# Signs and symptoms of Covid-19 in patients with multiple sclerosis

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**Abstract**

Background: Clinical outcomes of MS patients affected by Covid-19 have been deeply investigated, but a further analysis on main signs and symptoms and their risk factors still need attention.

Objective: The objective of this study is to group together based on similarity and describe the most common signs and symptoms of Covid-19 in MS patients and identify all factors associated with their manifestation.

Method: Logistic and linear regression models were run to recognize factors associated to each pooled group of symptoms and to their total number.

Results: From March 2020 to November 2021, data were collected from 1354 MS patients with confirmed infection of Covid-19. Ageusia and anosmia was less frequent in older people (OR:0.98; p=0.005) and more in smoker patients (OR:1.39; p=0.049). Smoke was also associated with an increment number of symptoms (OR:1.24; p=0.031); substance abuse (drugs or alcohol); conjunctivitis and rash (OR:5.20; p=0.042), and presence of at least one comorbidity with shortness

of tachycardia, or chest pain (OR:1.24; p=0.008). Some DMTs were associated with greater frequencies of certain Covid-19 symptoms (association between anti-CD20 therapies and increment of the number of concomitant symptoms: OR:1.29; p=0.05). Differences in frequencies among three waves were found for flu-like symptoms (G1, $p = 0.024$), joint or muscle pain (G2, $p = 0.013$), and ageusia and anosmia (G5, $p < 0.001$). All cases should be referred to variants up to the Delta.

Conclusion: Several factors, along with the choice of specific therapeutic approaches might have a different impact on the occurrence of some Covid-19 symptoms.



**Introduction**

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), responsible for coronavirus disease 2019 (Covid-19) pandemic, has a course extremely variable, with cases ranging from asymptomatic to mild, moderate, severe as well as critical or fatal[1].

Symptoms usually appear within the first two weeks after exposure to the virus and some are more likely to be associated with Covid-19 than others. The clinical manifestations of Covid-19 are mainly fever or chills, cough, anosmia and ageusia, and difficulty breathing, but a variety of other symptoms are also involved: sore throat, loss of appetite, extreme fatigue, tiredness, headache, body aches, nausea, vomiting, and diarrhoea[2].

However, new and unusual signs and symptoms have been found in newly infected patients from the beginning of the pandemic to date, following continuing viral mutations[3].

The association between symptoms and disease severity has already been explored in the general population: a recent study on 531 patients analyzed difference in symptoms of coronavirus disease among hospitalized and non-hospitalized patients: shortness of breath is more common in hospitalized patients than in those with mild forms of the disease, whereas fatigue, headache, and myalgia are mostly reported by not hospitalized subjects.[4]

For containing pandemic transmission, an early diagnosis is essential, by identifying sentinel symptoms so that infected persons can self-isolate themselves just before they get contagious and start spread the virus.[5]

However, due to their high non-specificity, neither the presence nor the absence of a singular symptom can be considered indicative of Covid-19 disease.[6]

Some particular Covid-19 symptoms are often related and tend to appear together, therefore combined into specific groups may predict Covid-19 very accurately.[7]

In Italy are counted more than 120000 people with multiple sclerosis (MS)[8], most of them treated with disease modifying therapies which alter the components of the immune system and are associated with a greater infectious risk, especially viral.[9] In addition, the association between dysimmune phenomena underlying MS and the defective control of some pathogens has driven researchers around the world to focus on clinical outcomes in MS patients affected by Covid-19.[10,11,12,13,14] However, a more in-depth analysis focusing on the major signs and symptoms and related risk factors for their occurrence still require further examination. This is even more so since a widely comprehension of main symptoms present during infection is essential for providing advice and monitoring the severity of long-term symptoms.[15]

The aim of this study is to identify and group for similarity the most common signs and symptoms of Covid-19 and evaluate all factors associated with their manifestation.

## Methods

All demographic and clinical information were extracted from a dedicated web-based platform set up for the Italian MuSC-19 project, that collect clinical-reported data regarding the impact of Covid-19 infection on people affected by MS. Missing data on baseline characteristics were replaced with a procedure of multiple imputation by chained equations algorithm, as detailed elsewhere.[10]

Patients with a detailed history of MS and a confirmed (by reverse transcription–Polymerase Chain Reaction or serological test) symptomatic Covid-19 infection were included in the sample.

Descriptive data were presented as mean with standard deviation (SD), median with range or interquartile range (IQR) for continuous variables, and number with percentage, for categorical variables, as appropriate.

Symptoms collected in MuSC-19 registry were based on patient reports along with physical examination performed during the routine visit. All of them were referred as symptoms associated with Covid infection, so presenting during or soon after Covid, and therefore they are supposed not to be present before Covid.

Symptoms were pooled as per similarity into categories as proposed in a previous work[16] and the degree of agreement between different groups of symptoms was measured by Cohen's kappa.

A patient was positive for a symptom group if he/she had at least one of the symptoms listed in that group.

Univariate and subsequent logistic regression models were run to recognize all factor associated to each group of symptoms, by controlling for baseline characteristics.

In addition, univariate and following multivariate linear regression models were applied to identify all predicting factors for an increase in the total number of symptom groups. Only variables which have previously resulted significantly associated with at least one group of symptoms were included in the model as independent factors.

Finally, an analysis on distribution of symptom groups among three pandemic waves was performed for discussing any differences in their frequencies of comparison (Chi square test).

The study was approved by the Regional Ethics Committee of Liguria (University of Genoa) (n 130/2020 – DB id10433) and on a national level by Agenzia Italiana del Farmaco (AIFA).

**Results**

From March 2020 to November 2021, data were collected from 2112 MS patients in care at 121 Italian Sites. Of them 1354 had a confirmed infection of Covid-19, presented at least one sign or symptom of disease, and showed a completed follow up until recovery (98.6%) or death (1.4%).

The mean age was 43.8 years (IQR: 34.0 – 53.0), 67.3% were females and, of them, pregnancy was reported in 2%.

On average, patients lived with 2 cohabitants, without children (IQR: 0.0 – 1.0) and with another one Covid-19 positive cohabitant besides them (IQR: 0.0 – 2.0).

As about lifestyle-related factors, 198 (14.6%) were current smokers, 260 (19.2%) were former, and 896 (66.2%) had never smoked. Alcohol was consumed by 56.0% of patients, with regular consumption in 2.0%. Abuse of substance, defined by the National Cancer Institute as "the use of illegal drugs or the use of prescription or over-the-counter drugs or alcohol for purposes other than those for which they are meant to be used, or in excessive amounts" was reported by 25 patients (1.8%).

Patients had a median EDSS of 2 (IQR: 1–3.5), and the proportion of progressive patients was 13.8%. One thousand one hundred and fifty-two (85.1%) patients were treated with a DMT, recent use of methylprednisolone was declared for 84 patients (6.2%). About two-thirds of patients (72.1%) had no comorbidities.

Covid-19 severity was defined by three levels: 1152 (85.1%) patients with mild disease not requiring hospitalization, 173 (12.8%) cases of pneumonia and/or hospitalization, and 29 (2.1%) admission in intensive care unit and/or death. (Table I)

Reported symptoms were grouped as follows:

- Group 1 (G1): Fever, chills, dyspnoea, cough, sputum production, lymph nodes enlarged, tonsil swelling, throat congestion, nasal congestion, sore throat, cold
- Group 2 (G2): Arthralgia, myalgia, bone joint, back pain
- Group 3 (G3): Shortness of breath, tachycardia, chest pain
- Group 4 (G4): Vomiting, nausea, diarrhoea, abdominal pain, loss of appetite, loss of weight, other gastrointestinal symptoms
- Group 5 (G5): Ageusia, anosmia
- Group 6 (G6): Symptoms of anxiety and depression, insomnia, headache, drowsiness, difficulty sleeping, loss of concentration, weakness, fatigue, asthenia
- Group 7 (G7): Conjunctivitis, rash

The frequency of occurrence of singular and grouped symptoms is reported in Figure 1, whereas table II details their grade of agreement.

Patients declared nearly three groups of symptoms (mean: 2.7, range 1 – 7). The most common was G1 in 1211 patients (89.4%), followed by G6 in 841 (62.1%) of the patients. None or slight agreement (Cohen's Kappa < 0.20) for each pairwise comparison was found (except a fair agreement between G2 and G6), confirming their independence from each other.

Figure 2 reports results from multivariate models regarding factors associated to each group of symptoms and factors associated to an increased number of symptoms

Males showed a lower risk for developing joint or muscle pain (G2) and gastrointestinal symptoms (G4) and for having an increment in the total number of symptom groups (OR: 0.86, 95%CI: 0.74 – 0.99; p = 0.037).

Ageusia and anosmia (G5) were less frequently reported in older people (OR: 0.98, 95%CI: 0.97-0.99; p = 0.005) and more common in smoker patients (OR: 1.39, 95%CI: 1.00 – 1.94; p = 0.049).

In addition, smoking habit demonstrated to be a risk factor for developing an increment in the total number of symptom groups (OR: 1.24, 95%CI: 1.02 – 1.51; p = 0.031).

Substance abuse was associated with the occurrence of greater frequency of conjunctivitis and rash (G7) (OR: 5.20, 95%CI: 1.06 – 25.54; p = 0.042), whereas the presence of at least one comorbidity was associated with shortness of breath, tachycardia, or chest pain (G3) (OR: 1.24; 95%CI:1.06 - 1.45; p = 0.008).

An increasing MS disease duration and EDSS were significantly associated with lower occurrences of several symptoms (G2, G4, G5, G6).

The use of some classes of MS therapies seems to be associated to the presence of some groups of symptoms, in particular the infusion of anti-CD20 therapies resulted to be associated with an increment of the number of concomitant symptoms (OR: 1.29, 95%CI: 1.00 - 1.67; p = 0.05).

Twenty-four patients (1.8%) resulted to be previously immunized against Covid-19. There were no differences in the frequency of occurrence of any of the symptom groups studied between vaccinated and unvaccinated patients before infection (always p>0.10, data not shown).

Figure 3 illustrates the distribution of group of symptoms during the three pandemic waves.

In all the waves the most frequent groups of signs and symptoms were fever and flu-like symptoms, although less commons in the second wave (87.9%) compared to the first (93.4%) and third (92.6%) (p = 0.024). Then, for all three waves, "mental" symptoms (G6) were very common (>50% of patients), followed by ageusia and anosmia in the first wave (36.8%) and joint/muscle pain in the second (39.8%) and third waves (44.3%).

In addition, differences in frequencies among three waves were found for joint or muscle pain (G2, p =0.013), and ageusia and anosmia (G5, p < 0.001) (Table III).

Finally, all cases should be referred to variants up to the Delta. Indeed, Omicron has been detected for the first time in Italy on November 11th 2021 and data are collected just from March 2020 to November 2021.

**Discussion**

A recent review state the most common symptoms were fever (68.8%), followed by cough (63.9%), fatigue/asthenia (51.2%). [17] The present study report in the same order fever and cough (89.4%), and fatigue and asthenia together with other "neurological" symptoms (62.1%). However, other than fatigue (48.8%) and headache (34.0%), there are few CNS symptoms, even in MS .

Several associations between comparison of some group of symptoms and other characteristics have been detected.

Males are less likely to develop some symptoms (i.e., bone and joint pain and gastrointestinal symptoms) and generally have a minor set of symptoms than females. In a self-reported survey, females declared a significantly higher frequency of gastrointestinal symptoms during Covid-19 compared to men[18].

Even the age influences the frequency of manifestation of some symptoms. In particular, the risk of developing anosmia decreased with the increasing age.[19] However, this result could be explained because unawareness of olfactory dysfunction may increase with older age.[20] In contrast, as age increases, the probability of shortness of breath, tachycardia, and chest pain increases. This symptomology is also much more common in subjects with pre-existing conditions.[21]

The effect of substance abuse on eyes and skin, already observed in other studies not Covid-19 related, is noticeable.[22,23]

Smoking plays an important role on amplifying the cases of ageusia and anosmia, with an increment trend from former to current smokers.[24] Also interesting is the effect (although not fully significant) on bone/joint pain and respiratory distress.

The impact of current smoking on Covid-19 progression is debated. Two systematic review published at the beginning of the pandemic described the relationship between smoking and Covid-19 suggesting the absence of association between active smoking and enhanced risk of Covid-19 progressing.[25,26] Subsequent papers have illustrated the most methodological problems with these studies (i.e. lack of detailed assessments of dose and duration for smoking, missing data), and promoted a worse Covid-19 progression and outcomes in smokers compared to other persons.[27,28]

In the present study, smoking is shown to be a risk factor in increasing the number of multiple symptoms that occur during Covid-19.

The association between lower EDSS and the presence of some symptoms is probably due to an already underlying presence of some common symptoms in most critical MS patients, which consequently for them were not reported.

Teriflunomide, natalizumab and fingolimod appear to have some sort of protective role in the development of shortness of breath, tachycardia, and chest pain, whereas the role of anti-cd20 in increasing the likelihood of neurological disorders (G6) and the occurrence of conjunctive and rash (G7) as well as determining increases in the total number of concomitant symptom groups, is interesting.

Patients in dimethyl-fumarate seems to increase flu or flu-like symptoms, a common effect already reported in other studies.[29]

It was demonstrated that interferon-alpha interferes with the normal regenerative processes of the olfactory mucosa, cause depletion of oligominerals (such as zinc) involved in both taste and smell perception and exert a neurotoxic action.[30] Higher cases of anosmia and ageusia in the present study have been found in patient treated with Interferon. Similar cases of association between loss of the sense of smell and loss of the sense of taste associated with the use of interferon have been reported in the medical literature. [31,32,33]

To date few studies have investigated and described clinical characteristics of COVID-19 patients by comparing the three waves.[34,35]

The period between the second and third wave does not correspond to a new increase in cases but rather to a long stagnation.[36]

A further analysis on symptoms distribution among the three pandemic waves showed some differences. The cause for these variations is not yet identified, although different Covid-19 variants may explain it.[37], even if Omicron seems to be detected for the first time after the follow up period of this study. In addition, unfortunately, this study has not collected the molecular characterization of the Covid infection, and therefore it is not possible to know the strains of each infection.

In addition, also the new treatments for patients introduced starting from the second wave may also have played a role in symptoms reshuffling.[38]

Knowing possible risk factors, modifying some lifestyle behaviors and more accurately analyze the choice of certain therapeutic approaches might minimize the occurrence of Covid-19 symptoms.

## 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).

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## Availability of data

The data that support the findings of this study are available from the corresponding author upon reasonable request

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**Table I - Baseline characteristics**

| | |
|---|---|
| Sex, females | 911 (67.3%) |
| Age, mean±S.D. | 43.8 ± 12.29 |
| Pregnancy (N = 911 females) | 18 (2.0%) |
| Number of cohabitants, median (IQR) | 2.0 (1.0 - 3.0) |
| Number of cohabitant children, median (IQR) | 0.0 (0.0 - 1.0) |
| Number of Covid positive cohabitants, median (IQR) | 1.0 (0.0 – 2.0) |
| Smoking habits | |

| | | |
|---|---|---|
| | *Never smoked* | 896 (66.2%) |
| | *Former smoker* | 260 (19.2%) |
| | *Current smoker* | 198 (14.6%) |
| Alcohol consumers | | |
| | *No consumption* | 596 (44.0%) |
| | *Occasional consumption* | 731 (54.0%) |
| | *Regular consumption* | 27 (2.0%) |
| Substance abusers | | 25 (1.8%) |
| Presence of at least one comorbidity | | 378 (27.9%) |
| Progressive MS | | 187 (13.8%) |
| MS disease duration, mean ±S.D. | | 10.4 ± 8.28 |
| Last EDSS, median (IQR) | | 2.0 (1.0 - 3.5) |
| Last DMD | | |
| | *Dimethyl fumarate* | 256 (18.9%) |
| | *No therapy* | 202 (14.9%) |
| | *Anti-CD20* | 184 (13.6%) |
| | *Natalizumab* | 176 (13.0%) |
| | *Fingolimod* | 161 (11.9%) |
| | *Interferon* | 127 (9.4%) |
| | *Glatiramer acetate* | 97 (7.2%) |
| | *Teriflunomide* | 91 (6.7%) |
| | *Cladribine* | 24 (1.8%) |
| | *Other* | 36 (2.7%) |
| Recent use of methylprednisolone | | 84 (6.2%) |
| Previous vaccination against Covid-19 | | 24 (1.8%) |
| Covid-19 severity | *Mild disease with no pneumonia nor requiring hospitalization* | 1152 (85.1%) |
| | *Pneumonia and/or hospitalization* | 173 (12.8%) |
| | *ICU and/or death* | 29 (2.1%) |

*Results are expressed as mean±SD, median (IQR), count (%)*

**Table II – Group of symptoms and their agreement degree**

| N (%) | | Cohen's kappa (p value) | | | | | |
|---|---|---|---|---|---|---|---|
| | | **G2** | **G3** | **G4** | **G5** | **G6** | **G7** |
| 1211 (89.4%) | **G1** | 0.05 (<0.001) | 0.03 (<0.001) | 0.01 (0.32) | -0.09 (<0.001) | 0.05 (0.007) | 0.00 (0.21) |
| 513 (37.9%) | **G2** | - | 0.17 (<0.001) | 0.13 (<0.001) | 0.11 (<0.001) | 0.27 (<0.001) | 0.02 (0.12) |
| 224 (16.5%) | **G3** | - | - | 0.08 (0.003) | 0.03 (0.13) | 0.09 (<0.001) | 0.03 (0.11) |
| 188 (13.9%) | **G4** | - | - | - | 0.04 (0.044) | 0.06 (<0.001) | 0.07 (<0.001) |
| 621 (45.9%) | **G5** | - | - | - | - | 0.06 (0.030) | 0.00 (0.79) |
| 841 (62.1%) | **G6** | - | - | - | - | - | 0.01 (0.12) |
| 29 (2.1%) | **G7** | - | - | - | - | - | - |

(G1): Fever, chills, dyspnoea, cough, sputum production, lymph nodes enlarged, tonsil swelling, throat congestion, nasal congestion, sore throat, cold. (G2): Arthralgia, myalgia, bone joint, back pain. (G3): Shortness of breath, tachycardia, chest pain. (G4): Vomiting, nausea, diarrhoea, abdominal pain, loss of appetite, loss of weight, other gastrointestinals. (G5): Ageusia, anosmia. (G6): Symptoms of anxiety and depression, insomnia, headache, drowsiness, difficulty sleeping, loss of concentration, weakness, fatigue, asthenia. (G7): Conjunctivitis, rash.

**Table III - Distribution of group of symptoms during the three pandemic waves**

| Group of symptoms | First wave (N = 238) | Second wave (N = 782) | Third wave (N = 122) | p |
|---|---|---|---|---|
| G1 | 226 (93.4%) | 687 (87.9%) | 113 (92.6%) | **0.024** |
| G2 | 74 (30.6%) | 311 (39.8%) | 54 (44.3%) | **0.013** |
| G3 | 47 (19.4%) | 115 (14.7%) | 24 (19.7%) | 0.12 |
| G4 | 33 (13.6%) | 102 (13.0%) | 16 (13.1%) | 0.97 |
| G5 | 89 (36.8%) | 392 (50.1%) | 42 (34.4%) | **<0.001** |
| G6 | 137 (56.6%) | 483 (61.8%) | 81 (66.4%) | 0.16 |
| G7 | 7 (2.9%) | 16 (2.0%) | 2 (1.6%) | 0.67 |

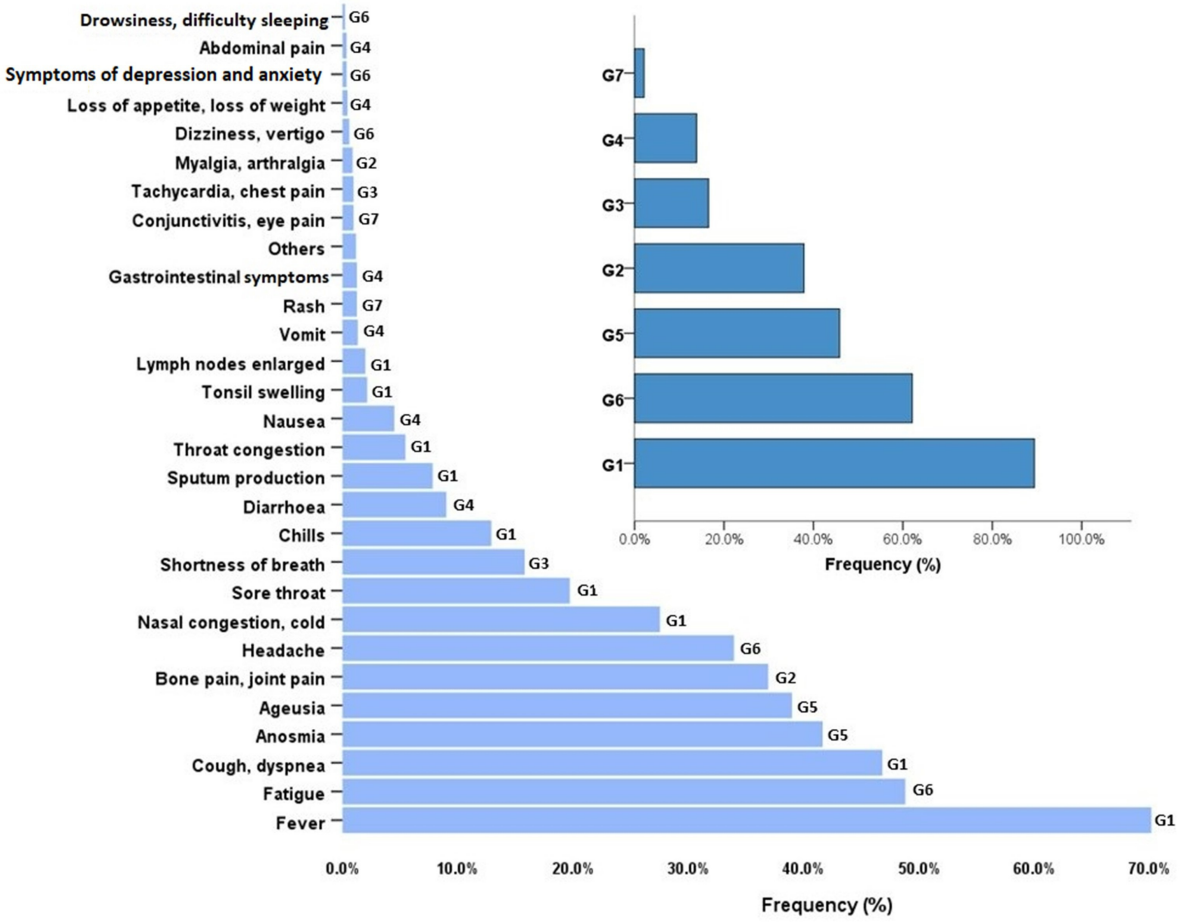
*As reported by Ministry of Health (Andamento della mortalità giornaliera (SiSMG) nelle città italiane in relazione all'epidemia di Covid-19 - 1 settembre 2020 - 16 novembre 2021): First wave (1 March – 10 May 2020); Second wave (1 September 2020 – 9 January 2021); Third wave (March 2021-May 2021).*

## FIGURE LEGENDS

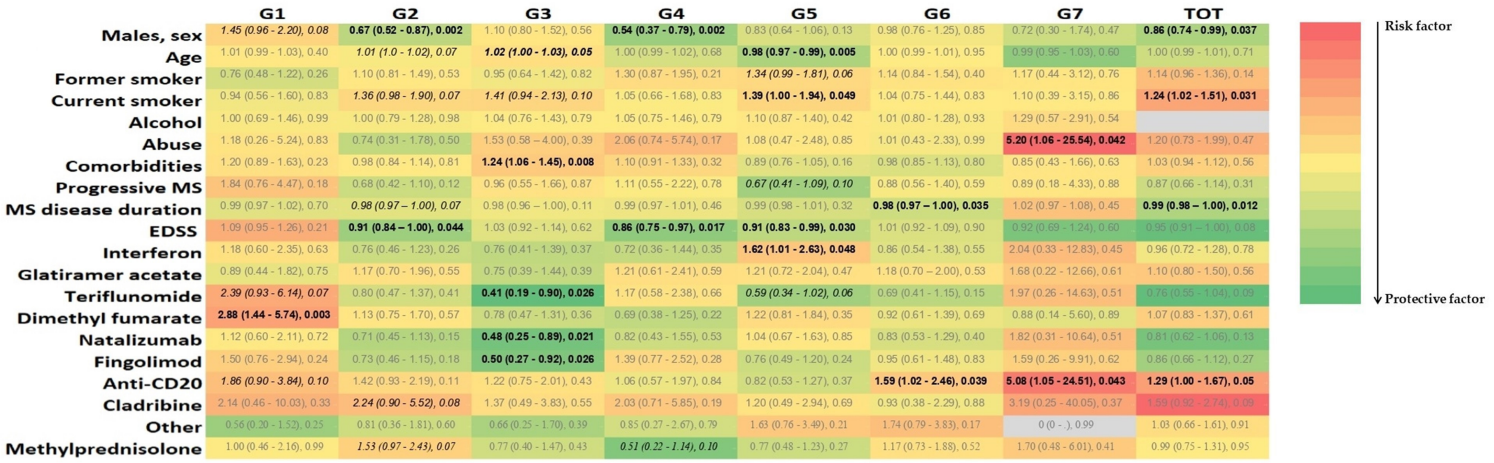
**Figure 1.** Frequency of single symptoms and grouped symptoms.

**Figure 2.** Heatmap of correlation, as measured by odds ratio estimates, between factors and each symptom group. Values above one (shade of red) indicate risk factors, below one (shade of green) protective factors.

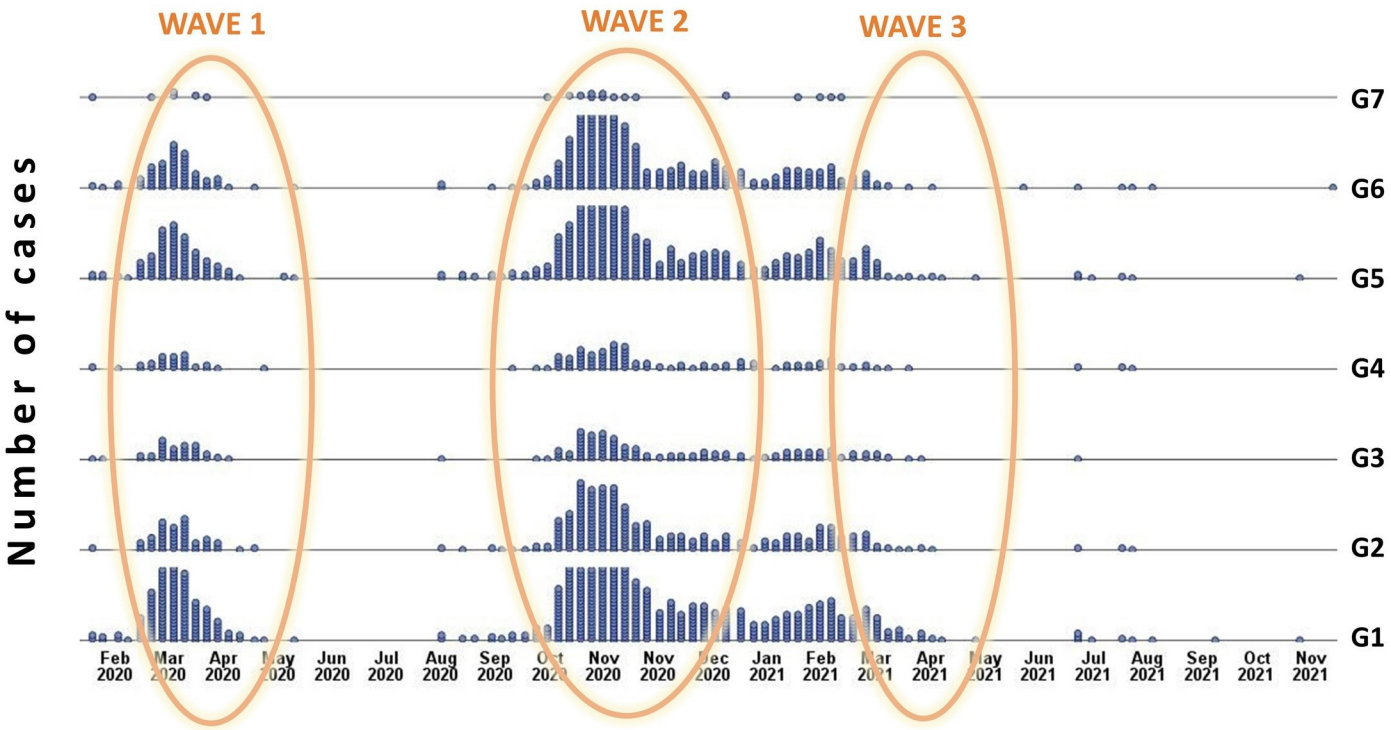
**Figure 3.** Distribution of symptoms groups over time, with identification of three pandemic waves.




ENE_15554_Figure 1.jpg




ENE_15554_Figure 2.jpg




ENE_15554_Figure 3.jpg

# MANAGE-PD

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- Identify PD patients inadequately controlled on oral medications
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