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ORIGINAL ARTICLE

The effect of air pollution on COVID-19 severity in a sample of patients with multiple sclerosis

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Abstract

Background and purpose: Some studies have shown that air pollution, often assessed by thin particulate matter with diameter below 2.5 μg/m^3 (PM2.5), may contribute to severe COVID-19 courses, as well as play a role in the onset and evolution of multiple sclerosis (MS). However, the impact of air pollution on COVID-19 has never been explored specifically amongst patients with MS (PwMS). This retrospective observational study aims to explore associations between PM2.5 and COVID-19 severity amongst PwMS.

Methods: Data were retrieved from an Italian web-based platform (MuSC-19) which includes PwMS with COVID-19. PM2.5 2016–2018 average concentrations were provided by the Copernicus Atmospheric Monitoring Service. Italian patients inserted in the platform from 15 January 2020 to 9 April 2021 with a COVID-19 positive test were included. Ordered logistic regression models were used to study associations between PM2.5 and COVID-19 severity.

Results: In all, 1087 patients, of whom 13% required hospitalization and 2% were admitted to an intensive care unit or died, were included. Based on the multivariate analysis, higher concentrations of PM2.5 increased the risk of worse COVID-19 course (odds ratio 1.90; $p = 0.009$).

Conclusions: Even if several other factors explain the unfavourable course of COVID-19 in PwMS, the role of air pollutants must be considered and further investigated.

KEYWORDS
air pollution, coronavirus, multiple sclerosis

INTRODUCTION

The first cases of SARS-CoV-2 infections were identified in Wuhan, China, in December 2019, and in February 2020 the disease caused by this novel coronavirus was officially named coronavirus disease 2019 (COVID-19) [1,2]. This virus rapidly spread all over the world and in March 2020 the World Health Organization declared a pandemic [3]. In Italy, the first cases of COVID-19 were reported in January 2020; clusters of infected individuals were shortly found in Veneto and Lombardy and in March 2020 the virus had already spread throughout Italy, reaching 105,792 cases at the end of the month [4,5]. In May 2021, Italy counted more than 4.1 million confirmed cases and more than 120,000 deaths [6]. However, the spread and severity of COVID-19 was not uniform amongst Italian regions [6,7] and air pollution has been identified as a possible co-factor to explain the highest lethality rates in north Italy [8]. Many studies have pointed out that air pollution may play a role in the severity of SARS-CoV-2 infections: exposure to particulate matter (PM), including PM2.5 (thin particulate matter with diameter below 2.5 μg/m^3), is linked to higher rates of COVID-19 mortality, hospitalization and intensive care unit (ICU) admission [9–13]. Although air pollution has been widely studied in the field of autoimmune diseases [14] and air pollutants have been identified as possible risk factors for MS onset and relapses [15–17], the impact of air pollution on COVID-19 severity has never been explored specifically amongst individuals with MS. The aim of this work consists in exploring the association between air pollution and COVID-19 severity specifically amongst MS patients, assessing air pollution by long-term exposures to PM2.5, which is the principal pollutant that impacts on human health.

METHODS

Demographic and clinical characteristics about COVID-19 severity were extracted from an Italian web-based platform (MuSC-19 project) containing clinician-reported data from 118 Italian MS centres. Details about data sharing agreements and ethical committee approval as well as about the variables collected in the platform and the

imputation methodology used to account for missing baseline characteristics have already been explained elsewhere [18]. Concerning environmental data, PM2.5 ground-level concentrations were derived from air quality model results, as provided by the Copernicus Atmospheric Monitoring Service [19], in correspondence with the place of exposure to SARS-CoV-2 reported by the patients. In particular, it is mainly the long-term exposure to bad air quality that can cause damage and weaken the cardiovascular and respiratory systems [20]. As such, in this study the PM2.5 yearly average for the 3-year period ending in 2018, which consists of the last year with available validated data, was considered. Adult MS patients with available PM2.5 concentrations and with a positive test (reverse transcription polymerase chain reaction on nasal and pharyngeal swabs) for SARS-CoV-2 or a positive serological test obtained at any point during the observation period (15 January 2020 to 9 April 2021) were included. Demographic and MS characteristics were presented as mean with standard deviation (SD), median with interquartile range (IQR = Q3–Q1) and number and percentage, depending on the nature of the variables. COVID-19 severity was defined on three levels as mild course, hospitalization and ICU admission or death. Ordered logistic regression models were used to study the association between PM2.5 and COVID-19 severity, running univariate models as well as a multivariate model controlling for the most relevant variables, also adjusting for geographical area (north, centre and south Italy) as a sensitivity analysis. Additionally, as a sensitivity analysis, ordered logistic regression models (univariate and multivariate) were also run using tertiles of PM2.5 concentrations, and interactions of PM2.5 with body mass index and with the presence of at least one comorbidity were investigated. In order to perform the ordered logistic regression models, the assumption of proportional odds was first checked for.

TABLE 1 Baseline demographic and clinical characteristics of included patients

	Confirmed COVID-19 *N* = 1087
Age, mean (SD)	44.14 (12.20)
Female sex, *N* (%)	747 (68.7%)
BMI, mean (SD)	24.19 (5.22)
Presence of comorbidities, *N* (%)	213 (19.6%)
MS phenotype, *N* (%)	
Primary progressive	55 (5.1%)
Relapsing–remitting	929 (85.5%)
Secondary progressive	103 (9.5%)
MS disease duration, median (IQR)	8.57 (3.42–15.32)
EDSS, median (IQR)	2 (1–3.5)
MS treatment, *N* (%)	
Untreated	153 (14.1%)
Interferon	108 (9.9%)
Glatiramer-acetate	90 (8.3%)
Teriflunomide	71 (6.5%)
Dimethyl-fumarate	194 (17.9%)
Natalizumab	138 (12.7%)
Fingolimod	126 (11.6%)
Anti-CD20	148 (13.6%)
Other	59 (5.4%)
Previous methylprednisolone, *N* (%)	30 (2.8%)
COVID-19 course, *N* (%)	
Mild	921 (84.7%)
Hospitalization	143 (13.2%)
ICU or death	23 (2.1%)

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; EDSS, Expanded Disability Status Scale; ICU, intensive care unit; IQR, interquartile range; MS, multiple sclerosis.

RESULTS

On 9 April 2021, 1087 PwMS with confirmed COVID-19 infection and with available PM2.5 exposure levels had completed their follow-up (full recovery or death) and were thus included. Baseline demographic and clinical characteristics of the cohort are presented in Table 1. The median age was 45 years (IQR 35–53), 68.7% of the patients were females and 14.6% were in a progressive phase. 934 (85.9%) patients were treated at the time of COVID-19 onset and the most used disease modifying therapy was dimethyl fumarate (17.9%). Most of the patients had a mild COVID-19 course (84.7%), 13.2% required hospitalization and 23 (2.1%) were admitted to the ICU or died (Table 1). Concentrations of PM2.5 were quite heterogeneous and are shown in Figure 1. The highest levels are clearly concentrated in the north of Italy (Po valley). Univariate and multivariate analysis evaluating factors associated with a risk of a severe COVID-19 are reported in Table 2. The results confirmed previous findings [18], indicating older age, higher Expanded Disability Status Scale, male sex and the presence of comorbidities as risk factors with a significant effect on the risk of severe COVID-19. Additionally, patients with progressive MS were at higher risk of severe COVID-19 compared to patients with relapsing–remitting MS ($p < 0.001$) based on the univariate analysis (results not shown). Amongst the disease modifying therapies, the effect of anti-CD20 that emerged in previous analyses [18] is also confirmed (odds ratio [OR] 1.84, $p = 0.038$) versus no treatment. A strong protective effect of interferon [21] is now confirmed (OR 0.30, $p = 0.016$) and a protective role of teriflunomide is also emerging (OR 0.36, $p = 0.041$) in this larger dataset. In the univariate analysis PM2.5 concentrations were not significantly associated with COVID-19 severity ($p = 0.09$), but after controlling for the other relevant variables higher concentrations of PM2.5 were significantly associated with increased odds of developing a worse COVID-19 prognosis (OR 1.90; $p = 0.009$). Results remained consistent when third versus first tertiles of PM2.5 concentrations were compared (Table 3). Also when geographical area was additionally adjusted for, a significant difference comparing third versus first tertiles of PM2.5 concentrations was found (OR 1.85; p value 0.017). No significant interactions of PM2.5 with body mass index or with the presence of comorbidities were found.

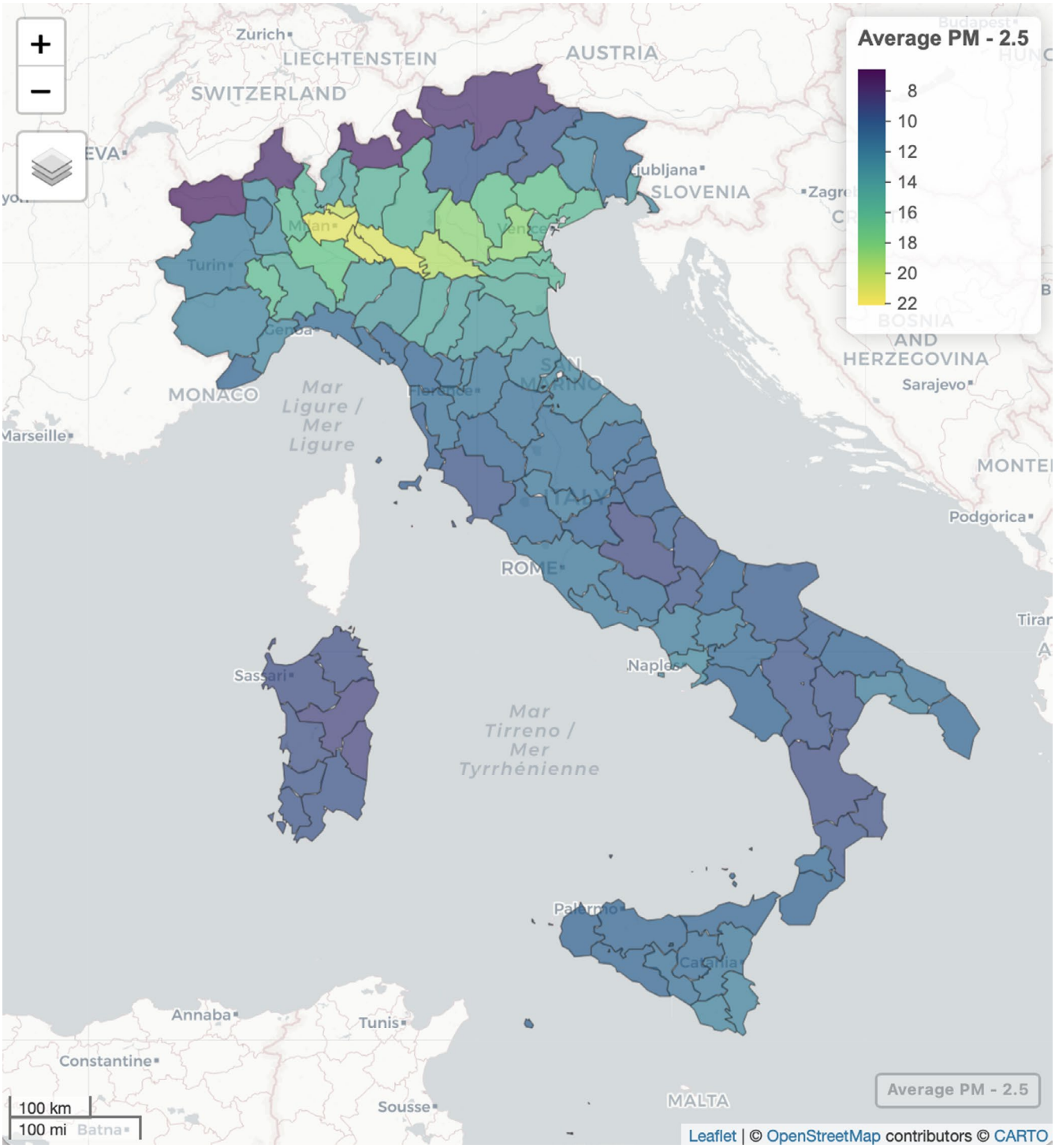

FIGURE 1 PM2.5 2016–2018 average concentrations in Italy [Colour figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

Air pollution is a major environmental cause of morbidity and mortality worldwide. Being a serious risk factor of respiratory infections and/or aggravation of existing pulmonary and cardiac diseases, it is responsible for about 4 million deaths each year [22]. In the past, during the 2003 SARS outbreak in the Republic of China, SARS patients from regions with high air pollution levels had a significantly higher risk of dying compared to those from regions with low air pollution [23]. The new SARS (SARS-CoV-2) can result in a self-limiting disease in about 80% of patients, but the remaining 20% get complicated by serious pneumonia with acute respiratory distress syndrome [24,25] possibly leading to death [26]. The rapid pandemic spread has involved all world countries [27], and Italy has emerged as one of the most affected countries with a very high number of deaths, the majority of which are in northern regions

TABLE 2 Univariate and multivariate ordinal logistic regression models evaluating risk factors for severe coronavirus disease 2019

	Univariate analysis		Multivariate analysis	
Variable	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
PM2.5 (10-unit)	1.44 (0.94–2.21)	0.09	1.90 (1.18–3.06)	0.009
Age (10-years increase)	2.14 (1.83–2.51)	<0.001	1.66 (1.36–2.03)	<0.001
Sex: male vs. female	1.60 (1.13–2.24)	0.007	1.47 (1.01–2.14)	0.045
EDSS	1.44 (1.33–1.55)	<0.001	1.17 (1.06–1.29)	0.002
MS treatment				
Untreated	1.00 (ref)	—	1.00 (ref)	—
Interferon	0.15 (0.06–0.38)	<0.001	0.30 (0.12–0.80)	0.016
Glatiramer-acetate	0.41 (0.20–0.83)	0.013	0.79 (0.36–1.73)	0.56
Teriflunomide	0.24 (0.10–0.60)	0.002	0.36 (0.14–0.96)	0.041
Dimethyl-fumarate	0.28 (0.16–0.51)	<0.001	0.75 (0.38–1.49)	0.41
Natalizumab	0.23 (0.11–0.47)	<0.001	0.74 (0.33–1.67)	0.47
Fingolimod	0.46 (0.25–0.84)	0.012	0.82 (0.41–1.61)	0.56
Anti-CD20	1.03 (0.62–1.71)	0.90	1.84 (1.03–3.26)	0.038
Other	0.55 (0.25–1.18)	0.12	0.59 (0.25–1.38)	0.23
Comorbidities: yes vs. no	4.29 (3.01–6.12)	<0.001	2.55 (1.70–3.82)	<0.001
Methylprednisolone: yes vs. no	2.40 (1.09–5.30)	0.030	2.05 (0.86–4.91)	0.11

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OR, odds ratio; PM2.5, particulate matter with diameter below 2.5 μg/m^3.

TABLE 3 Univariate and multivariate ordinal logistic regression models evaluating PM2.5 tertiles concentrations and the risk of severe COVID-19

	Univariate analysis		Multivariate analysis	
Variable	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p* value**
PM2.5 <11.57	1.00 (ref)	—	1.00 (ref)	—
PM2.5 11.57–15.55	0.92 (0.60–1.39)	0.68	1.09 (0.69–1.73)	0.71
PM2.5 ≥15.72	1.43 (0.97–2.10)	0.07	1.92 (1.24–2.97)	0.003

Note: Multivariate analysis included age, sex, EDSS, MS treatment, presence of at least one comorbidity and methylprednisolone use.

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; OR, odds ratio; PM2.5, particulate matter with diameter below 2.5 μg/m^3.

where air quality is a major concern. In the Po valley in northern Italy, PM concentrations are elevated due to high anthropogenic emissions, peculiar geographical features (the natural barrier of the Alps extending north) and low wind speed, which favour the accumulation of air pollutants. Recent studies indicated that acute and chronic exposure to air pollution is related to the incidence, prevalence, severity and mortality of COVID-19 [28]. Amongst air pollutants, PM2.5 is more toxic since it is easily respirable and can deposit more deeply in the lungs than larger particles [29]. The exposure to high levels of PM2.5 was associated with the risk of having autoimmune inflammatory diseases [14], as well as with the risk of MS developing [15] and exacerbations [30]. Taking into account

the above separately analysed relationships between air pollution exposure, MS and mortality from COVID-19, studying the different severities of COVID-19 infection in a large cohort of MS patients in relation to their previous exposure to air pollutants was considered. Our findings do not reveal a higher occurrence of severe COVID-19 infection in MS patients living in highly polluted areas but suggest that a high concentration of air pollutants might be a relevant co-factor of risk of unfavourable COVID-19 evolution when associated with the other already known risk factors, indicating that air pollutants could exert an additional impact on patients suffering from MS. This could occur through various mechanisms related not only to respiratory impairment but also to the inflammatory up-stimulation leading to the dreaded cytokine storm syndrome [31]. Air pollutants inhaled in the lower respiratory tract may stimulate lung resident dendritic cells (DCs) and, after migration to bronchial associated lymphoid tissue, induce a pro-inflammatory response with generation of Th17 cells and enhance their migratory properties, ultimately leading to inflammatory exacerbations [32]. This observation parallels previous evidence in experimental autoimmune encephalomyelitis, the animal model of MS, of a primary role of the lung in licensing auto-reactive lymphocytes to enter the central nervous system by boosting their migratory properties [33]. PM could increase interleukin 1beta (IL1beta), IL6 and IL23 production by DCs and enhance DC-dependent generation of IL17-producing T cells [32]. Finally, air pollution might trigger epigenetic changes, especially DNA methylation alterations, resulting in pro-inflammatory cytokine production [33]. In this regard and remembering that one of the factors associated with a severe evolution of COVID-19 is being overweight, it is interesting to note that the effects of PM exposure on the methylation of clock genes is particularly enhanced in subjects with obesity [34]. To conclude, chronic exposure to nanoparticles such as PM2.5, that are smaller than cells and their organelles, can contribute to the damage of lungs, heart and other organs and make them more vulnerable to viral attack, especially in elderly and fragile individuals [29]. Furthermore, the exposure to atmospheric pollution could induce modifications of the immune system, favouring pro-inflammatory and auto-aggressive responses leading to severe evolution of COVID-19, until death. Even if several other factors (comorbidities, genotype, gender–age composition, population density and mobility, socioeconomic status, different communities' behaviours, ICU availability) [35] may explain the unfavourable course of COVID-19, the role of air pollutants deserves to be taken into consideration and further investigated. Future research should surely take into consideration more pollutants than just PM2.5, in order to evaluate the complex nature of pollution as an environmental mixture. Additionally, this research can be improved by retrieving more details on the place of exposure of the patients: patient-reported place of infection to COVID-19 has been collected, but retrieving data about where they lived for the longest time would certainly be more appropriate for assessing their long-term exposure since it is possible that in the last few years some patients have moved or changed habits concerning regularly frequented places.

CONFLICT OF INTEREST

R. Bergamaschi has served on scientific advisory boards for Biogen, Merck-Serono, Novartis, Sanofi-Genzyme; received research support from Almirall, Bayer, Biogen, Merck-Serono, Novartis, Sanofi-Genzyme; received support for travel and congress from Biogen, Roche, Merck-Serono, Sanofi-Genzyme, Teva; received honoraria for speaking engagements from Biogen, Merck-Serono, Novartis, Sanofi-Genzyme. M. Filippi is Editor-in-Chief of the *Journal of Neurology*, Associate Editor of *Human Brain Mapping*, Associate Editor of *Radiology* and Associate Editor of *Neurological Sciences*; received compensation for consulting services and/or speaking activities from Alexion, Almirall, Bayer, Biogen, Celgene, Eli Lilly, Genzyme, Merck-Serono, Novartis, Roche, Sanofi, Takeda and Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Roche, Teva Pharmaceutical Industries, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla and ARiSLA (Fondazione Italiana di Ricerca per la SLA). He received speaker honoraria from the following companies: Biogen, Merck, Novartis, Roche, Sanofi-Genzyme and TEVA. M. Radaelli received speaker honoraria from Biogen Idec, Sanofi-Genzyme, Novartis and Merck Serono and funding for travel to scientific meetings from Biogen Idec, Sanofi-Genzyme, Novartis, Merck Serono, Teva and Roche. P. Immovilli reports personal fees from Roche, personal fees from Biogen, personal fees from Merck, outside the submitted work. M. Capobianco reports personal fees and non-financial support from Biogen, personal fees and non-financial support from Merck Serono, personal fees and non-financial support from Roche, personal fees and non-financial support from Novartis, personal fees and non-financial support from Sanofi, personal fees from Almirall, outside the submitted work. N. De Rossi received speaker honoraria from Biogen Idec, Genzyme, Novartis, Sanofi-Aventis; received funding for participation in advisory boards to Novartis, Biogen and Genzyme-Sanofi and for travel to scientific meetings from Biogen Idec, Teva, Sanofi-Genzyme, Roche, Almirall and Novartis. P. Confalonieri has received honoraria for speaking or consultation fees from Novartis and Biogen, has received funding for travel to attend scientific events or speaker honoraria from Merck Serono, Biogen Idec, Teva and Roche. He has also received institutional research support from Merk Serono, Novartis and Roche. He is also principal investigator in clinical trials for Biogen, Merck Serono, Roche. M. Inglese received research grants from NIH, DOD, NMSS, FISM and Teva Neuroscience; received fees for participating in advisory boards from Roche, Biogen, Merck and Genzyme. M. Trojano reports grants and personal fees from Biogen, grants and personal fees from Novartis, grants and personal fees from Roche, grants and personal fees from Merck, personal fees from Sanofi, personal fees from TEVA, outside the submitted work. V. Brescia Morra has received funding for travel, speaker honoraria, advisory board and research support from Merck Serono, Novartis, Biogen Idec, TEVA, Genzyme, Roche, Bayer, Almirall. G. Comi reports personal fees from Novartis, Teva Pharmaceutical Industries Ltd, Teva Italia Srl, Sanofi Genzyme, Genzyme Corporation, Genzyme Europe, Merck KGaA, Merck Serono SpA, Celgene Group, Biogen

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AUTHOR CONTRIBUTIONS

Roberto Bergamaschi: Conceptualization (equal); methodology (equal); supervision (equal); writing—original draft (equal); writing—review and editing (equal). Marta Ponzano: Conceptualization (equal); data curation (equal); methodology (equal); writing—original draft (equal); writing—review and editing (equal). Irene Schiavetti: Conceptualization (equal); data curation (equal); methodology (equal); writing—review and editing (equal). Luca Carmisciano: Conceptualization (equal); data curation (equal); writing—review and editing (equal). Cinzia Cordioli: Conceptualization (equal); writing—review and editing (equal). Massimo Filippi: Conceptualization (equal); writing—review and editing (equal). Marta Radaelli: Conceptualization (equal); writing—review and editing (equal). Paolo Immovilli: Conceptualization (equal); writing—review and editing (equal). Marco Capobianco: Conceptualization (equal); writing—review and editing (equal). Nicola De Rossi: Conceptualization (equal); writing—review and editing (equal). Giampaolo Brichetto: Conceptualization (equal); writing—review and editing (equal). Eleonora Cocco: Conceptualization (equal); writing—review and editing (equal). Cinzia Scandellari: Conceptualization (equal); writing—review and editing (equal). Paola Cavalla: Conceptualization (equal); writing—review and editing (equal). Ilaria Pesci: Conceptualization (equal); writing—review and editing (equal). Antonio Zito: Conceptualization (equal); writing—review and editing (equal). Paolo Confalonieri: Conceptualization (equal); writing—review and editing (equal). Girolama Alessandra Marfia: Conceptualization (equal); writing—review and editing (equal). Paola Perini: Conceptualization (equal); writing—review and editing (equal). Matilde Inglese: Conceptualization (equal); writing—review and editing (equal). Maria Trojano: Conceptualization (equal); writing—review and editing (equal). Vincenzo Brescia Morra: Conceptualization (equal); writing—review and editing (equal). Enrico Pisoni: Conceptualization (equal); writing—review and editing (equal). Gioacchino Tedeschi: Conceptualization (equal); writing—review and editing (equal). Giancarlo Comi: Conceptualization (equal); writing—review and editing (equal). Mario Alberto Battaglia: Conceptualization (equal); writing—review and editing (equal). Francesco Patti: Conceptualization (equal); writing—review and editing (equal). Marco Salvetti: Conceptualization (equal); writing—review and editing (equal). Maria Pia Sormani: Conceptualization (equal); data curation (equal); methodology (equal); supervision (equal); writing—original draft (equal); writing—review and editing (equal). Study MuSC-19: Conceptualization (equal); writing—review and editing (equal).

ETHICAL APPROVAL

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 (AIFA).

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

[Correction added on 15 December 2021, after first online publication: Supporting information containing list of contributors in MuSC-19 study group has been added.]

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