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COVID-19 Severity in Multiple Sclerosis

Putting Data Into Context

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Abstract

Background and Objectives

It is unclear how multiple sclerosis (MS) affects the severity of COVID-19. The aim of this study is to compare COVID-19–related outcomes collected in an Italian cohort of patients with MS with the outcomes expected in the age- and sex-matched Italian population.

Methods

Hospitalization, intensive care unit (ICU) admission, and death after COVID-19 diagnosis of 1,362 patients with MS were compared with the age- and sex-matched Italian population in a retrospective observational case-cohort study with population-based control. The observed vs the expected events were compared in the whole MS cohort and in different subgroups (higher risk: Expanded Disability Status Scale [EDSS] score > 3 or at least 1 comorbidity, lower risk: EDSS score ≤ 3 and no comorbidities) by the χ^2 test, and the risk excess was quantified by risk ratios (RRs).

Results

The risk of severe events was about twice the risk in the age- and sex-matched Italian population: RR = 2.12 for hospitalization ($p < 0.001$), RR = 2.19 for ICU admission ($p < 0.001$), and RR = 2.43 for death ($p < 0.001$). The excess of risk was confined to the higher-risk group (n = 553). In lower-risk patients (n = 809), the rate of events was close to that of the Italian age- and sex-matched population (RR = 1.12 for hospitalization, RR = 1.52 for ICU admission, and RR = 1.19 for death). In the lower-risk group, an increased hospitalization risk was detected in patients on anti-CD20 (RR = 3.03, $p = 0.005$), whereas a decrease was detected in patients on interferon (0 observed vs 4 expected events, $p = 0.04$).

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MuSC-19 Study Group coinvestigators are listed in the appendix at the end of the article.

Glossary

DMT = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **ICU** = intensive care unit; **ISS** = Istituto Superiore di Sanità; **MS** = multiple sclerosis; **RR** = risk ratio; **RT-PCR** = reverse transcriptase-polymerase chain reaction; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2.

Discussion

Overall, the MS cohort had a risk of severe events that is twice the risk than the age- and sex-matched Italian population. This excess of risk is mainly explained by the EDSS score and comorbidities, whereas a residual increase of hospitalization risk was observed in patients on anti-CD20 therapies and a decrease in people on interferon.

Several studies have assessed the impact of COVID-19 in patients with multiple sclerosis (MS), unanimously indicating older age, male sex, concomitant comorbidities, and higher disability as risk factors for a more severe disease course.[1-4] The possible association between immunotherapies and COVID-19 severity was also investigated, mostly indicating an increased risk for patients with MS who are on anti-CD20 therapies or who received methylprednisolone just before the COVID-19 onset[1,3,4] and suggesting a protective role of interferon.[1,4] A recent meta-analysis of all the published studies on COVID-19 in patients with MS suggested that MS did not significantly increase the mortality rate from COVID-19,[5] but the authors pointed out that these data should be interpreted with caution as patients with MS are more likely female and younger compared with the general population where age and male sex are risk factors for worse disease outcome.[5] Therefore, even if all the studies agree that data available so far are overall reassuring, excluding major safety issues,[1-4] comparisons with external control populations are lacking.

It is unclear whether and how MS biology—apart from treatments—affects the ability to cope with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This is not trivial as immunocompetence, in an immune-mediated disease such as MS, may be reduced. Moreover, SARS-CoV-2 interacts, in a way that is still poorly understood, with the genetic background predisposing to autoimmune diseases (including MS)[6] and misdirects host immune responses toward autoimmunity as part of COVID-19 pathophysiology.[7-9] It is therefore plausible that preexisting autoimmunity may exacerbate COVID-19 severity. Therefore, to understand whether patients with MS with COVID-19 are exposed to higher risks than the healthy population, a comparison with an external cohort is needed. The aim of this study is to compare the outcomes collected in an Italian cohort of patients with MS with COVID-19 (within the MuSC-19 project) with the outcomes expected in the age- and sex-matched Italian population, using data provided by the Italian Istituto Superiore di Sanità (ISS).

Methods

Data Sources: MuSC-19 Study

Data of patients with MS with suspected or confirmed COVID-19 were retrospectively collected at a national level in Italy from February 24, 2020, to February 2, 2021. Details on data collection methods and inclusion criteria were previously reported.[1] Briefly, we obtained clinician-reported demographic and clinical data on patients with MS with a confirmed or suspected COVID-19 infection from 118 Italian MS centers (eAppendix 2, links.lww.com/NXG/A493). We used a common web-based electronic Case Report Form to collect the data and a unified protocol to analyze them. Demographic, MS history, COVID-19 infection, and follow-up data were collected. For this analysis we included only patients with confirmed COVID-19. To be a confirmed case the patient must have a positive reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharynegal swab.

Data Sources: Italian Population

We made a specific data request to the ISS, who is the Italian governing body responsible for COVID-19 surveillance in Italy. Data requested (reported in Table 1) were about the percentage of patients who were hospitalized, who accessed intensive care unit (ICU), or who died for each sex and age class (0–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and >90 years), among those with a positive RT-PCR during the observation period (February 24, 2020, to February 2, 2021).

Statistical Analysis

The probability to be hospitalized, to be admitted to ICU, and to die was extracted from ISS data (Table 1) for each patient enrolled in the MuSC-19 data set, according to their age and sex. Then, the expected number of events (e.g., hospitalizations, ICU admissions, or deaths) in the MuSC-19 population and in specific subgroups of patients (detailed below) was estimated by summing up the probabilities for each patient in the group: as an example, if 2 patients have a probability to be hospitalized of 0.5, the expected number of hospitalizations in this 2-patient group is 1. The expected proportions of hospitalizations, ICU admissions, and deaths were compared with the observed proportions by a χ^2 test, and the relative

Table 1 COVID-19 Data From the Surveillance Program in Italy

	Females				Males			
Age	**Cases (N or n)**	**Hosp[a] (%)**	**ICU (%)**	**Death[b] (%)**	**Cases (N or n)**	**Hosp[a] (%)**	**ICU (%)**	**Death[b] (%)**
0–29	305,174	2.3	0.1	0.0	320,343	1.9	0.1	0.0
30–39	160,677	3.5	0.2	0.0	153,394	3.4	0.3	0.1
40–49	216,028	3.5	0.2	0.1	189,326	6.4	0.8	0.3
50–59	235,272	5.6	0.5	0.3	219,320	11.3	1.9	1.0
60–69	135,201	11.4	1.7	1.6	151,381	20.5	4.6	4.1
70–79	103,496	22.7	3.2	6.5	111,032	34.1	6.7	1.3
80–89	109,071	29.0	2.5	15.2	74,091	43.6	4.6	26.7
>90	53,545	22.7	1.3	21.8	15,884	40.6	2.6	37.6
Unk[c]	58	0	0	—	53	0	0	0
Total	1,318,522				1,234,824			

Abbreviation: ICU = intensive care unit.
[a] Admission at hospital.
[b] Data on deaths are relative to the January 29 report.
[c] Unknown age.

difference expressed as risk ratios (RRs). Binomial 95% CIs were calculated for the observed proportion of events.

After the comparison of the rate of hospitalization, ICU admission, and death between the MuSC-19 cohort and the age- and sex-matched Italian population was run, we tried to explain the differences observed between patients with MS and the general population by evaluating the role of MS related risk factors, that is, Expanded Disability Status Scale (EDSS) score, comorbidities, and disease-modifying therapy (DMT) exposure, as indicated by previous literature.[1-4] We focused this additional analysis on hospitalization rates only because the number of observed ICU admissions and deaths was too low to be evaluated in separate subgroups of patients. The same results on observed and expected deaths and ICU admissions are reported in eTable 1 (links.lww.com/NXG/A492).

The specific subgroups of patients were defined according to a cutoff of EDSS score = 3 and the presence of at least 1 comorbidity. The EDSS score cutoff was chosen based also on the EDSS distribution of the MuSC-19 cohort to have 2 balanced groups. Therefore, the lower-risk group included patients with EDSS score ≤ 3 and no comorbidities, whereas the higher-risk group included patients with EDSS score > 3 or at least 1 comorbidity. DMTs were grouped, according to previous literature, as no therapy, interferon therapy, anti-CD20 therapy (rituximab or ocrelizumab), and other DMTs. A χ^2 test for heterogeneity was used to compare the RR between groups.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Regional Ethics Committee of Liguria (University of Genoa) (n 130/2020—DB id 10433) and at a national level by Agenzia Italiana del Farmaco. Written informed consent was obtained from all participants before starting any study procedures.

Data Availability

MuSC-19 data that support the findings of this study are available on request from the first author (M.P.S). The data are not publicly available due to information that could compromise the privacy of research participants.

Results

In the MuSC-19 database 1,362 patients with MS had a positive RT-PCR swab for COVID-19 over the observation period and were included in the analysis. The characteristics of the included patients are reported in Table 2. In this cohort, we observed 174 hospitalizations (12.8%), 22 ICU admissions (1.62%), and 22 deaths (1.62%) (not mutually exclusive). The expected number of hospitalizations in an age- and sex-matched cohort extracted from the Italian population was 82 (6.0%), the expected number of ICU admissions was 10 (0.73%), and the expected number of deaths was 9 (0.66%).

In Figure 1, the number of observed and expected events is reported. As compared to an age- and sex-matched cohort extracted from the Italian population, the MuSC-19 MS cohort had an excess of hospitalizations (RR = 2.12, 95% CI = 1.83–2.44, $p < 0.001$), an excess of ICU admissions (RR = 2.19, 95% CI = 1.38–3.30, $p = 0.007$), and an excess of deaths (RR = 2.43, 95% CI = 1.53–3.66, $p = 0.007$).

We tried to explain this excess of risk in 2 steps. First, we checked the MS related risk factors (EDSS score and comorbidities), by splitting the cohort in 2 risk groups, as previously described. The MS lower-risk patients were 809 (60%), and the MS higher-risk

Table 2 Characteristics of Patients With MS

	Overall (N = 1,362)
Age, mean (SD)	44·1 (12.6)
Female sex, no. (%)	936 (68.7)
Comorbidities, no. (%)	
Hypertension, no. (%)	147 (10.8)
Major depressive disorder, no. (%)	49 (3.6)
Hematologic disease, no. (%)	38 (2.8)
Diabetes, no. (%)	47 (3.5)
Cancer, no. (%)	23 (1.7)
Coronary heart disease, no. (%)	15 (1.1)
MS duration, median (IQR)	8.9 (3.8–15.9)
EDSS score, median (IQR)	2.0 (1.0–3.5)
MS treatment, no. (%)	
Dimethyl fumarate	239 (17.5)
Natalizumab	188 (13.8)
Fingolimod	166 (12.2)
Ocrelizumab	149 (10.9)
Interferon	133 (9.8)
Copaxone	101 (7.4)
Teriflunomide	79 (5.8)
Cladribine	27 (2.0)
Rituximab	27 (2.0)
Azathioprine	26 (1.9)
Alemtuzumab	24 (1.8)
Methotrexate	3 (0.2)
Other	11 (0.8)
None	189 (13.9)

Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; MS = multiple sclerosis.

patients were 553 (40%). In the higher-risk group, 119 (22%) had both EDSS score > 3 and comorbidities, 150 (27%) had comorbidities and EDSS score ≤ 3, and 283 (51%) had EDSS score > 3 and no comorbidities. The observed vs expected number of events in these 2 groups is reported in Figure 2. The excess of risk of the MS cohort is mainly confined in the MS higher-risk group: the hospitalization RR was 2.85 (95% CI = 2.44–3.29, $p < 0.001$) in the higher MS group, whereas it was 1.12 (95% CI = 0.80–1.52, $p = 0.44$) in the lower-risk group (the 2 RRs were significantly heterogeneous, $p < 0.001$). The ICU admission RR was 2.52 (95% CI = 1.48–4.00, $p < 0.001$) in the MS higher-risk group and 1.52 (95% CI = 0.49–3.52, $p = 0.27$) in the MS lower-risk group (heterogeneity test, $p = 0.11$). Finally, the death RR was 2.71 (95% CI = 1.67–4.14, $p < 0.001$) in the MS higher-risk group and 1.19 (95% CI = 0.14–4.29, $p = 0.68$) in the MS lower-risk group (heterogeneity test, $p = 0.17$).

To try to understand the role of DMTs in explaining the small residual increase of risk in the MS lower-risk group, we split the observed and the expected hospitalization events in 4 groups: untreated patients, patients treated with interferon, patients treated with anti-CD20, and patients treated with other DMTs. In the lower-risk group (Figure 3A), the RRs were significantly heterogeneous among DMT groups ($p = 0.048$): there was no residual risk in untreated patients (RR = 1.15, 95% CI = 0.31–2.92, $p = 0.78$) nor in patients treated with other DMTs (RR = 1.09, 95% CI = 0.72–1.57, $p = 0.61$) as compared to the age- and sex-matched general population; patients with MS treated with interferon had no hospitalization (RR = 0, 95% CI = 0–3.7), whereas about 4 were expected, and the difference was statistically significant ($p = 0.042$). Patients treated with anti-CD20 had a significantly higher risk of hospitalization (RR = 3.03, 95% CI = 1.30–5.94, $p = 0.005$) than the age- and sex-matched general population, showing that the small increase of risk of patients with MS with EDSS score ≤ 3 and no comorbidities is confined to this class of patients.

In the MS higher-risk group (Figure 3B), the RRs were also significantly heterogeneous among DMTs groups ($p = 0.050$); the RR was 4.27 (95% CI = 2.91–6.18, $p < 0.001$) for patients under anti-CD20, 3.13 (95% CI = 2.40–4.04, $p < 0.001$) for untreated patients, 2.31 (95% CI = 1.74–3.04, $p < 0.001$) for patients under other DMTs, and 1.80 (95% CI = 0.66–4.42, $p = 0.50$) for patients under interferon.

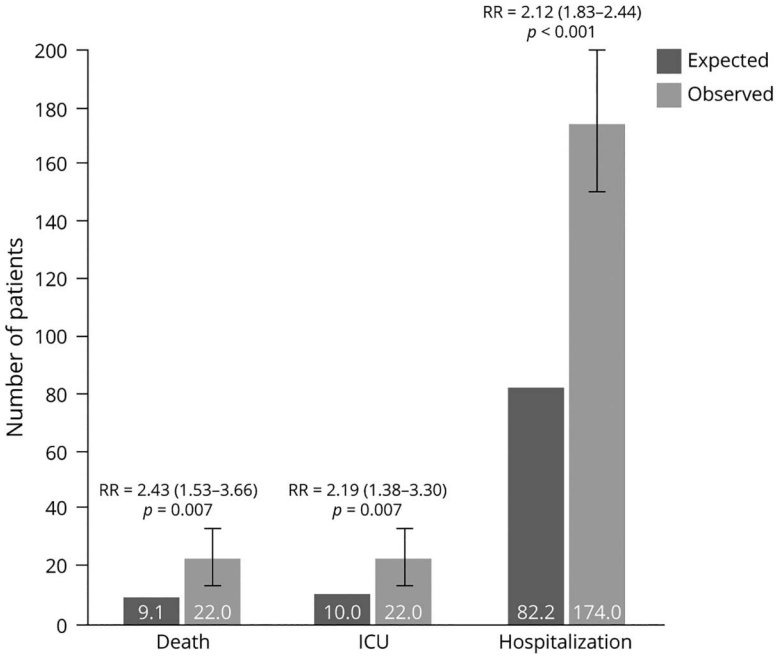
The number of deaths and ICU admissions according to DMT use in the lower- and in the higher-risk groups is reported in table e-1 (links.lww.com/NXG/A492). In the higher-risk group, the excess of death risk was mainly in the no therapy group (RR = 3.26, 95% CI = 1.77–5.37) and in the anti-CD20 group (RR = 5.40, 95% CI = 1.11–15.25), even if the low number of events does not allow to conclude for an heterogeneity of mortality risk according to the DMT group.

Discussion

Several registries reported the COVID-19 lethality rates of MS cohorts with heterogeneous results, ranging from estimates of 1.6% in an Italian cohort and 1.7% in a French cohort[4] to estimates of 3.6% in a US cohort.[3] Explaining these differences is not straightforward and can be linked to the intrinsic limitation of registry data analyses: they are based, in fact, on a voluntary reporting by health care professionals, that may bias collected data toward more severe cases. This may cause an overestimation of clinical severity, with less effect on the internal comparisons among risk factors but challenging external comparisons.

Moreover, comparing the lethality rate of the MS cohorts with the respective national lethality rates in the general population is not meaningful without an adjustment for age and sex. The

Figure 1 Observed Hospitalizations, ICU Admissions, and Deaths in the MuSC-19 Cohort and Age-Sex–Matched Italian Population

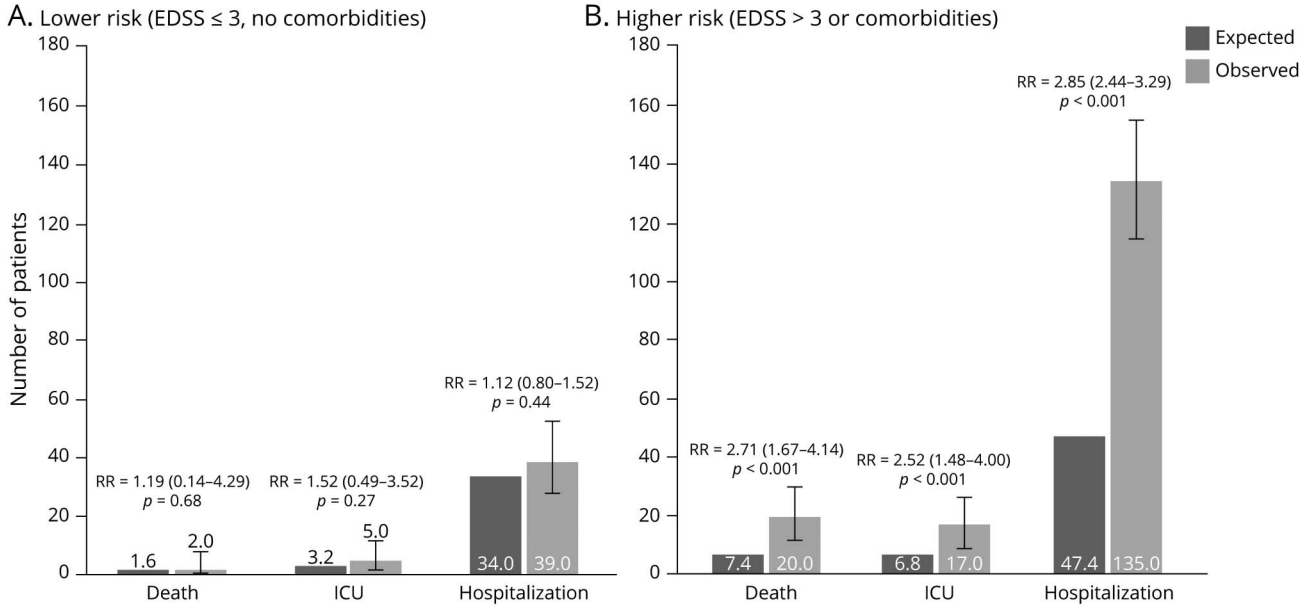


Observed hospitalizations, ICU admissions, and deaths in the MuSC-19 cohort (n = 1,362) as compared to the expected number of events in an age and matched cohort from the Italian population. ICU = intensive care unit; RR = risk ratio.

MS population is, in fact, more likely female and younger compared with the general population, and age and male sex are well known risk factors for COVID-19.

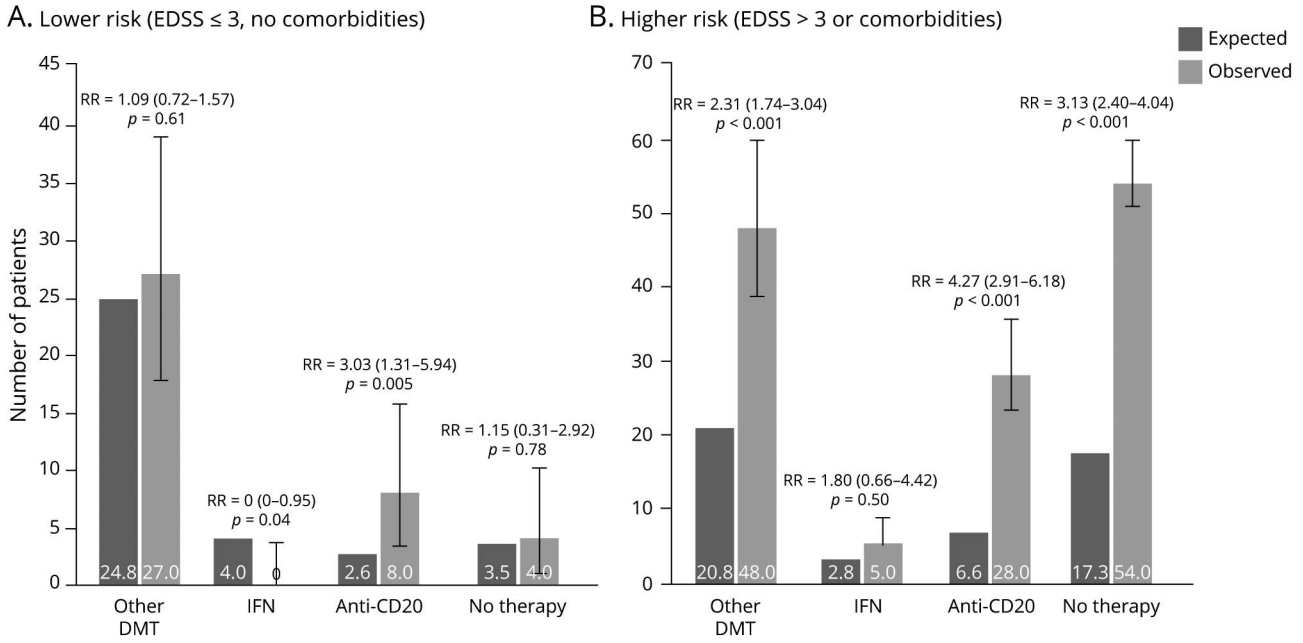
This study shows that overall, the patients with MS have a risk of developing a severe COVID-19 that is twice the risk of the age- and sex-matched Italian population. This excess of risk could be in part explained by the abovementioned bias affecting collected data toward more severe cases. However, in patients with MS with a low EDSS score (≤3) and no comorbidities, the risk of severe events is very close to the risk of the age- and sex-matched Italian population; in this lower-risk group, only patients under

Figure 2 Observed and Expected Hospitalizations, ICU Admissions, and Deaths in Lower-Risk (A) and Higher-Risk (B) Patients



Observed hospitalizations, ICU admissions, and deaths in the lower-risk patients (A; EDSS score ≤ 3 and no comorbidities, n = 809) and in the higher-risk patients (B; EDSS score > 3 or comorbidities, n = 553) as compared to the expected number of events in the age and matched cohort from the Italian population. EDSS = Expanded Disability Status Scale; ICU = intensive care unit; RR = risk ratio.

Figure 3 Observed and Expected Hospitalizations, ICU Admissions, and Deaths According to DMT and Lower-Risk (A) and Higher-Risk (B) Groups



Observed hospitalizations, ICU admissions, and deaths in the lower-risk patients (EDSS score ≤ 3 and no comorbidities, n = 809) and in the higher-risk patients (EDSS score > 3 or comorbidities, n = 553) according to the DMT taken as compared to the expected number of hospitalizations in the age- and sex-matched sample from the Italian population. In the interferon group, the RR = 0 because there were no observed events. DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; ICU = intensive care unit; IFN = interferon; RR = risk ratio.

anti-CD20 therapy show an increased risk of hospitalization than the age- and sex-matched Italian population. Of interest, the protective role of interferon previously suggested[1,3,4] is supported here because patients with MS taking interferon show a significantly lower number of hospitalization events than the age- and sex-atched Italian population. In patients with MS, the excess of risk of severe COVID-19 detected is confined to the group of patients with EDSS score > 3 or with additional comorbidities, were the RR ranges from 1.80 in patients treated with interferon to 4.27 in patients treated with anti-CD20.

The association with disability, and not with the disease itself, suggests that the immunologic defects determining MS do not impair the immunocompetence against SARS-CoV-2 infection. Furthermore, this result is consistent with data from the largest health analytic platforms[10] where neurologic diseases emerged as factors associated with COVID-19 severe outcome, independently of their immune-mediated pathogenesis. However, we cannot exclude that an increased attention to social distancing[11] may have counterbalanced the risk of COVID-19 linked to a dysfunctional immune system.

In conclusion, this study shows that in Italy, disability and comorbidities are determinants of an increased risk of severe COVID-19 in patients with MS. Among DMTs, a residual increase of hospitalization is associated with anti-CD20, whereas with interferon, the risk seems to be reduced. These results cannot be generalized because of possibly relevant differences in heritable and nonheritable factors affecting the response to SARS-CoV-2 in different populations.[12] However, the consistency of the results of previous studies on the impact DMTs on COVID-19 severity in MS, performed in different nations, supports the possibility that our results will be replicated also in other geographic areas and populations.

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Antonio Zito, MD	Multiple Sclerosis Research Center, IRCCS Mondino Foundation, Pavia	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Paolo Confalonieri, MD	Multiple Sclerosis Centre, Neuroimmunology Department—"Carlo Besta" Neurological Institute, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Girolama Alessandra Marfia, MD	Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine, Tor Vergata University, Rome, Italy	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Paola Perini, MD	Department of Neurology Multiple Sclerosis Center, University of Padua, Italy	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Matilde Inglese, MD	Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Italy; IRCCS Ospedale Policlinico San Martino, Genoa, Italy	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data

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Appendix 1 *(continued)*

Name	Location	Contribution
Maria Trojano, MD	Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Italy	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Vincenzo Brescia Morra, PhD	Federico II University of Naples, Italy	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Gioacchino Tedeschi, MD	Department of Advanced Medical and Surgical Sciences, University of Campania, Napoli, Italy	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Giancarlo Comi, MD	Università Vita Salute San Raffaele, Casa di Cura Privata del Policlinico, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Mario Alberto Battaglia, MD	Research Department, Italian Multiple Sclerosis Foundation, Genoa, Italy; Department of Life Sciences, University of Siena, Italy	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Francesco Patti, MD	Department of Medical and Surgical Sciences and Advanced Technologies, GF Ingrassia, University of Catania; Centro Sclerosi Multipla, Policlinico Catania, University of Catania	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Marco Salvetti, MD	Department of Neuroscience, Mental Health and Sensory Organs, Sapienza University of Rome, Italy; Unit of Neurology, IRCCS Neuromed, Pozzilli, Isernia, Italy	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Gianmarco Abbadessa	Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, 80138 Naples, Italy;	Site Investigator	Data collection
Umberto Aguglia	Department of medical and surgical sciences, Magna Graecia University Catanzaro	Site Investigator	Data collection
Lia Allegorico	Multiple Sclerosis Centre A. Cardarelli Hospital, Naples, Italy	Site Investigator	Data collection
Beatrice Maria Allegri Rossi	Centro SM Fidenza (PR)	Site Investigator	Data collection

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Maria Pia Amato	Università degli Studi di Firenze, Dipartimento NEUROFARBA, Firenze - IRCCS Fondazione Don Carlo Gnocchi, Firenze	Site Investigator	Data collection
Pietro Annovazzi	Centro Sclerosi Multipla Ospedale di Gallarate, ASST della Valle Olona	Site Investigator	Data collection
Carlo Antozzi	Centro Sclerosi Multipla, U.O Neurologia IV, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano	Site Investigator	Data collection
Lucia Appendino	SC Neurologia1 Ospedale Maria Vittoria- Torino	Site Investigator	Data collection
Sebastiano Arena	Dipartimento Scienze Mediche e Chirurgiche e Tecnologie Avanzate, GF Ingrassia, Università di Catania; Centro Sclerosi Multipla Policlinico "G Rodolico"- San Marco, Università di Catania	Site Investigator	Data collection
Viola Baione	Department of Human Neurosciences, Sapienza, University of Rome	Site Investigator	Data collection
Roberto Balgera	MS Center, ASST Lecco	Site Investigator	Data collection
Valeria Barcella	USS Neuroimmunologia, ASST Papa Giovanni XXIII	Site Investigator	Data collection
Damiano Baroncini	Centro Sclerosi Multipla Ospedale di Gallarate, ASST della Valle Olona	Site Investigator	Data collection
Caterina Barrilà	ASST Rhodense	Site Investigator	Data collection
Alessandra Bellacosa	Centro Sclerosi Multipla, UO Neurologia, Ospedale San Giacomo, Monopoli (Bari)	Site Investigator	Data collection
Gianmarco Bellucci	Department of Neuroscience, Mental Health and Sensory Organs Sapienza University S. Andrea Hospital-site Rome	Site Investigator	Data collection
Roberto Bergamaschi	IRCCS Mondino Foundation, Pavia	Site Investigator	Data collection
Valeria Bergamaschi	AISM Rehabilitation Service Liguria	Site Investigator	Data collection
Daiana Bezzini	Department of Life Sciences, University of Siena, Siena, Italy	Site Investigator	Data collection
Beatrice Biolzi	Centro SM Fidenza (PR)	Site Investigator	Data collection
Alvino Bisecco	Centro SM, I Clinica Neurologica, AOU-Policlinico, Università della Campania "Luigi Vanvitelli"	Site Investigator	Data collection

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Name	Location	Role	Contribution
Simona Bonavita	Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, 80138 Naples, Italy;	Site Investigator	Data collection
Giovanna Borriello	NCL Isituto di Neuroscienze Roma	Site Investigator	Data collection
Chiara Bosa	MS Center, Department of Neuroscience, City of Health and Science University Hospital of Turin, Turin, Italy	Site Investigator	Data collection
Antonio Bosco	Neurology Unit, Department of Medical, Surgical, and Health Sciences, Cattinara University Hospital, ASUGI, Trieste	Site Investigator	Data collection
Francesca Bovis	Department of Health Sciences, University of Genoa, Genoa, Italy.	Biostatistician	Support in statistical analysis
Marco Bozzali	Neurology II, Dept of Neuroscience, University of Turin	Site Investigator	Data collection
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Maria Buccafusca	Centro Sclerosi Multipla UOC Neurologia e Malattie Neuromuscolari, AOU Policlinico G. Martino Messina	Site Investigator	Data collection
Elisabetta Bucciantini	Ospedale Savigliano ASLCN1	Site Investigator	Data collection
Sebastiano Bucello	Centro SM Ospedale Muscatello Augusta (ASP8 SR)	Site Investigator	Data collection
Maria Chiara Buscarinu	Department of Neuroscience, Mental Health and Sensory Organs Sapienza University S. Andrea Hospital-site Rome	Site Investigator	Data collection
Maria Paola Cabboi	UOC Neurologia- centro SM- AUSL- IRCCS RE	Site Investigator	Data collection
Massimiliano Calabrese	The Multiple Sclerosis Center of University Hospital of Verona Dept. of Neuroscience, Biomedicine and Movements	Site Investigator	Data collection
Francesca Calabria	UO Neurologia A-Azienda Ospedaliera Universitaria Integrata Verona	Site Investigator	Data collection
Francesca Caleri	Multiple Sclerosis Center, Department of Neurology - Franz Tappeiner Hospital Meran (BZ), Italy	Site Investigator	Data collection

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Federico Camilli	IRCCS Istituto delle Scienze Neurologiche di Bologna, UOSI Riabilitazione Sclerosi Multipla	Site Investigator	Data collection
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Ruggero Capra	Centro Sclerosi Multipla ASST Spedali Civili di Brescia, Ospedale di Montichiari	Site Investigator	Data collection
Rocco Capuano	Centro SM, I Clinica Neurologica, AOU-Policlinico, Università della Campania "Luigi Vanvitelli"	Site Investigator	Data collection
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Maria Grazia Celani	Azienda Ospedaliera di Perugia, SC di Neurofisiopatologia	Site Investigator	Data collection
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Raffaella Cerqua	Clinica Neurologica Ospedali Riuniti Ancona	Site Investigator	Data collection
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Marinella Clerico	Clinical and Biological Sciences Dept, University of Torino	Site Investigator	Data collection
Gaia Cola	Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine, Tor Vergata University, Rome, Italy	Site Investigator	Data collection
Antonella Conte	1) Department of Human Neurosciences, Sapienza, University of Rome. 2) IRCCS Neuromed, Pozzilli (IS)	Site Investigator	Data collection
Marta Zaffira Conti	USS Neuroimmunologia, ASST Papa Giovanni XXIII	Site Investigator	Data collection

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Name	Location	Role	Contribution
Christian Cordano	UCSF, San Francisco, USA	Site Investigator	Data collection
Susanna Cordera	SC Neurologia Ausl Valle D' Aosta	Site Investigator	Data collection
Francesco Corea	Neurologia, Ospedale San Giovanni, Foligno	Site Investigator	Data collection
Claudio Correale	AISM Vicenza Rehabilitation Service	Site Investigator	Data collection
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Maura Chiara Danni	Clinica Neurologica Ospedali Riuniti Ancona	Site Investigator	Data collection
Alessia d'Arma	IRCCS Fondazione Don Carlo Gnocchi ONLUS, Milano	Site Investigator	Data collection
Vincenzo Dattola	UOC Neurologia, Grande Ospedale Metropolitano "Bianchi Melacrino Morelli", Reggio di Calabria	Site Investigator	Data collection
Stefano de Biase	Neurology Unit, Ospedale dell'Angelo, Venezia-Mestre, Italy	Site Investigator	Data collection
Giovanna De Luca	MS Centre, Department of Clinical Neurology, SS. Annunziata, University Hospital, Chieti, Italy	Site Investigator	Data collection
Stefania Federica De Mercanti	Clinical and Biological Sciences Dept, University of Torino	Site Investigator	Data collection
Paolo De Mitri	Emergency Department, Guglielmo da Saliceto Hospital, Piacenza, Italy	Site Investigator	Data collection

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Name	Location	Role	Contribution
Nicola De Stefano	Department of Medicine, Surgery and Neuroscience, University of Siena, Italy	Site Investigator	Data collection
Marco Della Cava	AISM Padova Rehabilitation Service	Site Investigator	Data collection
Mario di Napoli	Centro Sclerosi Multipla Rieti (Rieti)	Site Investigator	Data collection
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Anna Dutto	Ospedale Savigliano Aslcn1	Site Investigator	Data collection
Luana Evangelista	Demyelinating Disease Center, San Salvatore Hospital, L'Aquila	Site Investigator	Data collection
Salvatore Fanara	Department of Biomedicine, Neurosciences and Advanced Diagnsotics; University of Palermo	Site Investigator	Data collection
Diana Ferraro	Department of Biomedical, Metabolic and Neurosciences, University of Modena and Reggio Emilia, Modena, Italy	Site Investigator	Data collection
Maria Teresa Ferrò	Neuroimmunology, Center for Multiple Sclerosis, ASST, Crema, Italy	Site Investigator	Data collection
Cristina Fioretti	UO Neurologia Livorno	Site Investigator	Data collection
Mario Fratta	II Clinica Neurologica, Università della Campania Luigi Vanvitelli, Naples	Site Investigator	Data collection
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Marzia Fronza	Centro Sclerosi Multipla, ATS Sardegna/ Dpt Scienze Mediche e Sanità Publica, Università di Cagliari, Cagliari	Site Investigator	Data collection
Roberto Furlan	Institute of Experimental Neurology, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milano, Italy, and Italian Neuroimmunology Association-AINI	Site Investigator	Data collection

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Name	Location	Role	Contribution
Alberto Gajofatto	Dipartimento di Neuroscienze, Biomedicina e Movimento, Università di Verona	Site Investigator	Data collection
Antonio Gallo	Centro SM, I Clinica Neurologica, AOU-Policlinico, Università della Campania "Luigi Vanvitelli"	Site Investigator	Data collection
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Anna Ghazaryan	UO Neurologia	Site Investigator	Data collection
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Francesca Gobbin	Dipartimento di Neuroscienze, Biomedicina e Movimento, Università di Verona	Site Investigator	Data collection
Flora Govone	Department of Neurology, Regina Montis Regalis Hospital, Mondovì (CN)	Site Investigator	Data collection
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Maria Grazia Grasso	IRCCS Fondazione Santa Lucia	Site Investigator	Data collection
Angelica Guareschi	Centro SM Fidenza (PR)	Site Investigator	Data collection
Clara Guaschino	Centro Sclerosi Multipla Ospedale di Gallarate, ASST della Valle Olona	Site Investigator	Data collection
Simone Guerrieri	Neurology Department, Multiple Sclerosis Center, San Raffaele Hospital, Milan	Site Investigator	Data collection
Donata Guidetti	Emergency Department, Guglielmo da Saliceto Hospital, Piacenza, Italy	Site Investigator	Data collection
Pietro Iaffaldano	Department of Basic Medical Sciences, Neurosciences and Sense Organs - University of Bari Aldo Moro	Site Investigator	Data collection

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Antonio Ianniello	Centro SM S.Andrea Dip. Neuroscienze Umane Sapienza Roma	Site Investigator	Data collection
Luigi Iasevoli	IRCCS Fondazione Santa Lucia	Site Investigator	Data collection
Daniele Imperiale	SC Neurologia1 Ospedale Maria Vittoria- Torino	Site Investigator	Data collection
Maria Teresa Infante	Neurologia ASL 1 imperiese	Site Investigator	Data collection
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Aniello Iovino	Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy	Site Investigator	Data collection
Giovanna Konrad	AISM Aosta Rehabilitation Service	Site Investigator	Data collection
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Roberta Lanzillo	Federico II University of Naples	Site Investigator	Data collection
Caterina Lapucci	DINOGMI Universita' di Genova	Site Investigator	Data collection
Luigi Lavorgna	Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, 80138 Naples, Italy;	Site Investigator	Data collection
Maria Rita L'Episcopo	Centro Sclerosi Multipla ospedale San Lazzaro (Alba, CN)	Site Investigator	Data collection
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Giuseppe Liberatore	Neuromuscular and Neuroimmunology Service, IRCCS Humanitas Clinical and Research Institute, Rozzano, Milan, Italy	Site Investigator	Data collection
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Marco Longoni	Local Health Agency of Romagna, Maurizio Bufalini Hospital (Cesena) - Neurology Unit	Site Investigator	Data collection
Leonardo Lopiano	Neurology II, Dept of Neuroscience, University of Turin	Site Investigator	Data collection

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Appendix 2 *(continued)*

Name	Location	Role	Contribution
Lorena Lorefice	Centro Sclerosi Multipla, ATS Sardegna/ Dpt Scienze Mediche e Sanità Publica, Università di Cagliari, Cagliari	Site Investigator	Data collection
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Davide Maimone	Centro SM - UOC Neurologia - ARNAS Garibaldi - Catania	Site Investigator	Data collection
Maria Malentacchi	SCDO Neurologia e Centro di Riferimento Regionale Sclerosi Multipla, AOU San Luigi - Orbassano (TO)	Site Investigator	Data collection
Giulia Mallucci	IRCCS Mondino Foundation, Pavia	Site Investigator	Data collection
Simona Malucchi	SCDO Neurologia e Centro di Riferimento Regionale Sclerosi Multipla, AOU San Luigi - Orbassano (TO)	Site Investigator	Data collection
Chiara Rosa Mancinelli	Centro Sclerosi Multipla ASST Spedali Civili di Brescia, Ospedale di Montichiari	Site Investigator	Data collection
Luca Mancinelli	Local Health Agency of Romagna, Maurizio Bufalini Hospital (Cesena) - Neurology Unit	Site Investigator	Data collection
Paolo Manganotti	Neurology Unit, Department of Medical, Surgical, and Health Sciences, Cattinara University Hospital, ASUGI, Trieste	Site Investigator	Data collection
Giorgia Teresa Maniscalco	Multiple Sclerosis Centre "A. Cardarelli Hospital", Naples, Italy	Site Investigator	Data collection
	Neurological Clinic and Stroke Unit "A. Cardarelli Hospital", Naples, Italy;	Site Investigator	Data collection
Vittorio Mantero	MS Center, ASST Lecco	Site Investigator	Data collection
Sabrina Marangoni	Ospedale Santa Chiara, Trento. UO Neurologia (Trento)	Site Investigator	Data collection
Damiano Marastoni	The Multiple Sclerosis Center of University Hospital of Verona Dept. of Neuroscience, Biomedicine and Movements	Site Investigator	Data collection

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Fabiana Marinelli	Ospedale Fabrizio Spaziani Frosinone	Site Investigator	Data collection
	Asl Frosinone	Site Investigator	Data collection
Alessandro Marti	UOC Neurologia- centro SM Reggio Emilia- AUSL-IRCSS RE	Site Investigator	Data collection
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Laura Mendozzi	IRCCS Fondazione Don Carlo Gnocchi ONLUS, Milano	Site Investigator	Data collection
Giuseppe Meucci	UO Neurologia Livorno	Site Investigator	Data collection
Silvia Miante	Multiple Sclerosis Centre of the Veneto Region (CeSMuV), University Hospital of Padua, Italy.	Site Investigator	Data collection
Giuseppina Miele	Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, 80138 Naples, Italy;	Site Investigator	Data collection
Eva Milano	SC Neurologia1 Ospedale Maria Vittoria- Torino	Site Investigator	Data collection
Massimiliano Mirabella	Fondazione Policlinico Universitario Agostino Gemelli IRCCS - Università Cattolica del Sacro Cuore	Site Investigator	Data collection
Rosanna Missione	II Clinica Neurologica, Università della Campania Luigi Vanvitelli, Naples	Site Investigator	Data collection
Marcello Moccia	Federico II University of Naples	Site Investigator	Data collection
Lucia Moiola	Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy	Site Investigator	Data collection
Sara Montepietra	Responsabile del Centro Sclerosi Multipla - Reggio Emilia- UOC Neurologia-AUSL-IRCSS RE	Site Investigator	Data collection

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Name	Location	Role	Contribution
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	Italy	Site Investigator	Data collection
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Riccardo Orlandi	Dipartimento di Neuroscienze, Biomedicina e Movimento, Università di Verona	Site Investigator	Data collection
Anna Palmieri	UO Neurologia, Treviso	Site Investigator	Data collection
Damiano Paolicelli	Department of Basic Medical Sciences, Neurosciences and Sense Organs - University of Bari Aldo Moro	Site Investigator	Data collection
Livia Pasquali	Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy	Site Investigator	Data collection
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Name	Location	Role	Contribution
Elisabetta Pedrazzoli	AISM Padova Rehabilitation Service	Site Investigator	Data collection
Maria Petracca	Federico II University of Naples	Site Investigator	Data collection
Alfredo Petrone	Ospedale Annunziata (Cosenza)	Site Investigator	Data collection
Carlo Piantadosi	UOC Neurologia - Azienda Ospedaliera "San Giovanni-Addolorata" - Roma	Site Investigator	Data collection
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	2. University of Milan, Dino Ferrari Center, Milan, IT.	Site Investigator	Data collection
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Marta Ponzano	Department of Health Sciences, University of Genoa, Genoa, Italy.	Biostatistician	Support in statistical analysis
Emilio Portaccio	Università degli Studi di Firenze, Dipartimento NEUROFARBA, Firenze	Site Investigator	Data collection
Mattia Pozzato	1. IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy. Via Francesco Sforza 35, 20122	Site Investigator	Data collection
	2. Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy. Via Francesco Sforza 35, 20122	Site Investigator	Data collection
Carlo Pozzilli	Centro SM S.Andrea Dip.Neuroscienze Umane Sapienza Roma	Site Investigator	Data collection
Luca Prosperini	Dept Neurosciences, San Camillo Forlanini Hospital - Rome	Site Investigator	Data collection
Alessandra Protti	ASST GOM NIGUARDA, DIPARTIMENTO NEUROSCIENZE	Site Investigator	Data collection
Paolo Ragonese	Department of Biomedicine, Neurosciences and Advanced Diagnsotics; University of Palermo	Site Investigator	Data collection
Sarah Rasia	Centro Sclerosi Multipla ASST Spedali Civili di Brescia, Ospedale di Montichiari	Site Investigator	Data collection

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Appendix 2 *(continued)*

Name	Location	Role	Contribution
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Maria Teresa Rilla	Neurologia ASL 1 imperiese	Site Investigator	Data collection
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Marco Ronzoni	ASST Rhodense	Site Investigator	Data collection
Marco Rovaris	IRCCS Fondazione Don Carlo Gnocchi ONLUS, Milano	Site Investigator	Data collection
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Lorenzo Saraceno	ASST GOM NIGUARDA, DIPARTIMENTO NEUROSCIENZE	Site Investigator	Data collection
Alessia Sartori	Department of Pharmacy, Ospedale Guglielmo da Saliceto, Piacenza , Italy	Site Investigator	Data collection
Arianna Sartori	Neurology Unit, Department of Medical, Surgical, and Health Sciences, Cattinara University Hospital, ASUGI, Trieste	Site Investigator	Data collection
Elvira Sbragia	DINOGMI Universita' di Genova	Site Investigator	Data collection
Giuditta Ilaria Scarano	1. Departement of Psycology, University of Milano-Bicocca, Milan, Italy	Site Investigator	Data collection
	2. Departement of Psychology, Franz Tappeiner Hospital, Merano, Italy	Site Investigator	Data collection
Valentina Scarano	UOC Neurologia e Stroke AORN San Giuseppe Moscati Avellino	Site Investigator	Data collection
Valentina Schillaci	MS Center, Department of Neuroscience, City of Health and Science University Hospital of Turin, Turin, Italy	Site Investigator	Data collection
Maria Sessa	UOC Neurologia, USS Neuroimmunologia, ASST Papa Giovanni XXIII	Site Investigator	Data collection
Caterina Sgarito	AISM Como Rehabilitation Service	Site Investigator	Data collection
Grazia Sibilia	NEUROLOGY UNIT AND MS CENTER, ASL NAPOLI 1 CENTRO, NAPLES, ITALY	Site Investigator	Data collection
Gabriele Siciliano	Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy	Site Investigator	Data collection
Alessio Signori	Department of Health Sciences, University of Genoa, Genoa, Italy.	Biostatistician	Support in statistical analysis
Elisabetta Signoriello	II Clinica Neurologica, Università della Campania Luigi Vanvitelli, Naples	Site Investigator	Data collection
Leonardo Sinisi	NEUROLOGY UNIT AND MS CENTER, ASL NAPOLI 1 CENTRO, NAPLES, ITALY	Site Investigator	Data collection
Francesca Sireci	UOC Neurologia- centro SM Reggio Emilia- AUSL-IRCCS RE	Site Investigator	Data collection
Patrizia Sola	Neurology Unit, Ospedale Civile, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy	Site Investigator	Data collection
Claudio Solaro	Dept. of Rehabilitation, CRRF "Mons. Luigi Novarese", Moncrivello, Italy	Site Investigator	Data collection
Stefano Sotgiu	Dipartimento di Scienze Mediche, Chirurgiche e Sperimentali - Università di Sassari	Site Investigator	Data collection
Maddalena Sparaco	Department of Advanced Medical and Surgical Sciences, University of Campania Luigi Vanvitelli, 80138 Naples, Italy;	Site Investigator	Data collection
Maria Laura Stromillo	Department of Medicine, Surgery and Neuroscience, University of Siena, Italy	Site Investigator	Data collection
Silvia Strumia	MS center, Neurology Unit, Morgagni-Pierantoni Hospital, Forlì	Site Investigator	Data collection

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Emanuela Laura Susani	ASST GOM NIGUARDA, DIPARTIMENTO NEUROSCIENZE	Site Investigator	Data collection
Giulietta Tabiadon	Multiple Sclerosis Outpt.Clinic, Clinical Neurology and Stroke Unit Dep., Central Country Hospital, Bolzano, Italy	Site Investigator	Data collection
Francesco Teatini	Multiple Sclerosis Outpt.Clinic, Clinical Neurology and Stroke Unit Dep., Central Country Hospital, Bolzano, Italy	Site Investigator	Data collection
Valentina Tomassini	1. Institute for Advanced Biomedical Technologies (ITAB), Department of Neurosciences, Imaging and Clinical Sciences, University G. d'Annunzio of Chieti-Pescara, Chieti, Italy	Site Investigator	Data collection
	2. MS Centre, Department of Clinical Neurology, SS. Annunziata University Hospital, Chieti, Italy	Site Investigator	Data collection
Simone Tonietti	Centro Sclerosi Multipla Ospedale San Carlo Borromeo (Milano)	Site Investigator	Data collection
Valentina Torri Clerici	Centro Sclerosi Multipla, U.O Neurologia IV, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano	Site Investigator	Data collection
Carla Tortorella	Dept Neurosciences, San Camillo Forlanini Hospital - Rome	Site Investigator	Data collection
Simona Toscano	Dipartimento Scienze Mediche e Chirurgiche e Tecnologie Avanzate, GF Ingrassia, Università di Catania; Centro Sclerosi Multipla Policlinico "G Rodolico"- San Marco, Università di Catania	Site Investigator	Data collection
Rocco Totaro	Demyelinating Disease Center, San Salvatore Hospital, L'Aquila	Site Investigator	Data collection
Maria Trotta	Ospedale Annunziata (Cosenza)	Site Investigator	Data collection
Gabriella Turano	Department of Neurology, Regina Montis Regalis Hospital, Mondovì (CN)	Site Investigator	Data collection
Monica Ulivelli	Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy	Site Investigator	Data collection

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Manzo Valentino	Neurological Clinic and Stroke Unit "A. Cardarelli Hospital", Naples, Italy;	Site Investigator	Data collection
Giovanna Vaula	Neurology II, AOU Città della Salute e della Scienza -Turin	Site Investigator	Data collection
Domizia Vecchio	Neurology Unit, Maggiore della Carità Hospital, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy	Site Investigator	Data collection
Marco Vercellino	MS Center, Department of Neuroscience, City of Health and Science University Hospital of Turin, Turin, Italy	Site Investigator	Data collection
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Marika Vianello	UO Neurologia, Treviso	Site Investigator	Data collection
Eleonora Virgilio	Neurology Unit, Maggiore della Carità Hospital, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy	Site Investigator	Data collection
Francesca Vitetta	Neurology Unit, Ospedale Civile, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy	Site Investigator	Data collection
Stefano Vollaro	Emergency Department, Guglielmo da Saliceto Hospital, Piacenza, Italy	Site Investigator	Data collection
Mauro Zaffaroni	Centro Sclerosi Multipla Ospedale di Gallarate, ASST della Valle Olona	Site Investigator	Data collection
Mauro Zampolini	Neurologia, Ospedale San Giovanni, Foligno	Site Investigator	Data collection
Ignazio Roberto Zarbo	Dipartimento di Scienze Mediche, Chirurgiche e Sperimentali - Università di Sassari	Site Investigator	Data collection
Luigi Zuliani	Department of Neurology - Ospedale San Bortolo - AULSS8 Berica Vicenza		Data collection

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