ORIGINAL ARTICLE

Impact of vaccination on COVID-19 outcome in multiple sclerosis

Gabriel Bsteh[1] | Christiane Gradl[2] | Bettina Heschl[3] | Harald Hegen[4] |
Franziska Di Pauli[4] | Hamid Assar[5] | Fritz Leutmezer[1] | Gerhard Traxler[6] |
Nik Krajnc[1] | Gudrun Zulehner[1] | Maria-Sophia Hiller[7] | Paulus Rommer[1] |
Peter Wipfler[8] | Michael Guger[9] | Christian Enzinger[4] | Thomas Berger[1] |
for the AUT-MuSC investigators

[1]Department of Neurology, Medical University of Vienna, Vienna, Austria

[2]Department of Neurology, Medical University of St Pölten, St Pölten, Austria

[3]Department of Neurology, Medical University of Graz, Graz, Austria

[4]Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

[5]Department of Neurology, Kepler University Hospital, Linz, Austria

[6]Department of Neurology 2, Med Campus III, Kepler University Hospital, Linz, Austria

[7]Department of Neurology, Barmherzige Brüder Hospital, Eisenstadt, Austria

[8]Department of Neurology, Paracelsus Medical University of Salzburg, Salzburg, Austria

[9]Department of Neurology, Pyhrn-Eisenwurzen Hospital Steyr, Steyr, Austria

Correspondence
Gabriel Bsteh, Department of Neurology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.
Email: gabriel.bsteh@meduniwien.ac.at

Abstract

Background and purpose: COVID-19 continues to challenge neurologists in counseling persons with multiple sclerosis (pwMS) regarding disease-modifying treatment (DMT) and vaccination. The objective here was to characterize predictors of COVID-19 outcome in pwMS.

Methods: We included pwMS with polymerase chain reaction-confirmed COVID-19 diagnosis from a nationwide population-based registry. COVID-19 outcome was classified as either mild or severe. Impact of DMT, specifically anti-CD20 monoclonal antibodies (anti-CD20), and vaccination on COVID-19 outcome was determined by multivariate models adjusted for a priori risk (determined by a cumulative risk score comprising age, disability, and comorbidities).

Results: Of 317 pwMS with COVID-19 (mean age = 41.8 years [SD = 12.4], 72.9% female, median Expanded Disability Status Scale = 1.5 [range = 0–8.5], 77% on DMT [16% on anti-CD20]), 92.7% had a mild course and 7.3% a severe course, with 2.2% dying from COVID-19. Ninety-seven pwMS (30.6%) were fully vaccinated. After a median 5 months from vaccination to SARS-CoV-2 infection (range = 1–9), severe COVID-19 occurred in 2.1% of fully vaccinated pwMS compared to 9.5% in unvaccinated pwMS ($p = 0.018$).

A priori risk robustly predicted COVID-19 severity ($R^2 = 0.605$, $p < 0.001$). Adjusting for a priori risk, anti-CD20 treatment was associated with increased COVID-19 severity (odds ratio [OR] = 3.3, $R^2 = 0.113$, $p = 0.003$), but exposure to any other DMT was not. Fully vaccinated pwMS showed a significantly decreased risk for severe COVID-19 (OR = 0.21, $R^2 = 0.144$, $p < 0.001$).

Conclusions: In a population-based MS cohort, COVID-19 course is primarily predicted by a priori risk (depending on age, disability, and comorbidities) explaining about 60% of variance. Anti-CD20 treatment is associated with a moderately increased risk, whereas reassuringly vaccination provides protection from severe COVID-19.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated disease (coronavirus disease 2019 [COVID-19]) continues to challenge neurologists in counseling patients with multiple sclerosis (pwMS).

There is robust evidence that the risk for severe COVID-19 in pwMS is—similar to the general population—primarily determined by age and comorbidities [1–4]. Whereas higher physical disability represents an additional MS-specific risk factor, MS itself is not associated with increased risk of severe COVID-19 [1–4]. Reassuringly, B-cell-depleting anti-CD20 monoclonal antibodies (anti-CD20) remain the only treatment class among disease-modifying treatment (DMT) in MS associated with moderately increased COVID-19 severity [1, 5].

As a result of an unprecedented worldwide scientific effort, several vaccines against SARS-CoV-2 have been developed, relying on the concepts of mRNA- or adenovirus vector-based vaccination, with reported success rates of approximately 90% in phase 3 pivotal trials [6]. A number of studies have shown that immune response to SARS-CoV-2 vaccination is adequate under most DMTs, but consistently found impaired response in pwMS receiving anti-CD20 and sphingosine-1-phosphate receptor modulators (S1PM), although mostly focusing on humoral response [7–10]. More recently, studies have indicated that cellular response, mostly driven by T cells, is often intact when humoral response fails and might even compensate for the lack of humoral immune response [11, 12].

However, data on the impact of SARS-CoV-2 vaccines on the clinical severity of COVID-19 in pwMS are currently very scarce.

The objective of this study was to reevaluate predictors of COVID-19 outcome in pwMS in a nationwide population-based study, specifically focusing on the impact of vaccination.

METHODS

Patients and definitions

The Austrian MS-COVID-19 (AUT-MuSC) registry comprises patients with a confirmed diagnosis of MS aged ≥18 years and with a diagnosis of COVID-19 (defined by a positive SARS-CoV-2 polymerase chain reaction [PCR]) recruited in an ongoing nationwide multicenter prospective observational study. Details of the study design and the data collected are described elsewhere [3, 13].

For the present study, we included all patients from AUT-MuSC with (i) COVID-19 diagnosis established between 1 January 2020 and 28 February 2022, and (ii) complete data available.

Patients were classified regarding their a priori risk of COVID-19 severity according to an established risk score (MS-COV-risk; range from −6 to 15, with higher scores predicting increased COVID-19 severity) taking into account age, physical disability as measured by the Expanded Disability Status Scale (EDSS), smoking status, obesity (body mass index ≥30), arterial hypertension, cardiovascular disease (coronary heart disease and/or ischemic heart failure and/or cardiac valve disease), chronic pulmonary disease (asthma, obstructive pulmonary disease, or pulmonary fibrosis), diabetes mellitus, and chronic kidney disease [14].

The endpoint was severe COVID-19 defined as the clinical status at the most severe point requiring hospitalization and fulfilling at least one of five criteria (breathing rate > 30/min; SpO_2 ≤ 93%; PaO_2/FiO_2 ratio < 300; pulmonary infiltrate >50% within 24–48 h; requirement of noninvasive ventilation, high-flow oxygen, mechanical ventilation, or extracorporeal membrane oxygenation).

To account for differences in the risk for COVID-19 severity as well as differences in efficacy in preventing MS disease activity, DMT status was classified at the time of SARS-CoV-2 infection as either receiving no DMT, moderately effective DMT (M-DMT; comprising dimethyl fumarate, glatiramer acetate, interferon-beta preparations, and teriflunomide); highly effective DMT (H-DMT; comprising alemtuzumab, cladribine, fingolimod, natalizumab, ozanimod, ponesimod, and siponimod), or anti-CD20 (comprising ocrelizumab, ofatumumab, and or rituximab).

Full vaccination was defined as patients having received two doses of BNT162b2 (Pfizer-BioNtech), mRNA-1273 (Moderna), or ChAdOx nCoV-19 (Astra-Zeneca); or one dose of Ad26.COV2.S (Janssen). Booster vaccination was defined as fully vaccinated patients who had received another dose of either of the four SARS-CoV-2 vaccines.

Statistical analysis

Statistical analysis was performed using SPSS 26.0. Categorical variables were expressed in frequencies and percentages. Continuous variables were tested for normal distribution by Shapiro–Wilk test and expressed as mean and SD or median and range as appropriate. Univariate group comparisons were conducted by *t*-test, analysis of variance, Mann–Whitney *U*-test, Kruskal–Wallis test, or chi-squared test as appropriate. Univariate correlation analyses were calculated by Pearson or Spearman test as appropriate.

To investigate predictors of severe COVID-19, we performed multivariate binary logistic regression models with COVID-19 severity as the dependent variable and a priori risk (MS-COV-risk score), DMT groups (reference category: no DMT), and full vaccination (reference category: unvaccinated) as independent variables adjusted for sex (age is already included in the MS-COV-risk score). Contribution of variables of interest to explanation of variance was assessed by change in R^2 through stepwise removal from the regression models.

We conducted sensitivity analyses evaluating the robustness of results to the impact of any single DMT substance or vaccine type by

TABLE 1 Characteristics of 317 pwMS with COVID-19

N	317
Female[a]	231 (72.9)
Age, years[b]	41.8 (12.4)
BMI[b]	25.2 (5.0)
Smokers[a]	45 (14.2)
Ethnicity[a]	
Caucasian[a]	312 (98.4)
Other[a]	5 (1.6)
Disease duration, years[b]	11.5 (8.7)
Disease course[a]	
RRMS[a]	265 (83.6)
SPMS[a]	39 (12.3)
PPMS[a]	13 (4.1)
EDSS[c]	1.5 (0–8.5)
On DMT[a]	244 (77.0)
M-DMT[a]	109 (34.4)
Dimethyl fumarate[a]	51 (16.1)
Glatiramer acetate[a]	26 (8.2)
Interferon-beta[a]	20 (6.3)
Teriflunomide[a]	12 (3.8)
H-DMT[a]	83 (26.2)
Alemtuzumab[a]	3 (0.9)
Cladribine[a]	12 (3.8)
Fingolimod[a]	34 (10.7)
Natalizumab[a]	31 (9.8)
Ozanimod[a]	1 (0.3)
Ponesimod[a]	1 (0.3)
Siponimod[a]	1 (0.9)
Anti-CD20[a]	52 (16.4)
Ocrelizumab[a]	26 (8.2)
Ofatumumab[a]	1 (0.3)
Rituximab[a]	25 (7.9)
Lymphopenia at last lab before SARS-CoV-2 infection[a]	45 (14.2)
Grade 3 or lower[a]	22 (6.9)
Comorbidities[a]	
Any	102 (32.2)
Coronary heart disease	14 (4.4)
Arterial hypertension	35 (11.0)
Diabetes mellitus	9 (2.8)
Chronic kidney disease	6 (1.9)
Obesity, BMI > 30	56 (17.7)
Chronic obstructive pulmonary disease	5 (1.6)
MS-COV-risk score[c]	0 (−6 to 11)

Note: "MS-COV-risk score" indicates MS COVID-19 severity risk score (range from −6 to 15), with higher scores predicting an increased COVID-19 severity (see Bsteh et al. [14]).

(Continues)

TABLE 1 (Continued)

Abbreviations: anti-CD20, anti-CD20 monoclonal antibodies (ofatumumab, ocrelizumab, rituximab); BMI, body mass index; DMT, disease-modifying treatment; EDSS, Expanded Disability Status Scale; H-DMT, highly effective DMT, comprising alemtuzumab, cladribine, fingolimod, natalizumab, ozanimod, ponesimod, and siponimod; M-DMT, moderately effective DMT, comprising dimethyl fumarate, glatiramer acetate, interferon-beta preparations, and teriflunomide; MS, multiple sclerosis; PPMS, primary progressive MS; pwMS, patients with MS; RRMS, relapsing–remitting MS; SPMS, secondary progressive MS.
[a]Absolute number and percentage.
[b]Mean and SD.
[c]Median and minimum–maximum range.

stepwise removal from analyses. Robustness of the statistically significant differences to unidentified confounders was quantified with Rosenbaum sensitivity test for Hodges–Lehmann Γ [15]. Missing values were handled by multiple (20 times) imputation using the missing not at random approach with pooling of estimates according to Rubin's rules [16]. A two-sided *p*-value <0.05 was considered statistically significant.

Ethics

The study was designed and conducted in accordance with the Declaration of Helsinki, the General Data Protection Regulations, and the STROBE (Strengthening Reporting of Observational Studies in Epidemiology) guidelines and was approved by the ethics committee of the Medical University Vienna (ethical approval number: EK 1338–2020). Patients included were informed about the objective of the study, and written informed consent was obtained.

RESULTS

We included 317 pwMS, whose overall characteristics are given in Table 1.

Overall, 294 pwMS (92.7%) had a mild and 23 (7.3%) had a severe COVID-19 course, of whom seven (2.2%) died from COVID-19.

Of the seven deceased pwMS, all were ≥60 years old. Six pwMS had progressive MS (secondary progressive MS, *n* = 4; primary progressive MS, *n* = 2), all with EDSS ≥6; of those, four were without DMT and two were on rituximab, whereas one had relapsing–remitting MS (RRMS; EDSS = 1.0, on interferon beta).

In univariate analyses, severe COVID course was strongly correlated with higher MS-COV-risk score (Spearman rho = 0.506, *p* <0.001) and moderately correlated with higher EDSS (Spearman rho = 0.312, *p* <0.001), whereas sex and smoking status were not. Correspondingly, severe COVID-19 was significantly more frequent in patients with progressive MS (13/52 [25.0%]) than those with RRMS (10/250 [4.0%], *p* <0.001). Treatment with anti-CD20 was significantly associated with severe COVID-19 (8/52 [15.4%], *p* = 0.006) compared to M-DMT (3/109 [2.8%]) and H-DMT (4/83
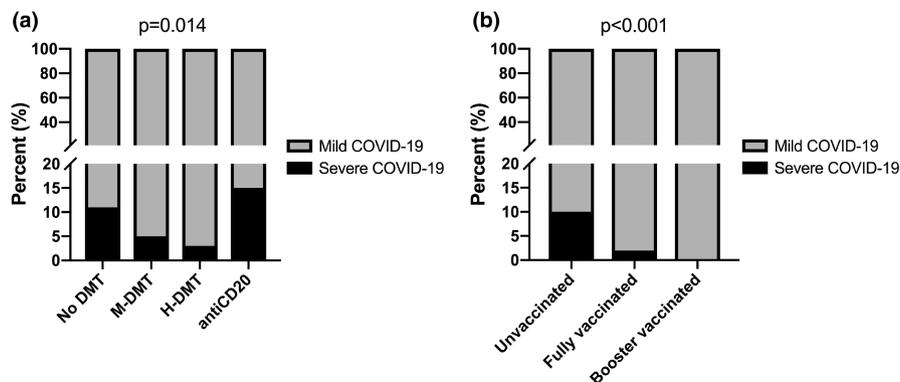
FIGURE 1 COVID-19 severity according to disease-modifying treatment (DMT) and vaccination status. antiCD20, anti-CD20 monoclonal antibodies, comprising ocrelizumab, ofatumumab, and rituximab; H-DMT, highly effective DMT, comprising alemtuzumab, cladribine, fingolimod, natalizumab, ozanimod, ponesimod, and siponimod; M-DMT, moderately effective DMT comprising dimethyl fumarate, glatiramer acetate, interferon-beta preparations, and teriflunomide. Probability values were calculated by chi-squared test

[4.8%]; see Figure 1a), but not lymphopenia (5/45 [11.1%] vs. 18/272 [6.6%], $p = 0.212$) or lymphopenia >Grade 3 (3/22 [13.6%] vs. 20/275 [7.3%], $p = 0.232$).

In the 51 patients receiving intravenous anti-CD20 (26 ocrelizumab, 25 rituximab), the median time since last infusion was 5 months, with a range of 0–9 months (ocrelizumab: median = 4 months [range = 0–7]; rituximab: median = 5 months [range = 1–9]). Time since last infusion did not significantly differ between patients with mild ($n = 44$, median = 5 months) and severe COVID-19 ($n = 8$, median = 4 months; $p = 0.892$). Due to the low number of patients with severe COVID-19, subgroup analyses of patients on ocrelizumab and rituximab was not feasible.

Of all 317 pwMS included, 97 (30.6%) were fully vaccinated. Twenty-two (6.9%) had already received booster vaccination. After a median 5 months from first vaccination to SARS-CoV-2 infection (range = 1–9), severe COVID-19 occurred in 2.1% of fully vaccinated pwMS (compared to 9.5% in unvaccinated pwMS, $p = 0.018$) and in 0% with booster vaccination (Figure 1b). There were no deaths among vaccinated patients. Time from first vaccination to SARS-CoV-2 infection did not correlate with COVID-19 severity (Spearman rho = −0.017, $p = 0.914$).

Seventeen of 52 pwMS receiving anti-CD20 treatment were fully vaccinated. Of those, only two (11.8%) had severe COVID-19 compared to six of 35 (17.1%) of anti-CD20-treated pwMS without full vaccination. In the subgroup of pwMS on S1PM, nine of 37 were fully vaccinated. There was no case of severe COVID-19 in the vaccinated or in the unvaccinated group.

Distribution of vaccine types used was as follows: 86 (88.7%) BNT162b2, two (2.3%) mRNA-1273, eight (8.2%) ChAdOx1-S, and one (1.0%) Ad26.COV2.S. Due to the low number of applied vaccines other than BNT162b2, we did not conduct further subgroup analyses in this regard.

In the multivariate model (Table 2; Figure 2), MS-COV-risk score significantly predicted COVID-19 severity (odds ratio [OR] = 1.3 per 1 point increase), explaining 60.5% of variability within the model. DMT status accounted for 11.3% of variability with anti-CD20

treatment significantly associated with an increased risk for severe COVID-19 (OR = 3.3, $p = 0.003$), whereas vaccination status was responsible for 14.4% of variation and fully vaccinated pwMS showed a significantly decreased risk for severe COVID-19 (OR = 0.21, $p < 0.001$). The number of booster vaccinated subjects ($n = 22$) did not allow for inclusion into a multivariate model.

DISCUSSION

From this study conducted in a nationwide population-based registry of PCR-confirmed COVID-19 in pwMS, we report three findings: (i) COVID-19 severity is primarily predicted by a priori risk (depending on age, degree of disability, and comorbidities); (ii) anti-CD20 treatment is associated with a moderately increased risk of severe COVID-19, whereas other DMTs are not; and (iii) fully vaccinated pwMS had an approximately fivefold decreased risk of severe COVID-19 compared to unvaccinated pwMS (2.1% vs. 9.5%) after adjusting for relevant covariates.

Our study reaffirms already robust evidence that the risk for severe COVID-19 in pwMS is primarily determined a priori, with age, degree of physical disability, and relevant concomitant comorbidities (obesity, cardiovascular disease, arterial hypertension, chronic pulmonary disease, diabetes mellitus, and chronic kidney disease) all contributing to a priori risk [1–4]. Based on the MS-COV-risk score, which cumulatively quantifies these factors, a priori risk explained 61% of variance in COVID-19 severity in pwMS [14].

In accordance with previous studies, anti-CD20 treatment was the only DMT class associated with an approximately threefold increased risk of severe COVID-19, explaining an additional 11% of variance in COVID-19 severity [1, 5]. This revises an earlier report from our registry, where we did not find a significant association between DMT and COVID-19 severity [3]. Most likely that was due to a smaller sample size and the different grouping of DMTs, as anti-CD20 were grouped together with other highly effective DMTs, which are not associated with COVID-19 severity [3]. Similar to

TABLE 2 Multivariate regression model of risk for severe COVID-19

	OR[a]	95% CI	p	Change in R^2
MS-COV-risk score, per point increase[b]	1.33	1.16–1.53	<0.001	0.605
DMT				
No DMT	Reference			0.113
M-DMT[c]	0.82	0.20–3.33	0.782	
H-DMT[d]	0.97	0.21–4.65	0.969	
Anti-CD20[e]	3.25	1.17–9.34	0.003	
Fully vaccinated[f]	0.21	0.07–0.78	<0.001	0.144

Note: R^2 overall: 0.862, $p < 0.001$. Values were calculated by a multivariate binary logistic regression model with severe COVID-19 as the dependent variable adjusted for sex (age is already included in the MS-COV-risk score) and lymphopenia. Contribution of variables of interest to explanation of variance was assessed by change in R^2 through stepwise removal from the regression models.

Abbreviations: CI, confidence interval; DMT, disease-modifying treatment; OR, odds ratio.

[a]Values >/< 1 indicate higher/lower probability of severe COVID-19.
[b]"MS-COV-risk score" indicates MS COVID-19 severity risk score (range from −6 to 15), with higher scores predicting an increased COVID-19 severity (see Bsteh et al. [14]).
[c]Defined as moderately effective DMT, comprising dimethyl fumarate, glatiramer acetate, interferon-beta preparations, and teriflunomide.
[d]Defined as highly effective DMT, comprising alemtuzumab, cladribine, fingolimod, natalizumab, ozanimod, ponesimod, and siponimod.
[e]Defined as anti-CD20 monoclonal antibodies, comprising ocrelizumab, ofatumumab, and rituximab.
[f]Defined as patients having received two doses of either BNT162b2 (Pfizer-BioNtech), mRNA-1273 (Moderna), or ChAdOx1 nCoV-19 (Astra-Zeneca); or one dose of Ad26.COV2.S (Janssen).

FIGURE 2 COVID-19 severity is associated with a priori risk, anti-CD20 monoclonal antibody treatment, and vaccination in multivariate analyses. Values were calculated by a multivariate binary logistic regression model with severe COVID-19 as the dependent variable adjusted for sex (age is already included in the MS-COV-risk score). Values >/< 1 indicate higher/lower probability of severe COVID-19. "Fully vaccinated" indicates having received two doses of BNT162b2 (Pfizer-BioNtech), mRNA-1273 (Moderna), or ChAdOx1 nCoV-19 (Astra-Zeneca); or one dose of Ad26. COV2.S (Janssen). "MS-COV-risk score" indicates MS COVID-19 severity risk score (range from −6 to 15), with higher scores predicting increased COVID-19 severity, taking into account age, Expanded Disability Status Scale, smoking status, obesity, arterial hypertension, cardiovascular disease (coronary heart disease and/or ischemic heart failure and/or cardiac valve disease), chronic pulmonary disease (asthma, obstructive pulmonary disease, or pulmonary fibrosis), diabetes mellitus, and chronic kidney disease [14]. antiCD20, anti-CD20 monoclonal antibodies, comprising ocrelizumab, ofatumumab, and rituximab; CI, confidence interval; H-DMT, highly effective DMT, comprising alemtuzumab, cladribine, fingolimod, natalizumab, ozanimod, ponesimod, and siponimod; M-DMT, moderately effective DMT comprising dimethyl fumarate, glatiramer acetate, interferon-beta preparations, and teriflunomide; OR, odds ratio

other studies, we also did not find an association between lymphopenia and COVID-19 severity [2, 17]. However, we did not have specific B-cell counts available for analysis, which might provide a means for further risk stratification specifically in pwMS on B-cell-depleting anti-CD20 treatment. Time since last anti-CD20 infusion did not significantly differ between patients with mild and severe COVID-19 in our cohort. As the median time since last infusion was 5 months, with a maximum of 9 months, most patients were not expected to have B cell repletion at the time of SARS-CoV-2 infection, which is the mechanism underlying the assumption of a correlation between time since last infusion and COVID-19 course. Therefore, and because of the low variation in time since last infusion, the lack of a correlation in our cohort is not surprising.

Looking at the protective effect of SARS-CoV-2 vaccination, fully vaccinated pwMS displayed severe COVID-19 in only 2% of cases as opposed to 10% in unvaccinated pwMS. After adjusting for a priori risk and DMT status in multivariate analyses, full vaccination was associated with a fivefold decreased risk of severe COVID-19, explaining another 14% of variation in COVID-19 severity in the overall cohort. This clearly shows that, albeit the majority of risk for severe
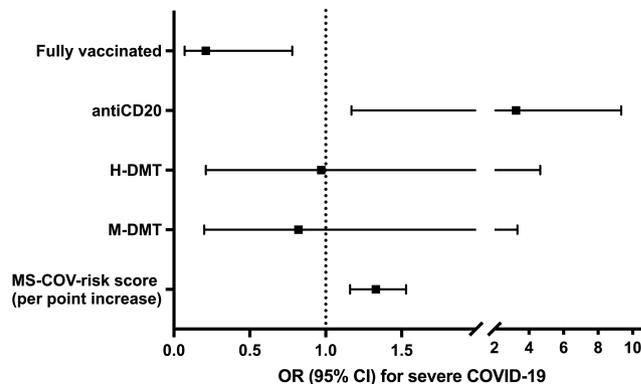
COVID-19 is a priori determined, SARS-CoV-2 vaccination independently further reduces this risk in pwMS.

Although immune response to SARS-CoV-2 vaccination is adequate under most DMTs, anti-CD20 and S1PM reduce and sometimes even lack development of a measurable response in humoral immunity, namely, antiSARS-CoV-2 antibodies [7–10]. However, the important question here is if and how much an impairment of humoral response translates to a decrease in protection from severe courses of COVID-19. That is particularly relevant because cellular response is often intact even in the absence of humoral response, which might provide sufficient immunity to prevent severe COVID-19 [11, 12, 18, 19]. Specifically looking at subgroups of DMTs associated with decreased vaccine response in our cohort, severe COVID-19 occurred in 12% (2/17) of vaccinated and 17% (6/35) of unvaccinated pwMS on anti-CD20 treatment, whereas there were no severe COVID-19 courses observed among nine vaccinated and 28 unvaccinated pwMS receiving S1PM. Although data on the impact of SARS-CoV-2 vaccines on clinical severity of COVID-19 in pwMS are currently very scarce, this is in line with two recently

published case series, where two of 10 and zero of 13 pwMS on anti-CD20, respectively, and zero of three and zero of four pwMS on S1PM required hospitalization, whereas none required intensive care unit admission [20, 21].

Nonetheless, larger prospective studies are needed to determine the clinical efficacy of SARS-CoV-2 vaccines in pwMS, especially those receiving anti-CD20 and S1PM treatment.

In the meantime, benefit–risk ratio is clearly in favor of continuing DMT while conducting SARS-CoV-2 vaccination, including anti-CD20 and S1PM when indicated by MS course in the respective individual pwMS. In case of little or no (humoral) response after complete antiSARS-CoV-2 vaccination including a booster, anti-SARS-CoV-2 monoclonal antibodies may represent a viable option in pwMS considered at high a priori risk of suffering severe COVID-19 if contracting the virus, either as early treatment or even as pre-exposition prophylaxis. The MS-COV-risk score provides an easily applicable tool for risk stratification in that regard [14]. Before initiating DMT, pwMS should be explicitly advised to complete vaccinations including anti-SARS-CoV-2 vaccination according to national vaccination guidelines. Consequently, most expert committees including the announced European Committee for Treatment and Research in Multiple Sclerosis–European Academy of Neurology consensus on vaccination in pwMS emphasize the need for evaluating immunization status, informing on the importance of vaccinations, and completing immunization as early as possible after diagnosis in all pwMS, while acknowledging the paramount need for ensuring optimal treatment of MS [22].

Strengths and limitations

The main strengths of this study are its population-based approach and the detailed characterization of the study cohort provided by the high-quality data from certified specialized MS centers. The AUT-MuSC-19 registry is likely to include most pwMS with symptomatic SARS-CoV-2 infections in Austria and is representative of a central European, primarily Caucasian MS population [3].

In addition to the limitations discussed above, some limitations inherent to the study design are acknowledged. Due to the sample size, results have to be interpreted with caution. There may be referral bias, as severe COVID-19 courses may be more likely to be reported. On the other hand, patients with advanced and progressive MS or patients not receiving DMT are less frequently seeing a neurologist regularly, and thus, this cohort might be underrepresented in this study.

We could not investigate the efficacy of vaccines against contracting SARS-CoV-2 or against having mild COVID-19, as we did not have a sufficient control group available. Also, we did not have sufficient sample size to examine the effect of booster vaccination in the multivariate model, and there was insufficient data to investigate the value of postvaccination and preinfection antibody levels or parameters of T-cell response, which could contribute to

understanding the COVID-19 outcome in patients with MS. As our study covers the whole duration of the pandemic, the cohort likely comprises infection with SARS-CoV-2 wild-type as well as a variety of variants. In Austria, delta and omicron variants caused the most significant waves of infection; therefore, we believe these variants encompass the majority of cases in the AUT-MuSC registry. However, we did not have PCR sequencing results available and therefore could not investigate the potential effect of SARS-CoV-2 variants. This may have influenced the results, potentially artificially enlarging the protective effect of vaccination, as vaccinated pwMS are more likely to be exposed to the omicron subtype, which is associated with less severe COVID-19 courses [23]. On the other hand, available SARS-CoV-2 vaccines are less effective against the omicron variant [24].

Our study is not sufficiently powered to investigate differences in the efficacy of single DMT substances or different SARS-CoV-2 vaccines applied. However, we conducted sensitivity analyses evaluating the robustness of results to the impact of single DMT substances and single vaccine types by stepwise removal, which did not indicate a significant change of results. There may also be other confounders influencing outcome of COVID-19 in pwMS unaccounted for in this study. However, Rosenbaum bounds did indicate only a small potential impact of hidden bias not accounted for in the multivariate models [15].

CONCLUSIONS

In a population-based MS cohort, COVID-19 course is primarily predicted by a priori risk (depending on age, degree of disability, and comorbidities), explaining about 60% of variance. Anti-CD20 treatment is associated with a moderately increased risk, whereas reassuringly vaccination provides protection from severe COVID-19. All pwMS should be vaccinated against SARS-CoV-2, and DMT decisions should then be focused on treating MS rather than the pandemic.

AUTHOR CONTRIBUTIONS

Gabriel Bsteh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Gabriel Bsteh: Study concept and design, patient recruitment, acquisition of data, statistical analysis and interpretation of data, drafting of manuscript. Christiane Gradl, Bettina Heschl, Franziska Di Pauli, Hamid Assar, Fritz Leutmezer, Gerhard Traxler, Nik Krajnc, Gudrun Zulehner, Maria-Sophie Hiller, Paulus Rommer, Peter Wipfler, Michael Guger, and Christian Enzinger: Patient recruitment, acquisition of data, critical revision of manuscript for intellectual content. Harald Hegen: Patient recruitment, acquisition of data, critical revision of manuscript for intellectual content, drafting of manuscript. Thomas Berger: Study concept and design, patient recruitment, interpretation of data, critical revision of manuscript for intellectual content, study supervision.

CONFLICT OF INTEREST

G.B. has participated in meetings sponsored by or received speaker honoraria or travel funding from Biogen, Celgene/BMS, Lilly, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva, and has received honoraria for consulting from Biogen, Celgene/BMS, Novartis, Roche, Sanofi-Genzyme, and Teva. He has received research grants from Celgene/BMS and Novartis. C.G. has participated in meetings sponsored by or received honoraria (lectures, consultations) and/or travel funding from Biogen, D-Pharma, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. H.H. has participated in meetings sponsored by or received speaker honoraria or travel funding from Bayer, Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, Siemens, and Teva, and has received honoraria for consulting Biogen, Celgene/BMS, Novartis, and Teva. F.D.P. has participated in meetings sponsored by or received honoraria (lectures, advisory boards, consultations) or travel funding from Almiral, Bayer, Biogen, Celgene/BMS, Janssen, Merck, Novartis, Sanofi-Genzyme, Roche, and Teva. Her institution has received research grants from Roche. H.A. has participated in meetings sponsored by or received honoraria (advisory boards, consultations) or travel funding from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, Celgene/BMS, Janssen-Cilag, and Teva. F.L. has participated in meetings sponsored by or received honoraria for acting as an advisor/speaker for Bayer, Biogen, Celgene, MedDay, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. G.T. has participated in meetings sponsored by or received honoraria (lectures, advisory boards, consultations) or travel funding from Biogen, Celgene/BMS, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. N.K. has participated in meetings sponsored by or received speaker honoraria or travel funding from Roche, Novartis, and Merck, and has held a grant for a Multiple Sclerosis Clinical Training Fellowship Programme from the European Committee for Treatment and Research in Multiple Sclerosis. G.Z. has participated in meetings sponsored by or received travel funding from Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva. P.R. has received honoraria for consultancy/speaking from AbbVie, Allmiral, Alexion, Biogen, Merck, Novartis, Roche, Sandoz, and Sanofi-Genzyme, and has received research grants from Amicus, Biogen, Merck, and Roche. P.W. has received funding for travel and honoraria (lectures, advisory boards) from Bayer, Biogen, Celgene/BMS, Janssen-Cilag, Merck, Novartis, Roche, Sandoz, Sanofi-Genzyme, and Teva. M.G. has received support and honoraria for research, consultation, lectures, and education from Almirall, Biogen, Celgene/BMS, Genzyme, Janssen, Merck, Novartis, Roche, Sanofi-Aventis, and Teva Ratiopharm. C.E. has received funding for travel and speaker honoraria from Biogen, Bayer, Merck, Novartis, Roche, Shire, Genzyme, and Teva; has received research support from Biogen, Merck, and Teva; and is serving on scientific advisory boards for Bayer, Biogen, Celgene/BMS, Merck, Novartis, Roche, and Teva. T.B. has participated in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for MS, including Allergan, Bayer, Biogen, Bionorica, Celgene/BMS, GSK, Janssen-Cilag, MedDay, Merck, Novartis, Octapharma, Roche, Sandoz, Sanofi-Genzyme, and Teva. His institution has received financial support in the past 12 months through unrestricted research grants (Bayer, Biogen, Celgene/BMS, Merck, Novartis, Sanofi Aventis, Teva) and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Bayer, Biogen, Celgene/BMS, Merck, Novartis, Octapharma, Roche, Sanofi-Genzyme, and Teva. Neither of the other authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request by a qualified researcher and can be accessed upon approval by the ethics committee of Medical University of Vienna.

ORCID

Gabriel Bsteh https://orcid.org/0000-0002-0825-0851
Harald Hegen https://orcid.org/0000-0002-2833-6337

Franziska Di Pauli https://orcid.org/0000-0001-6183-2394
Paulus Rommer https://orcid.org/0000-0001-5209-6647
Michael Guger https://orcid.org/0000-0001-8219-781X

REFERENCES

1. Sormani MP, Rossi ND, Schiavetti I, et al. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. *Ann Neurol.* 2021;89:780-789. doi:10.1002/ana.26028
2. Louapre C, Collongues N, Stankoff B, et al. Clinical characteristics and outcomes in patients with coronavirus Disease 2019 and multiple sclerosis. *JAMA Neurol.* 2020;77(9):1079-1088. doi:10.1001/jamaneurol.2020.2581
3. Bsteh G, Assar H, Hegen H, et al. COVID-19 severity and mortality in multiple sclerosis are not associated with immunotherapy: insights from a nation-wide Austrian registry. *Plos One.* 2021;16(7):e0255316. doi:10.1371/journal.pone.0255316
4. Barzegar M, Mirmosayyeb O, Gajarzadeh M, et al. COVID-19 among patients with multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm.* 2021;8(4):e1001. doi:10.1212/nxi.0000000000001001
5. Sormani MP, Salvetti M, Labauge P, et al. DMTs and Covid-19 severity in MS: a pooled analysis from Italy and France. *Ann Clin Transl Neur.* 2021;8(8):1738-1744. doi:10.1002/acn3.51408
6. Pascolo S. Vaccines against COVID-19: priority to mRNA-based formulations. *Cell.* 2021;10(10):2716. doi:10.3390/cells10102716
7. Achiron A, Mandel M, Dreyer-Alster S, et al. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. *Ther Adv Neurol Disord.* 2021;14:175628642110128. doi:10.1177/17562864211012835
8. Sormani MP, Inglese M, Schiavetti I, et al. Effect of SARS-CoV-2 mRNA vaccination in MS patients treated with disease modifying therapies. *Ebiomedicine.* 2021;72:103581. doi:10.1016/j.ebiom.2021.103581
9. Disanto G, Sacco R, Bernasconi E, et al. Association of disease-modifying treatment and anti-CD20 infusion timing with humoral response to 2 SARS-CoV-2 vaccines in patients with multiple sclerosis. *JAMA Neurol.* 2021;78(12):1529-1531. doi:10.1001/jamaneurol.2021.3609
10. Bsteh G, Hegen H, Traxler G, et al. Comparing humoral immune response to SARS-CoV2 vaccines in multiple sclerosis and healthy controls: an Austrian prospective multi-center cohort study. *Eur J Neurol.* 2022;29:1538-1544. doi:10.1111/ene.15265
11. Apostolidis SA, Kakara M, Painter MM, et al. Cellular and humoral immune responses following SARS-CoV-2 mRNA vaccination in patients with multiple sclerosis on anti-CD20 therapy. *Nat Med.* 2021;27:1-12. doi:10.1038/s41591-021-01507-2
12. Kornek B, Leutmezer F, Rommer PS, et al. B cell depletion and SARS-CoV-2 vaccine responses in neuroimmunologic patients. *Ann Neurol.* 2022;91(3):342-352. doi:10.1002/ana.26309
13. Bsteh G, Dürauer S, Assar H, et al. Humoral immune response after COVID-19 in multiple sclerosis: a nation-wide Austrian study. *Mult Scler J.* 2021;27:135245852110493. doi:10.1177/13524585211049391
14. Bsteh G, Bitschnau C, Hegen H, et al. Multiple sclerosis and COVID-19: how many are at risk? *Eur J Neurol.* 2020;28:3369-3374. doi:10.1111/ene.14555
15. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. *J Am Stat Assoc.* 1984;79(387):516-524. doi:10.2307/2288398
16. Council National Research. *The Prevention and Treatment of Missing Data in Clinical Trials. National Academies Press* (US); 2010. doi:10.17226/12955
17. Loonstra FC, Hoitsma E, van Kempen ZL, Killestein J, Mostert JP. COVID-19 in multiple sclerosis: the Dutch experience. *Mult Scler J.* 2020;26(10):1256-1260. doi:10.1177/1352458520942198
18. Gadani SP, Reyes-Mantilla M, Jank L, et al. Discordant humoral and T cell immune responses to SARS-CoV-2 vaccination in people with multiple sclerosis on anti-CD20 therapy. *EBioMedicine.* 2021;73:103636. doi:10.1016/j.ebiom.2021.103636
19. Bsteh G, Sellner J. T cells as the hoped-for savior for SARS-CoV-2 vaccination during CD20-depleting antibody therapy?: Commentary for: "discordant humoral and T cell immune responses to SARS-CoV-2 vaccination in people with multiple sclerosis on anti-CD20 therapy.". *EBioMedicine.* 2021;74:103692. doi:10.1016/j.ebiom.2021.103692
20. Rose DR, Mahadeen AZ, Carlson AK, et al. Clinical features and outcomes of COVID-19 despite SARS-CoV-2 vaccination in people with multiple sclerosis. *Mult Scler J - Exp Transl Clin.* 2021;7(4):20552173211057110. doi:10.1177/20552173211057110
21. Januel E, Seze JD, Vermersch P, et al. Post-vaccine COVID-19 in patients with multiple sclerosis or neuromyelitis optica. *Mult Scler J.* 2022;28(7):1155-1159. doi:10.1177/13524585211049737
22. Otero-Romero S, Lebrun-Frenay C, Reyes S, et al. ECTRIMS EAN consensus on vaccination in patients with multiple sclerosis. In press.
23. Hussey H, Davies MA, Heekes A, et al. Assessing the clinical severity of the omicron variant in the Western Cape Province, South Africa, using the diagnostic PCR proxy marker of RdRp target delay to distinguish between omicron and Delta infections – a survival analysis. *Int J Infect Dis.* 2022;118:150-154. doi:10.1016/j.ijid.2022.02.051
24. Andrews N, Stowe J, Kirsebom F, et al. Covid-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *New Engl J Med.* 2022;386:1532-1546. doi:10.1056/nejmoa2119451