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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, $p = 0.04$).

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.

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

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[,3,] and suggesting a protective role of interferon.[,] 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. Therefore, even if all the studies agree that data available so far are overall reassuring, excluding major safety issues,[,,] 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. 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).

Table 1

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COVID-19 Data From the Surveillance Program in Italy

Statistical Analysis

The probability to be hospitalized, to be admitted to ICU, and to die was extracted from ISS data () 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 i tient 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 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.[11] 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%).

Table 2

Characteristics of Patients With MS

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, $p = 0.007$).

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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.

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 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 explained 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, $p = 0.17$).

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.

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 hospit[illegible]vents 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.

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.

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 (). 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 to estimates of 3.6% in a US cohort. 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 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 morbidities, 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 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[9] 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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Disclosure

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Footnotes

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