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**Prevalence and factors associated with symptom persistence: a prospective study of 429
mild COVID-19 outpatients**

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Ethical statement

Consent to participate

All patients provided oral informed consent and did not object to the analysis of their data for research purposes (non-opposition regime).

Consent to publish

The participants consented to the publication of their data.

Ethics approval

The research was conducted according to the recommendations outlined in the Helsinki declaration. This study was approved by an institutional review board (CPP Ile-de-France X, Paris, France, N°47-2020). ClinicalTrials.gov Identifier: NCT04402905

Introduction

Coronavirus disease 2019 (COVID-19) caused by the novel coronavirus SARS-CoV-2 is a highly heterogeneous disease in terms of clinical manifestations, disease severity, and evolution [1,2]. While the severe acute respiratory distress had revealed COVID-19 to the world with initially high mortality rates in critically ill high-risk patients (up to 62% mortality rate in patients managed in intensive care units) [2–4], the mild-to-moderate form is by far the most frequent (around 80%) [1]. The clinical picture of mild-to-moderate COVID-19 includes flu-like symptoms [1,5] and some less common symptoms in a context of respiratory viral infection such as cutaneous manifestations [6], anosmia [7], dysgeusia [7], neurological [8] and cardiovascular [9] symptoms. A median time to recovery of approximately 2 weeks for mild cases was reported in 2020 [10], but recent studies reported persistence of symptoms after several months in a large proportion of patients [11–16].

While the first wave of the pandemic was spreading out in Europe in spring 2020 with lockdown measures, a remote surveillance system named COVIDOM – based on an alert system triggered by abnormal vital signs – was set up for home monitoring of patients with suspected or proven COVID-19 living in the Ile-de-France region [17]. To complement this alert system, as access to family physicians was limited, we set up in early spring 2020 a prospective weekly medical follow up of these COVID-19 outpatients. We aim to report our experience and to describe the dynamics of the disease in these outpatients, the prevalence and the risk factors for persistent symptoms.

Methods

This observational, prospective, single-center study enrolled all consenting symptomatic adult outpatients (>18 years), with a positive nasopharyngeal RT-PCR for SARS-CoV-2 or

positive anti-SARS-CoV-2 antibodies detected by ELISA (IgM or IgG) who self-registered in the COVIDOM Pitié-Salpêtrière (PSL) between March 10 and May 18, 2020. Initially hospitalized patients, patients from whom consent was not obtained, and patients with no follow-up visits were excluded from the analysis. The primary outcome was the probability of complete recovery defined as the absence of symptoms for at least three days at day 30 (D30). Secondary outcomes were the frequency of symptoms at disease onset and their evolution over time, the probability of complete recovery at day 60 (D60), the proportion of COVID-19 relapse defined as the proportion of individuals with reemergence of symptoms after complete recovery, the profile and factors associated with persistent disease defined as the persistence of symptoms at D30.

Mild COVID-19 was defined as having any of the various signs and symptoms of COVID-19, a positive nasopharyngeal RT-PCR for SARS-CoV-2 or positive anti-SARS-CoV-2 antibodies detected by ELISA and not requiring oxygen therapy or hospitalization.

Patients were prospectively followed with weekly phone visits by a physician from clinical onset of COVID-19 (day 0) until D30 (day 0, day 7, day 14, day 30) and D60 for patients with persistent symptoms at D30. Data were collected at each visit using a standardized questionnaire including demographic data, disease onset date, and all symptoms reported. All items were registered in the computerized data system NADISABL SA version 5.

The Cobas® test (Roche), the RealStar® Kit 1.0 assay (ALTONA), and a real-time RT-PCR (National Reference Center) were used to detect SARS-CoV-2 RNA on nasopharyngeal swabs. Only the cycle threshold (Ct) of Cobas® SARS-CoV-2 assay was used as a proxy for quantification for estimation of SARS-CoV-2 viral load. Detection of SARS-CoV-2 IgG antibodies was assessed using commercially available immunoassay (SARS-CoV-2 IgG,

Architect, and Abbott). The SARS-CoV-2 RT-PCR and serology results were collected through the database of our hospital virology laboratory.

Statistical analysis

Descriptive statistics included frequency analysis (percentages) for categorical variables and median and interquartile (IQR) for continuous variables. Chi-square/Fisher's exact test was used to compare categorical variables and Mann-Whitney U test for continuous variables. We compared the frequency of symptoms at disease onset according to age (<60 vs >60 years) and gender using Fisher's exact test. The probability of recovery and time to recovery were calculated using the Kaplan-Meier method and factors associated with persistent disease were evaluated using COX model accounting for staggered entries in the study. The following variables were assessed: age, sex, profession, SARS-CoV-2 RT-PCR Ct, time from onset until PCR, number of people per household, number and type of initial symptoms. Factors associated with baseline Ct provided for patients assessed with the RT-PCR E-Cobas gene Ct technique were evaluated using a linear regression model. Variables with univariable p -value <0.20 were retained for the multivariable analysis. Analyses were performed using the software SAS version 9.4 (SAS Institute, Cary, NC).

Ethics

This study was conducted in accordance with the Helsinki declaration. The research was approved by an institutional review board (CPP Ile-de-France X, Paris, France, N°47-2020; ClinicalTrials.gov Identifier: NCT04402905). All patients gave their consent.

Results

Out of 671 patients registered in the COVIDOM-PSL database between March 10 and May 18, 429 patients fulfilling inclusion criteria were assessed. We excluded from the analysis 242 individuals for the following reasons: prior COVID-19-related hospitalization (n=66), missing consent (n=30), absence of proven SARS-CoV-2 diagnosis (n=119), and absence of follow-up visits (n=27). A total of 1,710 visits were performed with a median of four [IQR 3-5] visits per patient; median follow-up duration was 27 [IQR 16-35] days. All 429 patients were followed up to D30 and 175 up to D60 with no loss to follow-up.

Patients were predominantly women (72.5%) with a median age of 41.6 years [IQR 30-51.5], mostly healthcare workers (72.5%). Diagnosis was assessed by RT-PCR in 412/429 (96%) performed within a median time of 3 days [IQR 1-6] from disease onset, or by positive SARS-CoV-2 antibody test in 17/429 (4%) within a median time of 66 days (IQR: 60-75). An RT-PCR Ct value using the E-Cobas gene Ct assay was available for 260 patients (63.1%); median value was 25.8 [IQR 21-32] at diagnosis.

Clinical symptoms presented by the 429 patients over the course of COVID-19 are shown in Table 1. The main symptoms (>60%) were cough (69.7%), asthenia (68.8%), anosmia (64.8%), headaches (64.6%), myalgia (62.7%), gastrointestinal symptoms (61.8%), fever (61.5%), and ageusia (60.8%). There were differences in terms of clinical presentation: diarrhea and fever were more frequent in patients >60 years (24.6% vs 15.4%, $p=0.02$ and 69.2% vs 48.8%, $p<0.001$, respectively), and anosmia was more prevalent in patients <60 years (42.1% vs 28.5%, $p=0.007$). Fever was more frequent in men (65.2 vs 51.1%, $p=0.08$) while headaches were more frequent in women (56.6 vs 45.8%, $p=0.04$).

By multivariable analysis, we found a higher SARS-CoV-2 viral load (lower Ct) in healthcare workers (HCW) compared with non-HCWs (-7.2Ct [95%CI -11.13 to -3.18]; $p<0.001$) and in

patients presenting with fever at disease onset compared with non-febrile patients (-2.4 Ct [95%CI -4.32 to -0.46]; $p=0.016$).

The median time to complete recovery was 27 days (95%CI: 25-29). Three male patients had to be hospitalized at day 13, 14, and 18 for acute respiratory failure (65 years), pulmonary embolism (34 years), and lower limb paresthesia (34 years), respectively.

Five patients had relapsing disease in a median time of 8 days [IQR 7-9] after an initial complete recovery with new symptoms in three of them. Relapse symptoms were chest pain (n=3), dyspnea (n=3), headaches (n=2), asthenia (n=2), cough (n=2), vertigo (n=2), and gastrointestinal symptoms (n=2). They all had completely recovered at D30 after the initial episode.

A total of 175 (40.8%) patients reported persistent symptoms at D30 (Figure 1) mainly consisting in asthenia (32.6%), anosmia (32.6%), and ageusia (30.4%). At D60, 28 (6.5%) patients were still symptomatic mainly with anosmia (75%), ageusia (53.6%), and dyspnea (14.3%). None of them required hospitalization after D30. Overall, the probability of complete recovery from COVID-19 was 56.3% (95%CI: 51.7-61.1) at D30, increasing to 85.6% (95%CI: 81.2-89.4) (Figure 2) at D60. By multivariable analysis, persistent symptoms at D30 were associated with the following baseline factors: female sex (HR 0.70), age >40 (HR 0.61), ageusia (HR 0.59), longer duration of symptoms prior to PCR testing (HR 0.96), and a higher viral load (HR 0.78) (Table 2 and Figure 3).

Discussion

This prospective study of 429 non-hospitalized patients shows that mild COVID-19 is a long infectious disease process as only 56% of individuals had cleared their COVID-19 symptoms at 1 month. Furthermore, 14% of patients had persistent symptoms after 2 months.

Initial COVID-19 clinical presentation in our population of young individuals with mild COVID-19 was consistent with other reports (most frequently cough, asthenia, headaches, fever, gastrointestinal symptoms, and anosmia/ageusia) [12,18,19]. Interestingly, we found, as reported in other studies, gender and age differences in initial clinical presentations with fever more frequently observed in men [18,20], headaches more frequent in women [18], anosmia more prevalent in young individuals while older patients more frequently had fever and diarrhea [18].

SARS-CoV-2 viral load has been shown to be a prognostic factor in critically ill patients [21,22] and a predictor of transmissibility [23,24]. One study correlated olfactory and taste dysfunction to a lower Ct value at diagnosis [25]. Higher viral load in HCWs may be explained by a faster access to RT-PCR earlier in the course of COVID-19. Similarly, for febrile patients, fever could have been a warning sign motivating early testing or/and a consequence of an inflammatory response to a higher viral load.

Persistence of symptoms beyond what is commonly expected in a flu-like syndrome, seems to be a common feature of COVID-19 [11–16,26]. Whereas in early 2020, the World Health Organization (WHO) reported a median time to recovery of 2 weeks in mild cases and 3-6 weeks in critically ill patients [10], several studies reported persistence of symptoms after several weeks in up to 80% of cases [11,12,26–28]. However, most of these persistent symptoms were reported in hospitalized patients and/or severe cases [11,12,27,28]. In our younger outpatient population of 429 individuals with a mild illness, the median time to

recovery was 4 weeks, longer than what was initially reported by the WHO [10] or by Lechien [18] with a mean disease duration of around 2 weeks.

Moreover, Petersen *et al.* from the Faroe Islands [26] reported at least one symptom after 2 months in 53% of 180 non-hospitalized COVID-19 patients. Logue *et al.* reported at least one symptom after 6 months in 32.7% of 150 COVID-19 outpatients [15] and Boscolo-Rizzo *et al.* reported at least one symptom after 12 months in 53% of 304 mild-to-moderate COVID-19 patients [14]. In contrast, in our cohort of 429 mild COVID-19 outpatients, the probability of persistent symptoms at 1 month was 46% and 14% after 2 months. Altogether these data suggest that SARS-CoV-2 infection is more complex than a standard respiratory viral infection.

Persistence of symptoms is not an uncommon finding in acute viral infections such as CMV infection or primary EBV infection [29–31]. Within the coronaviruses family, SARS-CoV-1 has also been associated with persistent symptoms, such as reported in 40% of individuals one year after initial infection with 25% meeting chronic asthenia syndrome criteria [32].

A better understanding of the risk factors for persistent symptoms is key to better advise patients with COVID-19 particularly in a context of mild illness where a rapid resumption to normal condition is expected. We identified four independent factors associated with symptom persistence: age over 40 years, female gender, ageusia, and high SARS-CoV-2 viral load.

Age is a marker of severity in COVID-19 [33,34], potentially related to a lesser immune response leading to longer persistence of the virus. While the mechanisms remain unknown, gender is a known risk factor for developing severe COVID-19 [33,34] and the role of estrogen as an immune response modulator has been suggested [35]. Experiencing anosmia

and ageusia has been reported to last potentially as long as several months as they may be due to SARS-CoV-2 injury to nerves [36,37]. Importantly, our study is the first to report the role of a higher baseline SARS-CoV-2 viral load in nasal cavities and of a long time between symptom onset and RT-PCR test in symptom persistence. This contrasts with a recent study by Peghin M *et al.* that did not find any correlation between Ct values and post-COVID-19 symptoms 6 months after acute infection among hospitalized and non-hospitalized patients [16]. SARS-CoV-2 high viral load and its persistence is a marker associated with severity and mortality in COVID-19 [21–24]. This is in accordance with many other viral diseases where the viral replication intensity is correlated with the severity of virus-induced damages either directly to the infected cells or tissues and/or indirectly through the inflammatory response [38,39], and delay in recovery is expected. This reinforces the urgent need for effective strategies on SARS-CoV-2 replication such as antiviral agents or monoclonal antibodies. Other studies, most of them including hospitalized patients, identified risk factors associated with persistent symptoms: older age [12,14,26], severe COVID-19 requiring hospitalization [12], body mass index [14], number of symptoms on admission [13] or in the acute phase [14], and presence of dyspnea [12].

Our study has several limitations. In the initial context of the first wave of COVID-19 during which this study was set up, the main focus was the symptoms of patients diagnosed with COVID-19, highly anxious about their immediate prognosis; therefore we did not thoroughly collect their medical history including comorbidities (even though they were young) and tobacco use. Nevertheless, comorbidities and tobacco use do not seem to be associated with persistent symptoms [12,13,18,26]. Weekly visits during the lockdown period were performed by phone calls which may have led to overestimate subjective perceptions from patients without any physical, biological, or imaging examination. Knowing that lockdowns

and social distancing can influence some common complaints (such as asthenia) and in the absence of a control group, it is difficult to determine the role of the viral illness itself in the clinical picture. We tried to control this bias by using a standardized questionnaire administered by medical doctors. For the above-mentioned reasons, we did not perform any psychological evaluation; we were thus not able to assess the influence of psychological disorders on symptom persistence. Moreover, our study mainly included HCWs, women, and people who registered in the COVIDOM system which could influence the generalizability of results to other populations since HCWs and patients registered in the COVIDOM system may be a unique population with high awareness of their medical condition. Finally, we presumed that our patients were infected by either the initial strain of SARS-CoV-2 or by the strain carrying the D614G mutation in the spike protein since they were the two dominant strains circulating globally at the time of the study [40]. It would be important, in the near future, to assess whether the emergence of new variants will impact the whole clinical course of COVID-19.

Conclusion

COVID-19 even in its mild clinical presentation is an acute infection with symptoms persisting over one month in up to 44% of outpatients. However, most of them had recovered at two months. Older people, women, individuals with a high nasal viral load, and patients with initial ageusia were more likely to suffer from persistent symptoms. A better understanding of the pathogenesis of persistent symptoms is highly needed. Decreasing virus load might help to shorten disease duration.

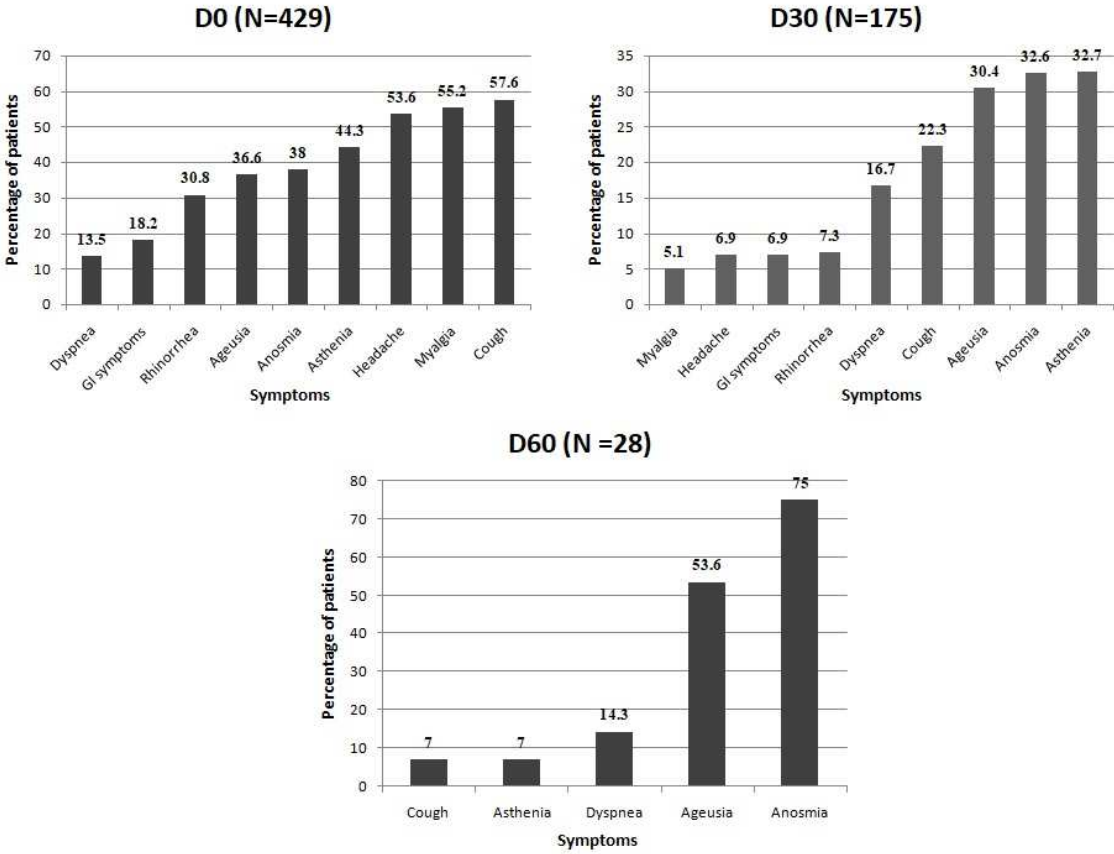
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Figure 1. Frequency of symptoms at Day 0, Day 30, and Day 60



GI: gastrointestinal

Figure 2. Probability of complete recovery from mild-to-moderate COVID-19 in 429 patients

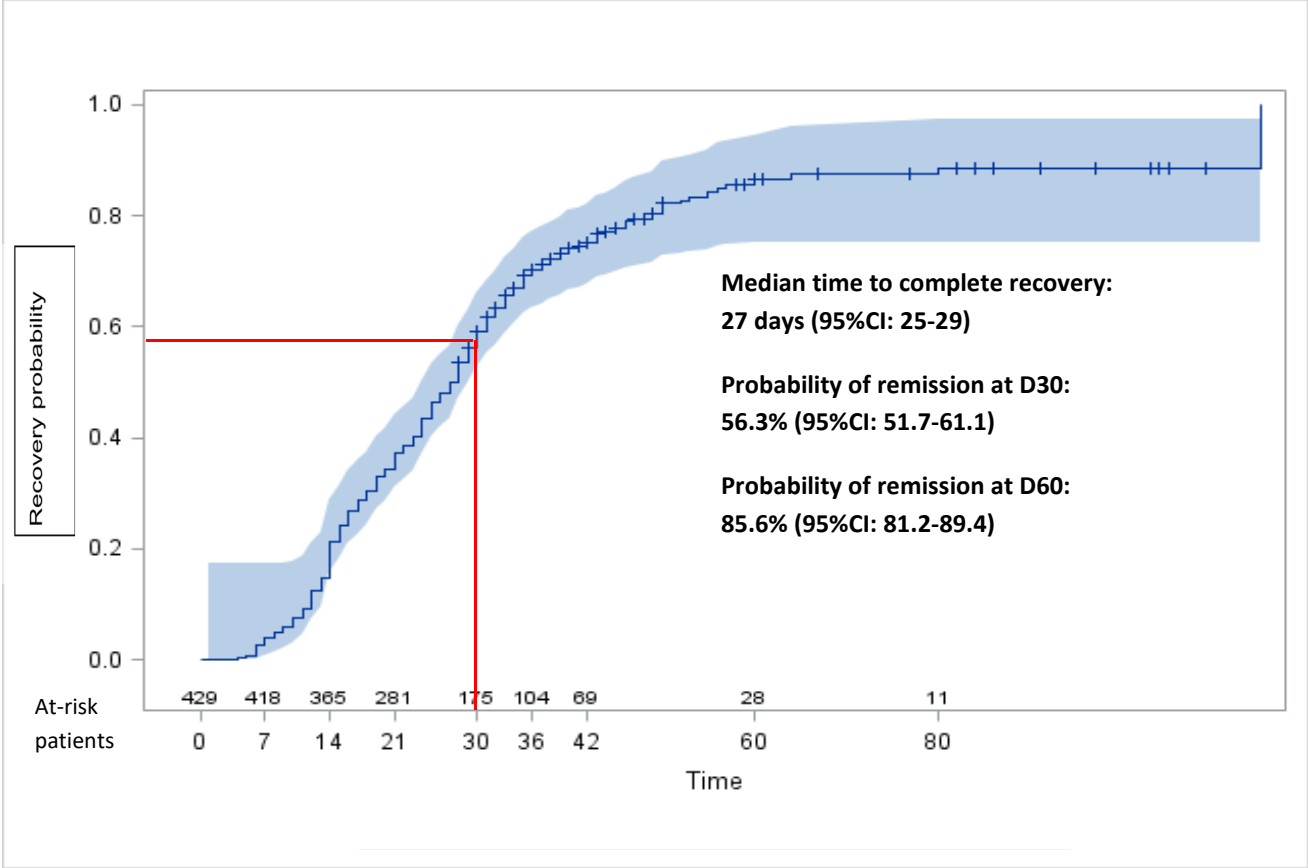
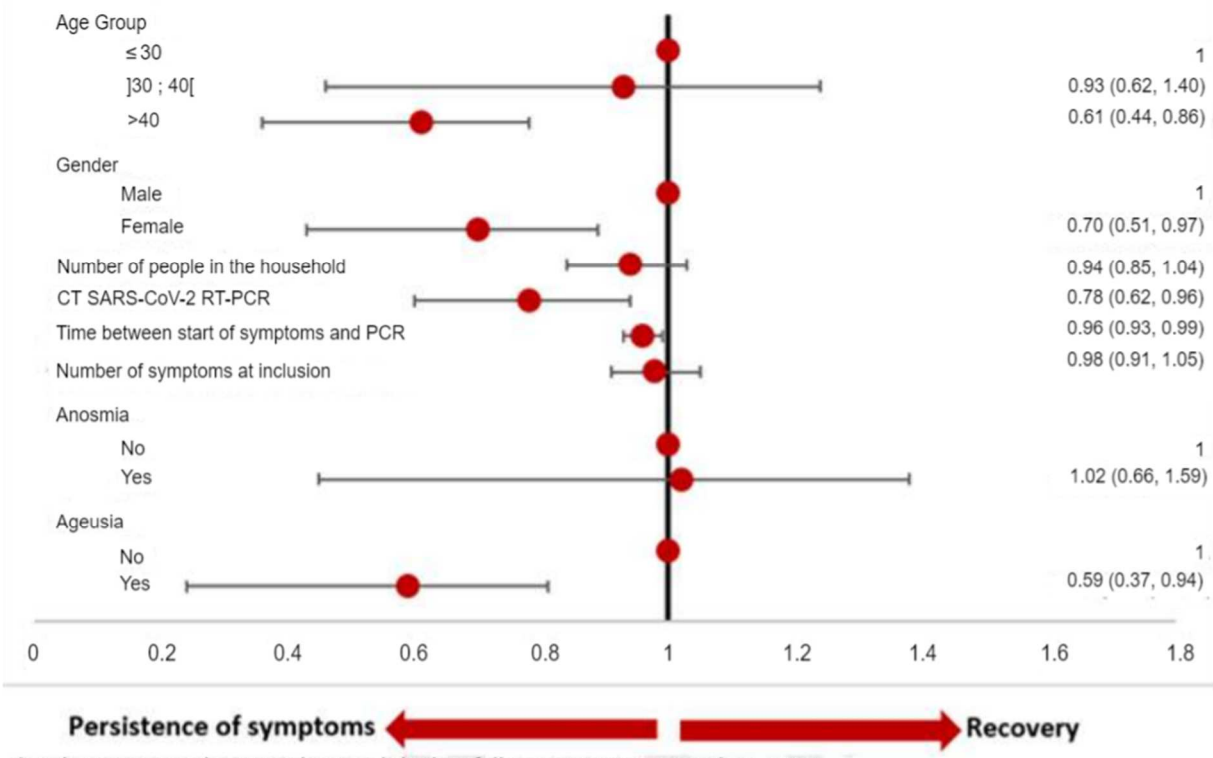


Figure 3. Multivariable analysis of factors associated with persistence of symptoms (between March 10 and July 3, 2020)*



* Inclusions started on March 10 and the last follow-up visit was on July 3, 2020

Table 1. Prevalence of symptoms associated with COVID-19 in 429 patients

| Symptoms | Frequency (%) |
|---------------------------|----------------------|
| Cough | 299 (69.7) |
| Asthenia | 295 (68.8) |
| Anosmia | 278 (64.8) |
| Headaches | 277 (64.6) |
| Myalgia | 269 (62.7) |
| Gastrointestinal symptoms | 265 (61.8) |
| Fever | 264 (61.5) |
| Ageusia | 261 (60.8) |
| Rhinorrhea | 190 (44.3) |
| Dyspnea | 139 (32.4) |
| Sore throat | 77 (17.9) |

Table 2. Univariable and multivariable analysis of factors associated with persistence of symptoms (between March 10 and July 3, 2020)*

| Variables | n | Complete resolution at day 30 | | Univariable analysis | | Multivariable analysis | |
|---|-------------------------|-------------------------------|------------------|----------------------|---------|------------------------|---------|
| | | No (n=175) | Yes (n=254) | HR (95%CI) | p value | HR (95%CI) | p value |
| Age | 429 | 44.9 (34.2-52.7) | 37.2 (29.4-50.2) | 0.99 (0.98-0.99) | 0.0058 | | |
| | ≤30 | 30 (28.0) | 77 (72.0) | 1 | | 1 | |
| | 429]30 ; 40] | 33 (33.3) | 66 (66.7) | 0.82 (0.61-1.11) | 0.0007 | 0.93 (0.62-1.40) | 0.0065 |
| | >40 | 112 (50.2) | 111 (49.8) | 0.62 (0.48-0.80) | | 0.61 (0.44-0.86) | |
| Gender | 429 | 38 (32.2) | 80 (67.8) | 1 | 0.0036 | 1 | 0.0332 |
| | Female | 137 (44.0) | 174 (56.0) | 0.71 (0.56-0.89) | | 0.70 (0.51-0.97) | |
| | Healthcare facility | 150 (39.6) | 229 (60.4) | 1 | | | |
| Place of work | 428 | 25 (51.0) | 24 (49.0) | 1.01 (0.73-1.42) | 0.941 | | |
| | Non-healthcare facility | | | | | | |
| Number of people in the household | 424 | 3 (2-4) | 2 (2-4) | 0.92 (0.85-0.99) | 0.02 | 0.94 (0.85-1.04) | 0.2532 |
| RT-PCR SARS-CoV-2 Ct, per additional 10 unit | 260 | 24.8 (20.6-32.5) | 25.9 (21.1-31.6) | 0.87 (0.71-1.06) | 0.1657 | 0.78 (0.62-0.96) | 0.0201 |
| Time from symptom onset to RT-PCR test | 411 | 4 (1-7) | 3 (1-5) | 0.97 (0.95-0.99) | 0.0112 | 0.96 (0.93-0.99) | 0.0161 |
| Number of symptoms at inclusion | 429 | 4 (3-6) | 4 (3-6) | 0.95 (0.90-1.00) | 0.0607 | 0.98 (0.91-1.05) | 0.5046 |

| | | | | | | | | |
|-------------------|-----|-----|------------|------------|------------------|--------|------------------|--------|
| Diarrhea | 429 | No | 140 (39.9) | 211 (60.1) | 1 | 0.6502 | | |
| | | Yes | 35 (44.9) | 43 (55.1) | 0.94 (0.71-1.24) | | | |
| Myalgia | 429 | No | 77 (40.1) | 115 (59.9) | 1 | 0.8001 | | |
| | | Yes | 98 (41.4) | 139 (58.6) | 1.03 (0.83-1.28) | | | |
| Asthenia | 429 | No | 95 (39.8) | 144 (60.2) | 1 | 0.2749 | | |
| | | Yes | 80 (42.1) | 110 (57.9) | 0.89 (0.72-1.10) | | | |
| Fever | 429 | No | 82 (42.5) | 111 (57.5) | 1 | 0.2768 | | |
| | | Yes | 93 (39.4) | 143 (60.6) | 1.13 (0.91-1.40) | | | |
| Cough | 429 | No | 69 (37.9) | 113 (62.1) | 1 | 0.5786 | | |
| | | Yes | 106 (42.9) | 141 (57.1) | 0.94 (0.76-1.17) | | | |
| Rhinorrhea | 429 | No | 125 (42.1) | 172 (57.9) | 1 | 0.9524 | | |
| | | Yes | 50 (37.9) | 82 (62.1) | 0.99 (0.79-1.25) | | | |
| Headaches | 429 | No | 89 (44.7) | 110 (55.3) | 1 | 0.7725 | | |
| | | Yes | 86 (37.4) | 144 (62.6) | 1.03 (0.83-1.28) | | | |
| Anosmia | 429 | No | 103 (38.7) | 163 (61.3) | 1 | 0.1658 | 1 | 0.9294 |
| | | Yes | 72 (44.2) | 91 (55.8) | 0.86 (0.69-1.07) | | 1.02 (0.66-1.59) | |
| Ageusia | 429 | No | 104 (38.2) | 168 (61.8) | 1 | 0.09 | 1 | 0.0248 |
| | | Yes | 71 (45.2) | 86 (54.8) | 0.82 (0.66-1.03) | | 0.59 (0.37-0.94) | |
| Dyspnea | 429 | No | 149 (40.2) | 222 (59.8) | 1 | 0.4923 | | |
| | | Yes | 26 (44.8) | 32 (55.2) | 0.89 (0.65-1.23) | | | |

HR=hazard ratio; Cox proportional hazard model was used to assess factors associated with symptom persistence.

* Inclusions started on March 10, 2020 and the last follow-up visit was on July 3, 2020.