Identification of Covid-19 suspect cases through a digital triage: a multicenter Italian-Iranian study on

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Abstract

Objective: To explore, through a digital triage monitoring, the frequency of demographic and clinical characteristics suggestive for COVID-19 among two large samples of people with Multiple Sclerosis (pwMS) and to evaluate the association between demographic and clinical characteristics of pwMS and the likelihood of being identified as COVID-19 suspect.

Methods: A Google Forms triage was e-mailed to 3500 pwMS. pwMS suspects for having COVID-19 were: A) patients who reported recent contact with a patient with suspicion or diagnosis of COVID-19 and the presence of at least one symptom suggestive of COVID-19; B) pwMS with at least two symptoms suggestive of COVID-19. Demographics, clinical characteristics, and DMT categories of COVID-19-suspect vs non-suspect pwMS were compared.

Results: 1035/1500 questionnaires were fulfilled by Italian pwMS and 1346/2000 by Iranian patients. 4.9% of Iranian and 1.5% of Italian pwMS met our criteria for the COVID-19-suspect case. Only diabetes and heart disease (OR: 5.374, 95%CI: 2.470 – 11.985, p-value<0.001) were independently associated with the likelihood of being suspect for COVID-19.

Conclusion: The results of a digital triage system applied to a large Italian-Iranian population of pwMS to identify suspect cases of COVID-19 were discussed. Demographic and clinical characteristics of pwMS suspect for COVID-19 and the factors influencing the likelihood of being COVID-19 suspect are comparable to those of previous studies. Therefore, we encourage the use of the digital triage in patients with this chronic and severely disabling disease to pinpoint suspect case of COVID-19 in order to promptly activate the second phase of the intervention.

1. Introduction

On March 11, 2020, the World Health Organization (www.who.it) recognized COVID-19 as a pandemic. The symptoms of COVID-19 are similar to those of influenza and include fever, dry cough, hyposmia/anosmia, and shortness of breath [2]. Most of the patients suffer from mild symptoms while a small proportion will develop a severe disease [3]. Risk factors are older age and comorbidities such as hypertension, diabetes, obesity, cardiovascular, and lung disease. It has been also assumed that people with multiple sclerosis (pwMS) on immunosuppressive or immunomodulatory drugs have a higher risk of infection and severe COVID-19 [4]. Thus, the management of these patients has become more challenging during the outbreak of the COVID-19. Despite data are still partial, recent evidence suggests that pwMS on immunotherapy do not present an increased risk of severe COVID-19 [5-7]. However, it is not clear whether the DMTs or other demographical and clinical variables could influence the risk of infection. In this cross-sectional study, we explored, through a digital triage monitoring, the frequency of the demographic and clinical characteristics suggestive for COVID-19 among two large samples of pwMS
and evaluated the association between demographic and clinical characteristics of pwMS and the likelihood of being identified as COVID-19 suspect.

2. Methods

This was a multicenter cross-sectional study conducted in Iran and Italy from April 14 to May 29, 2020. The study was performed in accordance with good clinical practice and the Declaration of Helsinki. The Ethical Committee of the University of Campania “Luigi Vanvitelli” has approved the study procedure in form of a web survey. All participants consented to the use of recorded surveys for scientific purposes on the aggregate level before filling out the online questionnaire. We followed the Legislative Decree n. 196/2003 "Code regarding the protection of personal data" (https://eur-lex.europa.eu/legal-content). In Italy and Iran, the Google Forms platform is compliant with the General Data Protection Regulation (EU Regulation 2016/679).

The Italian sample consisted of pwMS enrolled by five MS centers (2 Northern Italy, 1 Central Italy, 2 Southern Italy) whereas the Iranian population consisted of pwMS recruited from Kashani hospital of Isfahan University of medical sciences. The inclusion criteria were a diagnosis of MS, and the ability to use the internet.

A Google Forms questionnaire, including a translated version of the digital triage proposed by Bonavita et al [9] was e-mailed to 3500 pwMS (1500 in Italy and 2000 in Iran). The form included a demographic section (age and sex), a disease-related section (current DMT, previous DMTs, and the most recent lymphocyte count); co-morbidity related questions (presence of one or more conditions among hypertension, chronic kidney disease, diabetes, heart disease, respiratory disease, cancer on chemotherapy), and a COVID-19 related section (recent contact with a patient with COVID-19 diagnosis or with a suspect case of COVID-19; the presence of symptoms suggesting COVID-19 classified as follow, 1) sore throat, nasal congestion, runny nose, diarrhea; 2) dry cough; 3) fever; 4) shortness of breath; 5) hyposmia and/or ageusia; a question on whether these symptoms were getting worse or not, and if this was happening rapidly or not). Based on prior reports on the risk of infection [9], in the questionnaire DMTs were gathered into 4 groups: a) immunomodulant injectable therapy - very low risk of infection (Interferon or Glatiramer acetate/glatiramoids) b) immunomodulant oral therapy and cell trafficking inhibitor therapy -low risk of infections (Teriflunomide, Fingolimod, Siponimod, Dimethylfumarate, Natalizumab), c) depletive therapy with a moderate risk of infections (Ocrelizumab, Rituximab, Cladribine, Mitoxantrone, Cyclophosphamide); d) depletive therapy with a high risk of infections (Alemtuzumab, Hematopoietic Stem Cells Transplantation). The form included, also, an open-ended question to collect patients’ comments.

The questionnaire aimed to identify suspect cases of COVID-19, therefore, we defined the “suspect group” as A) pwMS who reported recent contact with a patient with COVID-19 diagnosis or with a suspect case of COVID-19 and the presence of at least one symptom suggestive of COVID-19; B) pwMS who reported
at least two symptoms suggestive of COVID-19 in the absence of any contact with suspect/confirmed case of COVID-19.

Statistical analysis

Differences in demographic and clinical characteristics between the suspect and non-suspect COVID-19 cases were tested using the Fisher exact test for categorical variables. Previous DMT was treated only as dummy variables (very low/low risk of infection treatments vs moderate/high risk of infection treatments) whereas ongoing DMT was treated either way, as categorical and dummy variable. To determine whether any variable was independently associated with the “suspect COVID-19 status”, we applied a logistic regression model where the suspect COVID-19 status was the dependent variable and the predictors were the following: age, sex, comorbidities (exploring each one as a single independent variable), lymphocyte count and ongoing DMT category. We analyzed the Italian and Iranian populations separately. Lymphocyte count was available only for the Italian population. Analyses were performed using Stata 16.1 (StataCorp, TX).

3. Results

3.1 Italian population

3.1.1 Suspect vs non-suspect COVID-19 pwMS.

One thousand and thirty-five from 1500 questionnaires were fulfilled (response rate =69%) in full and mailed back. Fifty-three pwMS fulfilled the questionnaires twice, therefore 106 responses were not included in the analysis. The Italian sample consisted of 929 pwMS. Fourteen (1,5%) fulfilled our criteria for the COVID-19-suspect case. Five were identified for reporting at least two symptoms. Nine pwMS were diagnosis based on the presence of at least one symptom and recent contact with a confirmed case of COVID-19 (by PCR analysis) or with a suspect case of COVID-19. Among the 14 pwMS identified as COVID-19 suspect cases, two (14,3%) pwMS reported symptoms worsening, and one of them a rapid worsening of symptoms. Table 1 reports demographic and clinical data of the whole Italian sample and the two subgroups, suspect and non-suspect COVID-19 pwMS.
There was no statistically significant difference in age, sex, lymphocyte count, previous DMTs, ongoing DMTs category, and prevalence of comorbidities between the two subgroups. Between the two subgroups, there was a significant difference between pwMS that reported to be on DMTs with very low/low risk of infection compared to those who reported being on moderate/high-risk DMTs (Table 1). 46.1% (n. 6 out of 13) of patients were on DMTs with moderate/high risk of infection and 53.7% (n. 7 out of 13) were on DMTs with very low/low risk of infection in the suspected COVID-19 group whereas in the non-suspected COVID-19 group only 21.9% (n. 169 out of 772) of patients were on DMTs with moderate/high risk of infection and 78.1% (n. 603 out of 772) were on DMTs with very low/low risk of infection (p-value<0.047). In the multivariable logistic regression model, no variables were independently associated with the likelihood of being in the COVID-19 suspect group.

3.1.2 Comparison between symptomatic vs asymptomatic suspect COVID-19 pwMS.

Forty-one out of 929 (4.4%) pwMS reported recent contact with a confirmed case of COVID-19 (by PCR analysis) or with a suspect case of COVID-19 and among them, 9 (21.9%) developed symptoms afterward. There was no statistically significant difference in sex, comorbidities, lymphocyte count, ongoing and previous DMTs category between pwMS with the suspect of COVID-19 who developed symptoms and those pwMS who did not (symptomatic vs asymptomatic). Instead, there was a higher likelihood to develop symptoms after contact with a confirmed or suspect case of COVID-19 in older (over the age of 50) than in younger patients. 55.5% (n. 5 out of 9) of pwMS in the group that developed symptoms and 15.6% (n. 5 out of 32) in the group that did not develop symptoms, were older than 50 years (p-value = 0.029). In the multivariable logistic regression model, no variables were independently associated with the likelihood of being in the group of patients that developed symptoms.

3.2 Iranian population

3.2.1 Suspect vs non-suspect COVID-19 pwMS.

1346/2000 questionnaires were fulfilled in full and mailed back (response rate = 67%). Sixty-six (4.9%) fulfilled our criteria for COVID-19-suspect case. Forty-seven (3.4%) were identified for reporting at least two symptoms. Nineteen pwMS were diagnosed based on the presence of at least one symptom and a history of recent contact with a confirmed case of COVID-19 (by PCR analysis) or with a suspect case of COVID-19. On 66 (4.9%) pwMS identified as suspect, 10 (15.1%) patients reported to have worsening...
symptoms but none of them reported a rapid worsening of symptoms. The demographic and clinical characteristics of the whole Iranian sample and the two subgroups, suspect and non-suspect COVID-19 pwMS, are summarized in Table 2. There was no statistically significant difference in age, sex, ongoing DMTs, previous DMTs, and comorbidities, except that for diabetes or heart disease, between the two groups. 15.15% (n. 10 out of 66) of patients in the COVID-19-suspect group reported diabetes or heart disease while only 3.8% (n. 49 out of 1280) of patients among non-suspect COVID-19 group reported diabetes or heart disease (p-value<0.001). In the multivariable logistic regression model diabetes/heart disease was independently associated with the likelihood of being in the COVID-19-suspect group (Table 3). Reporting diabetes or heart disease was associated with an increased likelihood of being in the COVID-19-suspect group (OR: 5.374; 95%CI: 2.470 – 11.985; p-value<0.001).

3.2.2 Comparison between symptomatic vs asymptomatic suspect COVID-19 pwMS.

Fifty-two out of 1346 (3.9%) pwMS reported recent contact with a confirmed case of COVID-19 (by PCR analysis) or with a suspect case of COVID-19 and among them, 19 (35.8%) developed symptoms afterward. There was no statistically significant difference in age, sex, previous DMTs, and comorbidities between patients that developed symptoms and patients that did not. The difference in the proportion of pwMS on different DMT categories between the two groups reached statistical significance (p-value = 0.045): 5.2% (n. 1 out of 19) of patients who developed symptoms were on depletive therapy with a moderate risk of infection vs 3.0% (n. 1 out of 33) of patients who did not were on depletive therapy with a moderate risk of infection. Patients treated with very low and low risk of infection therapy had a lower chance to develop symptoms after contact with a confirmed or a suspect case of COVID-19: the proportion of very low and low risk of infection medications-treated patients were 26.3% (n. 5 out of 19) and 5.3% (n. 1 out of 19) among patients that developed symptoms and 52.5% (n. 17 out of 33) and 18.2% (n. 6 out of 33), among patients that did not develop symptoms, respectively. In the multivariable logistic regression model, no variables were independently associated with the likelihood of being in the group of patients that developed symptoms.

4. Discussion

In this study, we have applied a digital triage system on two large populations of pwMS to identify suspect cases of COVID-19. We have further explored whether clinical or demographic characteristics of pwMS could have influenced the triaging results. 4.9% of Iranian and 1.5% of Italian pwMS were identified as COVID-19 suspect cases. In a recent study on 712 Iranian pwMS, that applied a comparable triaging procedure with similar criteria to pinpoint suspect case of COVID-19, Safavi and colleagues found a proportion of about 5% of patients that satisfied their criteria for COVID-19 suspect case. In the study of
Safavi and colleagues, there was no association between the degree of observing quarantine recommendations and the risk of being in the COVID-19 suspect group. The authors speculated that, since the study was conducted in the early days of the epidemic, the lack of sufficient time for the quarantine measures to become effective might have influenced the results [6]. Despite we used the digital triage tool later in the pandemic, when the effectiveness of quarantine measures might have affected the risk of infection, we confirmed the same proportion of COVID-19 suspect cases in the Iranian population. We may argue that the less stringent selection criteria used in our study might have conducd to these results. On the other hand, in the Italian population, the proportion of patients pinpointed as suspect cases of COVID-19 was lower. Bearing in mind that Iranian pwMS were younger, reported fewer comorbidities and were on DMTs with moderate/high risk of infection less frequently compared to Italian pwMS, we speculate that the higher proportion of suspect cases in the Iranian population could be due to the different quarantine measures adopted in the two countries. A second or alternative reason could be that 66% of patients who fulfilled the questionnaire in the Italian population came from the south and central Italy, regions with low ongoing transmission.

Despite the higher proportion of suspect cases in the Iranian population compared to the Italian one, the course of the disease was superimposable between the two populations and is not more severe than in the general population [5, 11, 12].

Concerning the possible influence of demographic and clinical parameters on the triaging results, in the Iranian population pwMS that reported diabetes or heart disease were at higher risk to be identified as COVID-19 suspect cases. As already shown, cardiovascular disease and diabetes are the most frequent comorbidities in COVID-19 patients, and two of the main risk factors for a severe disease course [13]. This result has not been confirmed in the Italian population, more likely, due to the small number of patients identified as suspect cases.

Despite the significance has been reached only when ongoing DMTs was treated as a dummy variable and only in the Italian population, the distribution of patients for each ongoing DMTs category between the two groups (suspect vs not suspect) revealed, in both samples, a higher likelihood for being identified as COVID-19 suspect case for pwMS on depletive therapies. In parallel, it has been shown a lower chance for being in the COVID-19 suspect group for pwMS on very low/low risk of infection DMTs (table 1 and table 2). We have also explored the influence of clinical and demographic characteristics on the likelihood to develop symptom/s suggestive of COVID-19 after contact with a confirmed or a suspect case of COVID-19. Older age and ongoing depletive DMTs are a risk factor for developing symptoms suggestive of COVID-19 after contact with a confirmed or a suspect case of COVID-19, whereas pwMS on injectable therapies have a lower chance to develop symptoms suggestive of COVID-19. The effect of the age on the likelihood of developing symptoms was revealed only in the Italian population. This is because in the Iranian population among the 19 pwMS that developed symptoms suggestive of COVID-19, only one patient was older than 50. In the regression model, the effect of the age got close to the threshold of significance but did not reach it, probably due to the small sample size. Although the effect of the age on the course of COVID-19 is established, it is still unknown whether pwMS are at increased risk of a SARS-
CoV-2 infection or of a more severe course of COVID-19 compared with the general population and whether the different DMTs play any role [4, 14, 15]. The difference in the proportion of ongoing DMTs category between the suspect and the non-suspect COVID-19 group and in pwMS that developed versus patients that did not develop symptoms was not confirmed at the regression analysis. Since at the beginning of the outbreak it was supposed that pwMS on depletive therapy, could be at higher risk of infection and/or of severe disease course, drug infusions were either delayed or temporarily discontinued. Recent work of the UK’s Intensive Care National Audit & Research Centre compared 2249 patients with severe COVID-19 to 4759 patients with other viral pneumonia who were admitted to intensive care unit and revealed a lower percentage of immunocompromised patients among the COVID-19 group [16]. This, at least in a non-MS population, implies that immunosuppressive therapies may be associated with better disease outcome. In support of a favorable course in pwMS, very recent evidence of the Italian study group on COVID-19 on pwMS revealed a good outcome in MS patients with COVID-19 [17]. Moreover, a recent Chinese study on a large population of pwMS and NMOSD patients screened with PCR analysis for SARS-CoV-2, argues against a significantly increased risk of COVID-19 pwMS and NMOSD treated with DMTs [10]. In this study among a population of about 3000 MS/NMOSD screened patients, 489 were on B cell depletive drugs. None of the pwMS treated with DMTs were diagnosed with COVID-19. Only two NMOSD patients were diagnosed with COVID-19 related pneumonia and both patients had received oral methylprednisolone as maintenance therapy to prevent relapses, and none had been treated with DMTs. These data questioned the assumption that pwMS on depletive DMTs are at higher risk of infection and/or of severe disease course and highlighted the importance to carefully consider the possible consequences of delaying treatment, especially in patients with highly active disease.

Our data, in line with the literature, seem to be encouraging; however, we should consider that this information could be biased, in that those patients with more severe disease (for example, those who were still hospitalized or in intensive care unit) were less likely to answer the questionnaire. Moreover, the stringent measures of quarantine, which have undoubtedly minimized the exposure of these patients, might have contributed to the absence or low rates of SARS-CoV-2 infection.

5. Conclusion

In this study, we have presented and discussed the results of a digital triage system applied to a large Italian-Iranian population of pwMS, during the period of highest ongoing transmission of SARS-CoV-2 in these two countries. The advantage of using a digital triage was to allow a time-saving screening of many patients and to obtain results in real-time.

The demographic and clinical characteristics of pwMS pinpointed as COVID-19 suspect as well as the factors influencing the likelihood of being COVID-19 suspect are comparable to those of previous studies. Therefore, during this unprecedented time of great strain on healthcare systems, these results encourage
the use of digital triage systems in patients with this chronic and severely disabling disease to pinpoint suspect cases of COVID-19 in order to promptly activate the second phase of the intervention.

References

1. Engineering CCfSSa. Coronavirus COVID-19 global cases [online]. Available at: gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ef6. Accessed April 13, 2020.

2. Huang C, Wang Y, Li X, et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395(10223):497-506. org/10.1016/S0140-6736(20)30183-5

3. Guan WJ, Ni ZY, Hu Y, et al (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 382(18):1708-1720. doi:10.1056/NEJMoa2002032

4. Giovannoni G (2020) Anti-CD20 immunosuppressive disease-modifying therapies and COVID-19. Mult Scler Relat Disord 41:102135. doi:10.1016/j.msard.2020.102135

5. Berger JR, Brandstadter R, Bar-Or A (2020) COVID-19 and MS disease-modifying therapies. Neurol Neuroimmunol Neuroinflamm 7(4):e761. doi:10.1212/NXI.0000000000000761

6. Safavi F, Nourbakhsh B, Azimi AR (2020) B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients with multiple sclerosis during the early COVID-19 epidemic in Iran. Mult Scler Relat Disord 43:102195. doi:10.1016/j.msard.2020.102195

7. Fan M, Qiu W, Bu B, et al. (2020) Risk of COVID-19 infection in MS and neuromyelitis optica spectrum disorders. Neurol Neuroimmunol Neuroinflamm 7(5):e787. doi:10.1212/NXI.0000000000000787

8. Ghajarzadeh M and Bonavita S (2020) Are patients with multiple sclerosis (MS) at higher risk of COVID-19 infection? Neurol Sci 1-2. doi:10.1007/s10072-020-04570-8.

9. Bonavita S, Tedeschi G, Atreja A, Lavorgna L (2020) Digital triage for people with multiple sclerosis in the age of COVID-19 pandemic. Neurol Sci 41(5):1007-1009. doi:10.1007/s10072-020-04391-9

10. Winkelmann A, Loebermann M, Reisinger EC, Hartung HP, Zettl UK (2016) Disease-modifying therapies and infectious risks in multiple sclerosis. Nat Rev Neurol 12(4):217-233. doi:10.1038/nrneurol.2016.21

11. Baker D, Amor S, Kang AS, Schmierer K, Giovannoni G (2020) The underpinning biology relating to multiple sclerosis disease modifying treatments during the COVID-19 pandemic. Mult Scler Relat Disord 43:102174. doi:10.1016/j.msard.2020.102174

12. Ciampi E, Uribe-San-Martin R, Cárcamo C (2020) COVID-19 pandemic: The experience of a multiple sclerosis centre in Chile. Mult Scler Relat Disord 42:102204. doi:10.1016/j.msard.2020.102204

13. Ceriello A, Schnell O (2020) COVID-19: Considerations of Diabetes and Cardiovascular Disease Management. J Diabetes Sci Technol 14(4):723-724. doi:10.1177/1932296820930025
14. Giovannoni (2020) The COVID-19 pandemic and the use of MS disease-modifying therapies. *Mult Scler Relat Disord* 39:102073. doi:10.1016/j.msard.2020.102073

15. Ghajarzadeh M, Mirmosayyeb O, Barzegar M, et al (2020) Favorable outcome after COVID-19 infection in a multiple sclerosis patient initiated on ocrelizumab during the pandemic. *Mult Scler Relat Disord* 43:102222. doi:10.1016/j.msard.2020.102222

16. Icnarc Website (2020) Intensive Care National Audit & Research Centre.

17. Sormani MP (2020) Italian Study Group on COVID-19 infection in multiple sclerosis. An Italian programme for COVID-19 infection in multiple sclerosis [published correction appears in Lancet Neurol. Lancet Neurol 19(6):481-482. doi:10.1016/S1474-4422(20)30147-2.

**Tables**

Table 1 - Demographic, clinical characteristics and symptoms of the whole Italian population, and of COVID-19-suspect patients compared to the non-suspect COVID-19 patients.
|                          | Whole Italian sample (n. 929) | COVID-19 suspect group (n. 14) | Non-suspect COVID-19 group (n. 915) | p-value |
|--------------------------|-------------------------------|---------------------------------|--------------------------------------|---------|
| **Sex**                  |                               |                                 |                                      |         |
| Female                   | 631 (67,92%)                  | 12 (86,67%)                     | 619 (67,79%)                         | 0,164   |
| Male                     | 298 (32,08%)                  | 2 (13,33%)                      | 296 (32,31%)                         |         |
| **Age (years)**          |                               |                                 |                                      | 0,467   |
| < 18                     | -                             | -                               | -                                    |         |
| 19-50                    | 662 (71,26%)                  | 8 (60%)                         | 654 (71,52%)                         |         |
| 51-70                    | 258 (27,77%)                  | 6 (40%)                         | 252 (27,49%)                         |         |
| > 70                     | 9 (0,97%)                     | 0 (0%)                          | 9 (0,99%)                            |         |
| **Region of Italy n. 904**|                               |                                 |                                      | 0,725   |
| South                    | 507 (56,02%)                  | 7 (50%)                         | 500 (56,18%)                         |         |
| Centre                   | 94 (10,39%)                   | 2 (14,29%)                      | 92 (10,34%)                          |         |
| North                    | 303 (33,59%)                  | 5 (35,71%)                      | 298 (33,48%)                         |         |
| **Comorbidities**        |                               |                                 |                                      |         |
| Hypertension             | 125 (13,46%)                  | 0 (0%)                          | 125 (13,69%)                         | 0,112   |
| Diabetes/heart disease   | 51 (5,49%)                    | 1 (6,67%)                       | 50 (5,48%)                           | 0,575   |
| Kidney disease           | 4 (0,43%)                     | 0 (0%)                          | 4 (0,44)                             | 0,973   |
| Cancer on chemotherapy   | 7 (0,75%)                     | 0 (0%)                          | 7 (0,77%)                            | 0,892   |
| **Ongoing DMT (as dummy variable) n. 785** |                       |                                 |                                      | 0,047   |
| Moderate/High risk of infection DMTs | 175 (22,36%) | 6/13 (46,15%) | 169/772 (21,89%) |         |
| Very low/low risk of infection DMTs | 610 (77,64%) | 7/13 (53,85%) | 603/772 (78,11%) |         |
| **Previous DMT (as dummy variable) n. 636** |                       |                                 |                                      | 0,483   |
| Moderate/High risk of infection DMTs | 50 (7,85%) | 1/8 (12,5%) | 49/628 (7,80%) |         |
| Very low/low risk of infection DMTs | 586 (92,15%) | 7/8 (87,50%) | 579/628 (92,20%) |         |
| **Ongoing DMT category** |                               |                                 |                                      | 0,082   |
| No therapy               | 142 (15,39%)                  | 1 (6,67%)                       | 141 (15,55%)                         |         |
| Injection therapies      | 154 (16,47%)                  | 0 (0%)                          | 154 (16,76%)                         |         |
| Oral therapy or immune cell trafficking-inhibitor | 457 (49,19%) | 7 (53,33%) | 450 (49,18%) |         |
| Low risk depletive therapies | 144 (15,50%) | 5 (33,33%) | 139 (15,12%) |         |
| High risk depletive therapies | 32 (3,44%) | 1 (6,67%) | 31 (3,4%) |         |
| **Lymphocyte count n. 234** |                               |                                 |                                      | 0,227   |
| > 1400/mm³               | 82 (35,04%)                   | 6/14 (40%)                      | 76/220 (34,93%)                      |         |
| 701-1400/mm³             | 72 (30,77%)                   | 0/14 (0%)                       | 72/220 (31,44%)                      |         |
| 501-700/mm³              | 20 (8,55%)                    | 0/14 (0%)                       | 20/220 (8,73%)                       |         |
| 200-500/mm³              | 60 (25,64%)                   | 8/14 (60%)                      | 52/220 (24,89%)                      |         |
| **Contact**              |                               |                                 |                                      | <0,001  |
| No contact               | 842 (90,64%)                  | 4 (26,67%)                      | 840 (91,79%)                         |         |
| Contact with people from high risk or lock-down areas | 46 (4,95%) | 2 (13,33%) | 44 (4,82%) |         |
| Contact with a suspect case of COVID-19 infection | 22 (2,37%) | 6 (46,67%) | 14 (1,53%) |         |
| Contact with a confirmed case of COVID-19 | 19 (2,05%) | 2 (13,33%) | 17 (1,86%) |         |
| **Symptoms**             |                               |                                 |                                      |         |
| Sore throat, Nasal congestion, Runny nose, Diarrhea | 45 (4,85%) | 11 (80%) | 34 (3,62%) | <0,001  |
| Dry cough                | 17 (1,83%)                    | 3 (20%)                         | 14 (1,54%)                           | <0,001  |
| Fever                    | 4 (0,43%)                     | 2 (13,33%)                      | 2 (0,22%)                            | <0,001  |
Table 2 - Demographic, clinical characteristics and symptoms of the whole Iranian sample, and of COVID-19-suspect patients compared to the non-suspect COVID-19 patients.

| Symptom                                      | Iranian Sample | Non-suspect COVID-19 Sample | Suspect COVID-19 Sample | p-value |
|----------------------------------------------|----------------|-----------------------------|-------------------------|---------|
| Breathing difficulties, shortness of breath  | 17 (1.83%)     | 4 (33.33%)                  | 13 (1.32%)              | <0.001  |
| Loss or reduced sense of smell and/or taste  | 9 (0.97%)      | 1 (6.67%)                   | 8 (0.88%)               | <0.001  |
|                                      | Whole Iranian sample (n 1346) | COVID-19 suspect group (n 66) | Non.suspect COVID-19 group (n 1280) | p-value |
|--------------------------------------|------------------------------|-------------------------------|------------------------------------|---------|
| **Sex**                              |                              |                               |                                    |         |
| Female                               | 1062 (78,9%)                | 56 (84,85%)                  | 1006 (78,59%)                     | 0,144   |
| Male                                 | 284 (21,1%)                 | 10 (15,15%)                  | 274 (21,41%)                      |         |
| **Age (years)**                      |                              |                               |                                    |         |
| <18                                  | 10 (0,74%)                  | 0 (0%)                       | 10 (0,78%)                        |         |
| 19-50                                | 1204 (94,45%)               | 61 (92,42%)                  | 1143 (93,30%)                     |         |
| 51-70                                | 131 (9,73%)                 | 5 (7,58%)                    | 126 (9,84%)                       |         |
| >70                                  | 1 (0,07%)                   | 9 (0%)                       | 1 (0,08%)                         |         |
| **Comorbidities**                    |                              |                               |                                    |         |
| Hypertension                         | 0 (0%)                      | 0 (0%)                       | 0 (0%)                            | -       |
| Kidney disease                       | 7 (0,52%)                   | 0 (0%)                       | 7 (0,55%)                         | 0,703   |
| Diabetes/Heart disease               | 59 (4,38%)                  | 10 (15,15%)                  | 49 (3,83%)                        | <0,001  |
| Cancer on chemotherapy               | 6 (0,45%)                   | 1 (1,52%)                    | 5 (0,39%)                         | 0,261   |
| **Ongoing DMT (as dummy variable)**  |                              |                               |                                    | 0,195   |
| n. 914                               |                              |                               |                                    |         |
| Moderate/High risk of infection DMTs | 36 (3,94%)                  | 3/39 (7,69%)                 | 33/878 (3,77%)                    |         |
| Very low/low risk of infection DMTs  | 878 (96,06%)                | 36/39 (92,31)                | 842/878 (96,23%)                  |         |
| **Previous DMT (as dummy variable)** |                              |                               |                                    | 0,2     |
| n. 759                               |                              |                               |                                    |         |
| Moderate/High risk of infection DMTs | 5 (0,66%)                   | 1/33 (3,03%)                 | 4/754 (0,55%)                     |         |
| Very low/low risk of infection DMTs  | 754 (99,34%)                | 32/33 (96,97%)               | 722/754 (99,45%)                  |         |
| **DMT category**                     |                              |                               |                                    | 0,201   |
| No therapy                           | 432 (32,1%)                 | 27 (40,91%)                  | 405 (31,62%)                      |         |
| Injection therapies                  | 596 (44,28%)                | 23 (34,85%)                  | 573 (44,77%)                      |         |
| Oral therapy or immune cell trafficking-inhibitor | 282 (20,95%) | 13 (19,70%)                  | 269 (21,02%)                      |         |
| Low risk depletive therapies         | 36 (2,67%)                  | 3 (4,55%)                    | 33 (2,58%)                        |         |
| High risk depletive therapies        | 0 (0%)                      | 0 (0%)                       | 0 (0%)                            |         |
| **Lymphocyte count**                 |                              |                               |                                    | -       |
| >1400/mm³                            | NA                          | NA                            | NA                                 |         |
| 701-1400/mm³                         | NA                          | NA                            | NA                                 |         |
| 501-700/mm³                          | NA                          | NA                            | NA                                 |         |
| 200-500/mm³                          | NA                          | NA                            | NA                                 |         |
| **Contact**                          |                              |                               |                                    |         |
| No contact                           | 1193 (88,63%)               | 41 (62,12%)                  | 1152 (90%)                        | <0,001  |
| Contact with people from high risk or lock-down areas | 101 (7,5%) | 6 (9,09%)                  | 95 (7,42%)                        |         |
| Contact with suspect case of COVID-19 infection | 33 (2,45%) | 11 (16,67%)                  | 22 (1,72%)                        |         |
| Contact with confirmed case of COVID-19 | 19 (1,41%) | 8 (12,12%)                  | 11 (0,86%)                        |         |
| **Symptoms**                         |                              |                               |                                    |         |
| Sore throat, Nasal congestion, Runny nose, Diarrhea | 91 (6,76%) | 41 (62,12%)                  | 50 (3,91%)                        | <0,001  |
| Dry cough                            | 51 (3,79%)                  | 20 (46,97%)                  | 31 (1,56%)                        | <0,001  |
| Fever                                | 23 (1,71%)                  | 15 (22,73%)                  | 8 (0,62%)                         | <0,001  |
| Breathing difficulties, shortness of breath | 63 (4,68%) | 31 (46,97%)                  | 32 (2,5%)                         | <0,001  |
| Loss or reduced sense of smell and/or taste | 48 (3,57%) | 25 (37,88%)                  | 23 (1,80%)                        | <0,001  |
Table 3 – Results of logistic regression model in the Iranian population.

|                                | Odds Ratio | 95% CI       | P value |
|--------------------------------|------------|--------------|---------|
| Sex                            | 0.592      | 0.295 – 1.188| 0.141   |
| Age                            | 0.558      | 0.235 – 1.326| 0.187   |
| **DMT category (compared to no DMT)**       |            |              |         |
| Injection therapies             | 0.576      | 0.322 – 1.029| 0.062   |
| Oral therapy or immune cell trafficking-inhibitor | 0.604      | 0.300 – 1.216| 0.159   |
| Low risk depletive therapies   | 1.384      | 0.382 – 5.010| 0.620   |
| High risk depletive therapies* | NA         | NA           | NA      |
| Hypertension*                  | NA         | NA           | NA      |
| Renal*                         | NA         | NA           | NA      |
| Diabetes/Heart Disease         | 5.374      | 2.470 – 11.695| < 0.001 |
| Cancer on chemotherapy         | 2.410      | 0.227 – 25.508| 0.465   |

* No patients in the COVID-19 suspect group reported hypertension, renal impairment or to receive high risk depletive therapy.

Legend to table 1, 2 and 3

DMT: disease modifying therapy