 6.00 [4.00, 6.50] | 5.50 [4.00, 6.50] | 6.00 [4.12, 6.50] | 0.13 |
| Delay from MS onset | 13.78 [8.83, 21.75] | 14.10 [9.41, 21.57] | 13.67 [8.63, 22.16] | 0.54 |
| MS course | | | | 0.09 |
| - Primary progressive | 95 (42.0) | 37 (35.6) | 58 (47.5) | |
| - Secondary progressive | 131 (58.0) | 67 (64.4) | 64 (52.5) | |
| Comorbidities | | | | |
| - Cardiovascular disease | 16 (7.1) | 6 (5.8) | 10 (8.2) | 0.61 |
| - Diabetes | 11 (4.9) | 5 (4.8) | 6 (4.9) | 1.00 |
| - Obesity | 16 (7.1) | 4 (3.8) | 12 (9.8) | 0.14 |
| - Pulmonary disease | 6 (2.7) | 1 (1.0) | 5 (4.1) | 0.22 |
| - Smoking | 22 (9.7) | 10 (9.6) | 12 (9.8) | 1.00 |
| Number of cycles of antiCD20 treatment | 5.00 [3.00, 8.00] (38) | 4.00 [3.00, 6.00] (22) | 6.00 [4.00, 8.00] (16) | 0.004 |
| Delay between last anti-CD20 cycle and COVID-19 | 3.91 [2.00, 5.29] (23) | 3.86 [1.81, 5.14] (12) | 3.94 [2.28, 5.42] (11) | 0.43 |
| High dose methylprednisolone during the month before COVID-19, | 1 (0.4) | 0 (0.0) | 1 (0.8) | 1.00 |
| Vaccinated against COVID-19 | 94 (41.6) | 50 (48.1) | 44 (36.1) | 0.09 |
| Sars-COV-2 variant | | | | 0.002 |
| - Original-alpha | 111 (49.1) | 42 (40.4) | 69 (56.6) | |

| | | | | |
|---|---|---|---|---|
| - delta | 46 (20.4) | 18 (17.3) | 28 (23.0) | |
| - omicron | 69 (30.5) | 44 (42.3) | 25 (20.5) | |
| Anti-COVID-19 Monoclonal antibody treatment | 7 (3.1) | 2 (1.9) | 5 (4.1) | 0.46 |
| Lymphocyte count/mm3 | 1400 [1040, 1820] | 1530 [1074, 1955] | 1389 [987, 1626] | 0.12 |
| Immunoglobulin G, mg/dL, mean (SD) (NA) | 925 (235) (94) | 934 (212) (58) | 920 (247) (36) | 0.74 |
| Outcome | | | | |
| - Hospitalization or higher severity | 56 (25.0) | 16 (15.7) | 40 (32.8) | 0.005 |
| - Hospitalization with oxygen or higher severity | 40 (17.9) | 12 (11.8) | 28 (23.0) | 0.05 |
| - Non-invasive or invasive ventilation or higher severity | 23 (10.3) | 5 (4.9) | 18 (14.8) | 0.03 |
| - Death | 3 (1.3) | 0 (0.0) | 3 (2.5) | 0.31 |
| - NA | (2) | (2) | (0) | |

Data are N (%) / median (P25; P75) and (NA:number non available), unless otherwise specified

**e-table 2: Subgroup analysis of the association of anti-CD20 and severe COVID-19 in recurrent-remittent and progressive MS patients, unadjusted and propensity weighted analysis**

| | Included Remittent Recurrent Multiple Sclerosis Patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Unadjusted analysis | | | | Propensity Weighted analysis | | | |
| | Not treated with anti-CD20, N (%) | Treated with anti-CD20, N (%) | OR (95% CI) | P value for interaction | Not treated with anti-CD20, % | Treated with anti-CD20, % | Adjusted-OR (95% CI) | P value for interaction |
| Age (years) | | | | 0.64 | | | | 0.94 |
| [17;39[ | 4/260 (1.5) | 19/200 (9.5%) | 6.68 (2.12; 21.1) | | 1.9% | 9.3% | 5.42 (1.73;17) | |
| [39-75[ | 10/262 (3.8) | 32/198 (16.2%) | 4.84 (2.33;10.06) | | 3.9% | 17.4% | 5.12 (2.38;10.99) | |
| Gender | | | | 0.94 | | | | 0.68 |
| Males | 3/132 (2.3) | 9/90 (10.0) | 5.03 (1.31;19.23) | | 2.3% | 13.4% | 6.73 (1.66;27.3) | |
| Females | 11/391 (2.8) | 42/310 (13.5) | 5.33 (2.69;10.57) | | 3.1% | 13.4% | 4.85 (2.43;9.69) | |
| EDSS | | | | 0.34 | | | | 0.59 |
| <6 | 12/483 (2.5) | 43/343 (12.5) | 13.16 (1.44;120.46) | | 2.6% | 12.8% | 5.5 (2.8;10.82) | |
| >=6 | 2/23 (8.7) | 8/38 (21.1) | 2.30 (0.48;11.07) | | 7.1% | 20.5% | 3.31 (0.60;18.34) | |
| Post-vaccine | | | | 0.63 | | | | 0.57 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No | 13/384 (3.4) | 40/242 (16.5) | 5.65 (2.94; 10.89) | 3.9% | 16.6% | 4.87 (2.48;9.59) | |
| Yes | 1/140 (0.7) | 11/159 (6.9) | 9.38 (1.29;68.04) | 0.9% | 7% | 8.85 (1.26;62.12) | |

Included Progressive Multiple Sclerosis Patients

| | Unadjusted analysis | | | | Propensity Weighted analysis | | | |
|---|---|---|---|---|---|---|---|---|
| Severity | Not treated with anti-CD20, N (%) | Treated with anti-CD20, N (%) | OR (95% CI) | P value | Not treated with anti-CD20, (%) | Treated with anti-CD20, (%) | Adjusted-OR (95% CI) | P value for interaction |
| Age (years) | | | | 0.05 | | | | 0.03 |
| [25;54[ | 7/83 (8.4) | 21/131 (16.0) | 2.07 (0.84;5.13) | | 6.6% | 17.2% | 2.96 (1.12;7.82) | |
| [54-70[ | 33/117 (28.2) | 19/93 (20.4) | 0.68 (0.35;1.30) | | 25.4% | 21% | 0.78 (0.39;1.55) | |
| Gender | | | | 0.26 | | | | 0.14 |
| Males | 20/76 (26.3) | 28/102 (27.5) | 1.07 (0.55;2.10) | | 17.9% | 29.1% | 1.88 (0.91;3.9) | |
| Females | 20/124 (16.1) | 12/122 (9.8) | 0.59 (0.28;1.28) | | 13.6% | 11.5% | 0.82 (0.36;1.87) | |
| EDSS | | | | 0.06 | | | | 0.009 |
| <6 | 6/80 (7.5) | 15/103 (14.6) | 4.96 (0.80;30.6) | | 4.4% | 15.1% | 3.86 (1.37;10.87) | |
| >=6 | 34/120 (28.3) | 25/121 (20.7) | 0.33 (0.10;1.13) | | 26.9% | 22% | 0.77 (0.41;1.44) | |
| Post-vaccine | | | | 0.28 | | | | 0.16 |
| No | 38/168 (22.6) | 28/132 (21.2) | 0.93 (0.54;1.62) | | 20.8% | 21.3% | 1.03 (0.58;1.83) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Yes | 2/32 (6.2) | 12/92 (13.0) | 2.32 (0.49;11.05) | | 4.3% | 13.7% | 3.51 (0.71;17.34) |

Propensity-weighted analysis (ATE estimand). Variables used in the propensity score estimation: age, gender, delay from MS onset, EDSS score, comorbidities (cardiovascular disease, pulmonary disease, diabetes, obesity, active tobacco smoking), exposure to high dose methylprednisolone the month before COVID-19, post-vaccine COVID-19, COVID-19 variant (Original-Alpha, Delta or Omicron), and treatment of COVID-19 with monoclonal antibody

**e-table 3: Association of anti-CD20 exposure and COVID-19 outcomes in recurrent-remittent and progressive MS patients, unadjusted analysis and propensity weighted analysis**

| Included Remittent Recurrent Multiple Sclerosis Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Unadjusted analysis | | | | Propensity Weighted analysis | | | |
| Severity | Not treated with anti-CD20, N (%) | Treated with anti-CD20, N (%) | OR (95% CI) | P value | Not treated with anti-CD20, % | Treated with anti-CD20, % | Adjusted-OR (95% CI) | P value |
| >= Hospitalization | 18 (3.4%) | 61 (15.2%) | 5.01 (2.92;8.57) | <0.001 | 3.7% | 16.0% | 4.92 (2.83;8.56) | <0.001 |
| >= Hospitalization with O2 | 14 (2.7%) | 51 (12.7%) | 5.32 (2.89;9.81) | <0.001 | 2.9% | 13.4% | 5.2 (2.78;9.71) | <0.001 |
| >= Hospitalization with noninvasive ventilation or ICU | 4 (0.8%) | 19 (4.7%) | 6.23 (2.11;18.38) | 0.001 | 0.8% | 4.5% | 5.72 (1.92;17.02) | 0.002 |
| Death | 0 (0.0%) | 2 (0.5%) | - | - | 0.0% | 0.4% | - | - |
| Included Progressive Multiple Sclerosis Patients | | | | | | | | |
| | Unadjusted analysis | | | | Propensity Weighted analysis | | | |

| Severity | Not treated with anti-CD20, N (%) | Treated with anti-CD20, N (%) | OR (95% CI) | P value | Not treated with anti-CD20, (%) | Treated with anti-CD20, (%) | Adjusted-OR (95% CI) | P value |
|---|---|---|---|---|---|---|---|---|
| >= Hospitalization | 50 (25.0%) | 56 (25.0%) | 1.01 (0.65;1.57) | 0.97 | 19.5% | 26.3% | 1.47 (0.91;2.38) | 0.11 |
| >= Hospitalization with O2 | 40 (20.0%) | 40 (17.9%) | 0.88 (0.54;1.43) | 0.59 | 15.5% | 19% | 1.28 (0.76;2.16) | 0.36 |
| >= Hospitalization with noninvasive ventilation or ICU | 22 (11.0%) | 23 (10.3%) | 0.94 (0.5;1.75) | 0.81 | 8.9% | 10.9% | 1.25 (0.65;2.42) | 0.51 |
| Death | 5 (2.5%) | 3 (1.3%) | 0.55 (0.13;2.34) | 0.39 | 1.8% | 1.5% | 0.83 (0.19;3.63) | 0.80 |

Propensity-weighted analysis (ATE estimand). Variables used in the propensity score estimation: age, gender, delay from MS onset, EDSS score, comorbidities (cardiovascular disease, pulmonary disease, diabetes, obesity, active tobacco smoking), exposure to high dose methylprednisolone the month before COVID-19, post-vaccine COVID-19, COVID-19 variant (Original-Alpha, Delta or Omicron), and treatment of COVID-19 with monoclonal antibody

**E-table 4: Risk factors for hospitalization with oxygen or higher severity among recurrent-remittent-MS patients treated with anti-CD20 therapies**

| | All anti-CD20 RR-MS patients (N=418) | Anti-CD20 RR-MS patients without severe COVID-19 (N=350) | Anti-CD20 RR-MS patients with severe COVID-19 (N=51) | Univariate OR (IC95%) | P-value | Multivariate OR (IC95%) | P-alue |
|---|---|---|---|---|---|---|---|
| N (%) * | 418 | 350 (87.3) | 51 (12.7) | | | | |
| Gender | | | | | | | |
| - Male | 91 (21.8) (1) | 81 (23.2) (1) | 9 (17.6) (0) | 1 (ref) | | | |
| - Female | 326 (78.2) (1) | 268 (76.8) (1) | 42 (82.4) (0) | 1.37 (0.64;2.92) | 0.42 | | |
| Age, years | 39.15 (31.22, 45.81) (3) | 38.61 (31.06, 44.80) (3) | 45.68 (32.49, 49.95) (0) | 1.04 (1.01;1.07) | 0.009 | 1.03 (0.99;1.06) | 0.11 |
| EDSS | 2.00 (1.00, 4.00) (26) | 2.00 (1.00, 3.50) (20) | 3.00 (2.00, 4.25) (0) | 1.22 (1.05;1.41) | 0.01 | 1.11 (0.94;1.32) | 0.21 |
| Delay from MS onset, years | 8.96 (4.70, 14.78) (11) | 8.87 (4.44, 14.67) (9) | 11.84 (6.05, 15.36) (1) | 1.03 (0.99;1.07) | 0.10 | | |
| Comorbidities | | | | | | | |
| - Cardiovascular disease | 11 (2.6) | 9 (2.6) | 2 (3.9) | 1.51 (0.32;7.22) | 0.61 | | |
| - Diabetes | 7 (1.7) | 6 (1.7) | 1 (2.0) | 1.12 (0.13;9.55) | 0.92 | | |
| - Obesity | 19 (4.5) | 17 (4.9) | 2 (3.9) | 0.78 (0.17;3.5) | 0.75 | | |
| - Pulmonary disease | 12 (2.9) | 10 (2.9) | 1 (2.0) | 0.71 (0.09;5.83) | 0.75 | | |
| - Smoking | 42 (10.0) | 38 (10.9) | 4 (7.8) | 0.68 (0.23;2) | 0.49 | | |
| Anti-CD20 treatment | | | | | | | |
| - Ocrelizumab | 350 (83.7) | 302 (86.3) | 36 (70.6) | 1 (ref) | | 1 (ref) | |
| - Rituximab | 68 (16.3) | 48 (13.7) | 15 (29.4) | 2.59 (1.29;5.19) | 0.008 | 1.72 (0.8;3.74) | 0.17 |
| Number of cycles of antiCD20 treatment | 4.00 (2.00, 5.00) (61) | 3.00 (2.00, 5.00) (51) | 4.50 (4.00, 6.00) (9) | 1.15 (1.01;1.32) | 0.04 | 1.14 (0.98;1.34) | 0.09 |
| Delay between last anti-CD20 cycle and COVID-19, months | 3.35 (1.54, 5.03) (30) | 3.61 (1.51, 5.16) (25) | 2.64 (1.58, 4.07) (3) | 0.94 (0.84;1.04) | 0.23 | | |

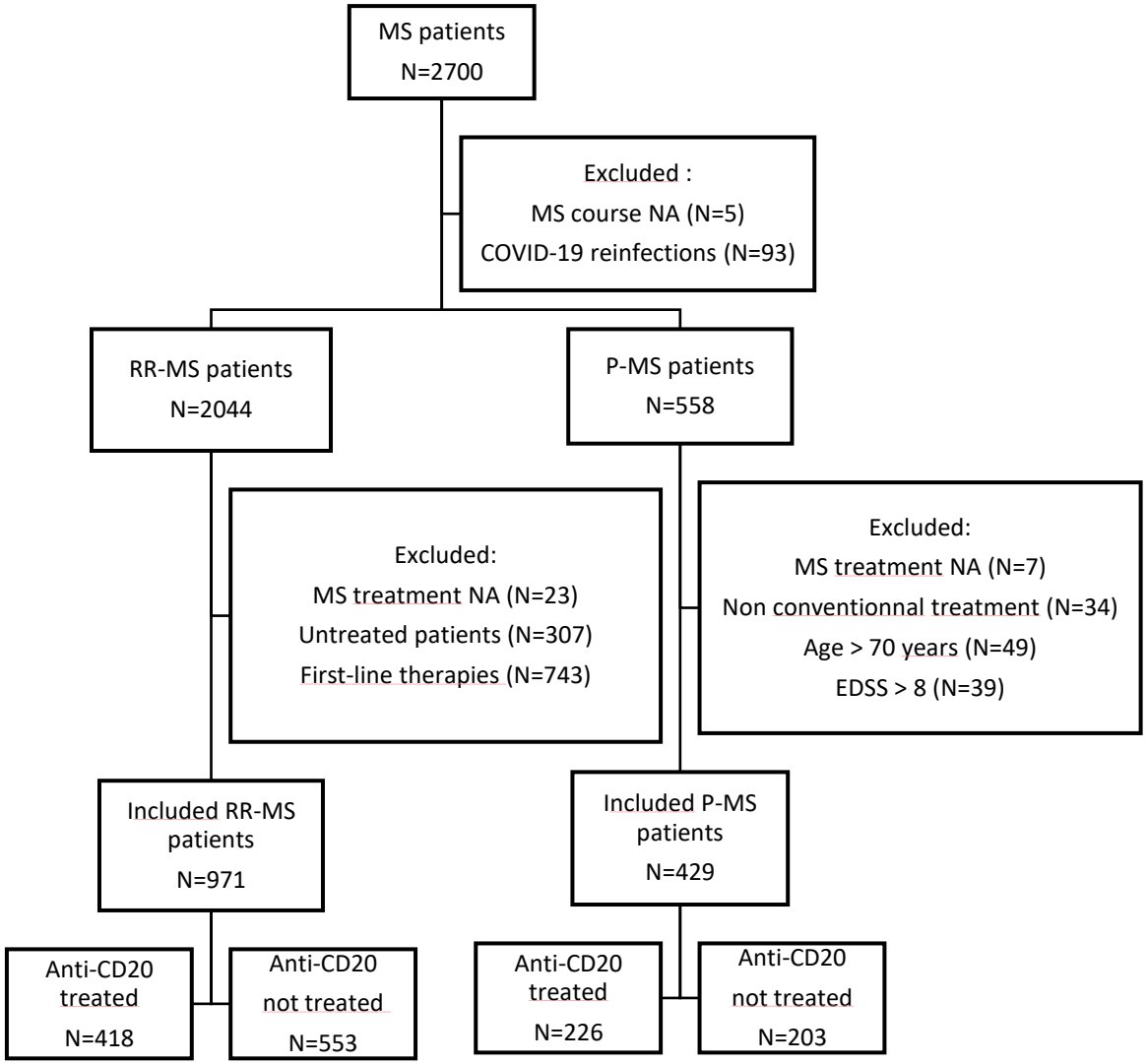
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| High dose methylprednisolone during the month before COVID-19 | 4 (1.0) (1) | 4 (1.1) (1) | 0 (0.0) (0) | | | | |
| Vaccinated against COVID-19 | 169 (40.4) | 148 (42.3) | 11 (21.6) | 0.4 (0.2;0.79) | 0.009 | 0.41 (0.14;1.16) | 0.09 |
| Sars-COV-2 variant | | | | | 0.01 | | 0.06 |
| - Original-alpha | 211 (50.5) | 171 (48.9) | 34 (66.7) | 1 (ref) | | 1 (ref) | |
| - delta | 70 (16.7) | 55 (15.7) | 11 (21.6) | 1 (0.47;2.11) | | 1.82 (0.67;4.99) | |
| - omicron | 137 (32.8) | 124 (35.4) | 6 (11.8) | 0.26 (0.11;0.65) | | 0.52 (0.15;1.74) | |
| Anti-COVID-19 Monoclonal antibody treatment | 17 (4.1) | 14 (4.0) | 2 (3.9) | 0.89 (0.2;4.03) | 0.88 | | |
| Lymphocyte count/mm3 | 1500 (1150, 1955) (132) | 1500 (1142, 1933) (112) | 1480 (1104, 1677) (17) | 0.94 (0.62;1.42) | 0.77 | | |
| Immunoglobulin G, mg/dL, mean (SD) (NA) | 930 (244) (142) | 938 (240) (121) | 847 (258) (16) | 0.88 (0.76;1.02) | 0.10 | | |

*17 patients (4.1%) with non-available outcome

Data are N (%) / median (P25; P75) and (NA: number non available), unless otherwise specified

RR-MS: relapsing remitting multiple sclerosis. Severe COVID-19: severity score ≥ 4, i.e. hospitalization with oxygen, or higher severity. High dose methylprednisolone: methylprednisolone >= 500 mg / J for at least one day; Complete vaccination: infection occurring at least 7 days after the second dose of COVID-19 vaccine; Sars-COV-2 variant: the variant was considered dominant when it was present in more than 50% of the samples for a given week : “Original-Alpha”: before 30/06/2021, “Delta”: from 30/06/2021 to 27/12/2021, and “Omicron”: after 27/12/2021; Anti-COVID-19 Monoclonal antibody treatment: treatment with COVID-19 monoclonal antibody in the 5 days after symptoms onset.

e-figure1: Flow chart

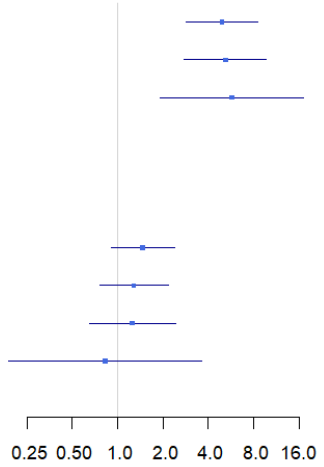



Excluded non-conventional treatments for P-MS patients: cyclophosphamide, alemtuzumab, mycophenolate mofetil, azathioprine, methotrexate; NA: non-available

e-figure 2: **Association between anti-CD20 exposure and COVID-19 outcomes (COVID-19 severity score ≥ hospitalization; ≥5; ≥hospitalization with O2; ≥ Non-invasive ventilation or ICU; death) among RR-MS and P-MS**

**Impact of anti-CD20 exposure on the risk of severe COVID-19 among RR-MS and P-MS**

| | Treated with anti-CD20 N/tot (%)* | Not treated with anti-CD20 N/tot (%)* | Adjusted OR (95%CI) | |
|---|---|---|---|---|
| RR-MS patients | | | | |
| >= Hospitalisation | 61/401 (16%) | 18/524 (3.7%) | 4.92 (2.83;8.56) | <0.001 |
| >= Hospitalisation with O2 | 51/401 (13.4%) | 14/524 (2.9%) | 5.2 (2.78;9.71) | <0.001 |
| >= Noninvasive ventilation-ICU | 19/401 (4.5%) | 4/524 (0.8%) | 5.72 (1.92;17.02) | 0.002 |
| Death | 2/401 (0.5%) | 0/524 (0%) | | |
| P-MS patients | | | | |
| >= Hospitalisation | 56/224 (26.3%) | 50/200 (19.5%) | 1.47 (0.91;2.38) | 0.112 |
| >= Hospitalisation with O2 | 40/224 (19%) | 40/200 (15.5%) | 1.28 (0.76;2.16) | 0.361 |
| >= Noninvasive ventilation-ICU | 23/224 (10.9%) | 22/200 (8.9%) | 1.25 (0.65;2.42) | 0.506 |
| Death | 3/224 (1.5%) | 5/200 (1.8%) | 0.83 (0.19;3.63) | 0.801 |




*Observed numbers of events are reported in the non-weighted population without imputation of missing data. Percentages and odd ratios are estimated on the weighted population with imputation of missing data (including outcomes). Propensity-weighted analysis (ATE estimand). Variables used in the propensity score estimation: age, gender, delay from MS onset, EDSS score, comorbidities (cardiovascular disease, pulmonary disease, diabetes, obesity, active tobacco smoking), exposure to high dose methylprednisolone the month before COVID-19, post-vaccine COVID-19, COVID-19 variant (Original-Alpha, Delta or Omicron), and treatment of COVID-19 with monoclonal antibody

ICU: intensive care unit