Clinical characteristics of SARS-CoV-2 patients: a French cross-sectional study in primary care

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Abstract

Background: The early identification of patients suffering from SARS-CoV-2 infection in primary care is of outmost importance in the current pandemic.

Aim: To gain a better understanding of the specific symptoms of SARS-CoV-2 infection in primary care.

Design and setting: We conducted a cross-sectional study between March 24 and May 7, 2020, involving consecutive patients undergoing RT-PCR testing in two community-based laboratories in Lyon (France) for a suspicion of COVID-19.

Methods: We examined the association between various symptoms and a positive test using univariate and multivariate logistic regression, adjusted for clustering within the laboratories.

Results: Of the 1561 patients tested, 1543 agreed to participate (participation rate: 99%). Among them, 253 were positive for SARS-Cov-2 (16%). In multivariate analysis, loss of taste (OR 3.8 [95%CI 3.3-4.4], p-value<0.001), loss of smell (OR 3.0 [95%CI 1.9-4.8], p-value<0.001), muscle pain (OR 1.6 [95%CI 1.2-2.0], p-value 0.001) and dry nose (OR 1.3 [95%CI 1.1-1.6], p-value 0.01) were significantly associated with a positive result. The strength of association with taste and smell disorders was higher for symptom combinations (OR 6.5 [95%CI 3.9-10.8] for loss of taste and smell, OR 6.7 [95%CI 5.9-7.5] for loss of taste or smell). In contrast, sore throat (OR 0.6 [95%CI 0.4-0.8], p-value 0.003), stuffy nose (OR 0.7 [95%CI 0.6-0.7], p-value<0.001), diarrhea (OR 0.6 [95%CI 0.5-0.6], p-value<0.001) and dyspnea (OR 0.5 [95%CI 0.3-0.7], p-value<0.001) were inversely associated with a positive test.

Conclusion: Our data could further facilitate targeted screening and contribute to the triage and early identification of new clusters of cases.

How This Fits In

As with any emerging infectious disease, researchers focused initially on describing the clinical features of hospitalized patients with severe SARS-CoV-2 infections.

Only few data are available for outpatients or general populations, and, to our knowledge, there have been no published studies describing the clinical characteristics of primary care patients.

We showed that dry nose, loss of taste and/or smell and muscle pain were more frequent in patients with a positive test, while sore throat, stuffy nose, dyspnea and diarrhea were more frequent in patients with a negative result.

We also showed that the two symptoms most strongly associated with a positive test were loss of taste and loss of smell, and that the combination of these two symptoms resulted in an even stronger association.

Introduction

After its emergence in China in December 2019, [1,2] severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) hit Europe, which quickly became the epicenter of the epidemic in the spring of 2020. On 11 March 2020, WHO declared the outbreak of coronavirus disease 2019 (COVID-19) a pandemic, [3] and in all countries, primary care and emergency services have had to face the difficult diagnostic challenge defined by this new disease. [4]

In France, after the first three cases identified on 24 January 2020 in travelers returning from China, [5] the epidemic spread rapidly throughout the country, and put strong pressure on health systems, particularly hospitals. With nearly 30,000 deaths recorded at the end of May 2020, France is, as the UK, among the most bereaved countries in the world. [6]

As with any emerging infectious disease, researchers focused initially on describing the clinical features of hospitalized patients with severe infections. [7–11] However, as general practitioners (GPs), we are often on the front line in treating patients with mild to moderate disease, and we found that their symptoms did not always correspond to the clinical pictures described in the literature. Only few data are available for outpatients or general populations, [12–15] and, to our knowledge, there have been no published studies describing the clinical characteristics of primary care patients. Several symptoms appear specific to the infection, some of them being relatively frequent (e.g. smell and taste disorders), [16–18] others much rarer (such as frostbite). [19]

It is of utmost importance to gain a better understanding of the specific symptoms of SARS-CoV-2 infection in primary care settings in order to help GPs triage patients and anticipate medical follow-up. Indeed, if certain symptoms were found to be very specific to SARS-CoV-2 infection, this would facilitate targeted screening and rapid referral to RT-PCR testing. It could also limit the need to perform the test in certain patients with a very high probability of infection, knowing that this test is not always available, is relatively expensive, potentially unpleasant for the patient and risky for the caregiver performing it (risk of contamination). Although the political moto in several countries has been “test-test-test”, most of us have been faced with a limited capacity to do so. [4]

We therefore conducted a cross-sectional study in two community-based laboratories located in Lyon (France), equipped to receive primary care patients suspected of being infected with SARS-CoV-2, and to compare symptoms of patients with positive and negative RT-PCR tests. We hypothesized that in primary care patients infected with SARS-CoV-2 compared to those who are not, certain symptoms were more prevalent (mainly smell and taste disorders).

Methods

Study site and study population

This cross-sectional study was conducted between March 24 and May 7, 2020 in two community-based laboratories in Greater Lyon (a French city of almost 3 million inhabitants), to which general practitioners (GPs) refer patients with suspected COVID-19 for a nasopharyngeal smear (RT-PCR). Following the screening policy in France, patients were either referred by their GP or consulted spontaneously if they were healthcare professionals. We already published preliminary data from this study, focusing on smell and taste disorders. Here we extend the analysis to the entire sample of patients and the entire range of symptoms they present. [16]

Data Collection

Prior to being tested, patients were interviewed by the laboratory nurses using a pre-formatted questionnaire about their gender, age and medical conditions (asthma, hypertension, diabetes, immunosuppression, lung disease, pregnancy, stroke, ischemic heart disease, heart failure, obesity and cancer). They were also asked to report their symptoms (by answering yes or no) using a pre-determined list based on previous literature and expert opinion. [8,10] This list was separated into ENT symptoms (dry throat, dry nose, sore throat, stuffy nose (nasal congestion), loss of taste, loss of smell) and other symptoms (fever, fatigue, headache, muscle pain, chest pain, palpitations, cough, dyspnea, diarrhea, nausea). All questions were asked in plain language. There were no exclusion criteria for this study. Two study investigators (CC and MF) transcribed the paper-based responses into an Excel database, which was then transferred to STATA version 15.1.

Confidentiality and ethical approval

All data collected for the study were kept confidential. The study investigators did not know the names of the patients participating in the survey. Before completing the questionnaire, patients were required to read the information form and sign the consent form. The study was approved by the Ethics Committee of the *Collège National des Généralistes Enseignants* (number 200423163).

Diagnosis of COVID-19

Diagnosis of COVID-19 was based on the results of real-time RT-PCR (RT-qPCR), using respiratory samples obtained by nasopharyngeal swab. Two diagnostic kits were used in the study: Allplex 2019-nCoV Assay kit (SEEGENE) for the detection of RdRP and N genes specific for SARS-CoV-2 and E gene for all *Sarbecoviruses* including SARS-CoV-2, and Cobas SARS-CoV-2 Assay kit (ROCHE) for the detection of ORF1ab gene specific for SARS-CoV-2 and E gene for all *Sarbecoviruses* including SARS-CoV-2. [20]

Statistical analyses and sample size

We used frequency tables to summarize sociodemographic characteristics, except for age (median and interquartile range). We then used univariate logistic regression adjusted for clustering within the laboratories to examine the association between patient-reported symptoms and SARS-CoV-2 test positivity. We only examined symptoms that were frequently reported by patients (i.e. reported by at least 5% of patients). Nausea and palpitations were not included in the analysis (reported by less than 1.5% of

patients). Using multivariate logistic regression, we finally adjusted the data for gender, age group (five categories: <19, 20-39, 40-59, 60-79, and ≥ 80 years), patient population (health care provider vs. other), RT-PCR date (March, April or May 2020) and all other symptoms frequently reported by patients. Then, in order to estimate the diagnostic performance of each of these symptoms, we calculated their positive predictive value, i.e. the probability that the SARS-CoV-2 test will be positive in patients with these symptoms.

We also conducted sensitivity analyses for missing data. We repeated the bi- and multivariate comparison analyses after assigning the subgroup mean (conditional mean) to the missing data. The objective was to estimate the effect that the missing data might have on the observed differences between the groups.

We calculated the sample size required for our study using the formula for proportions estimated with a given precision. We anticipated symptom prevalence between 10 and 50%, and we wanted to be able to provide a 95% confidence interval width of about 0.05 for the estimate. The minimum required sample size ranged from 553 (for symptoms with 10% prevalence) to 1537 (for symptoms with 50% prevalence). Statistical significance was set at a two-tailed p-value ≤ 0.05 .

All statistical analyses were performed using STATA version 15.1 (College Station, USA).

Results

Of the 1561 patients tested in the two laboratories between March 24th and May 7th 2020, 1543 agreed to participate and were included in the study (participation rate: 99%). They were patients living in Greater Lyon. Table 1 summarizes their socio-demographic characteristics and medical conditions. They were predominantly female (63%) and their median age was 44 years. More than one-fourth were healthcare professionals. The most common medical problems encountered were asthma (13%) and hypertension (11%). Of the 1543 RT-PCR tests performed, 253 were positive for SARS-CoV-2 (16%). The proportion of positive tests decreased over time. In March, the proportion was 28%, in the first two weeks of April 22%, in the last two weeks of April 9%, and in May 4%.

Table 2 shows the proportion of symptoms reported by patients who tested negative and positive for SARS-CoV-2. The three most frequently reported ENT and non-ENT symptoms in patients who tested positive were dry throat (42%), loss of smell (36%) and loss of taste (31%), respectively fever (58%), cough (52%) and headache (45%). Compared to patients who tested negative, those who tested positive were significantly more likely to complain of dry nose, loss of taste, loss of smell, fever and muscle pain. On the other hand, they complained significantly less frequently about sore throat, stuffy nose, chest pain, headache, dyspnea and diarrhea.

Table 3 shows the association between these symptoms and test positivity in unadjusted and adjusted analyses. In multivariate analysis, loss of taste (OR 3.8 [95%CI 3.3-4.4]), loss of smell (OR 3.0 [95%CI 1.9-4.8]), muscle pain (OR 1.6 [95%CI 1.2-2.0]) and dry nose (OR 1.3 [95%CI 1.1-1.6]) were significantly

associated with a positive result. The strength of the association with smell and taste disorders was higher for symptom combinations (OR 6.5 [95%CI 3.9-10.8] for loss of taste and smell, OR 6.7 [95%CI 5.9-7.5] for loss of taste or smell. In contrast, sore throat (OR 0.6 [95%CI 0.4-0.8]), stuffy nose (OR 0.6 [95%CI 0.6-0.7]), diarrhea (OR 0.6 [95%CI 0.5-0.6]) and dyspnea (OR 0.5 [95%CI 0.3-0.7]) were inversely associated with a positive test. We estimated the positive predictive value for the two symptoms most strongly associated with a positive test (i.e. loss of taste and smell). This value was 53% (95%CI 44%-61%) in patients with loss of taste (79 patients tested positive out of 150 patients with loss of taste) and 50% (95%CI 43%-58%) in patients with loss of smell (90 out of 180 patients). This probability was 57% (95%CI 47%-67%) in the presence of both symptoms (56 out of 98 patients) and 49% (42%-55%) in the presence of at least one of the two symptoms (113 out of 232 patients).

We repeated the bi- and multivariate comparison analyses after assigning the subgroup mean (conditional mean) to the missing data. Results were similar and differences remained statistically significant between patients with positive and negative tests (data not shown).

Discussion

Summary

Our study sample consisted of 1543 primary care patients tested in two laboratories in the Lyon area (France), with 16% positive tests for SARS-CoV-2. We found that dry nose, loss of taste and/or smell and muscle pain were more frequent in patients with a positive test, while sore throat, stuffy nose, dyspnea and diarrhea were more frequent in patients with a negative result. We also found that the two symptoms most strongly associated with a positive test were loss of taste and smell, and that the combination of these two symptoms resulted in an even stronger association. The odds of having a positive test were more than six times greater than the odds of having a negative test if patients had loss of taste and/or smell.

Strengths and limitations

Several limitations must be kept in mind when considering the results. The study took place in a single French region (Greater Lyon). Our results are therefore not necessarily generalizable to other regions in France or to other countries. Due to the heavy workload in the SARS-CoV-2 screening laboratories, we did not ask the healthcare professionals receiving the patients to report the characteristics of those who refused to participate. We do not know if these 18 patients had different clinical presentations than those who agreed to participate. For the same reason (time constraint), we have only limited data on the socio-demographic characteristics of the participants. In particular, we do not have information on their socioeconomic level. We had a few dozen missing data for some important variables. However, if we carried out the bi- and multivariate comparison analyses after assigning the subgroup mean (conditional mean) to the missing data, the differences observed between the two groups of patients (patients with positive and negative tests) remained statistically significant. Finally, our results are also limited by the diagnostic performance of the nasal swabs for RT-PCR testing. The diagnostic performance (positive predictive

value) of the symptoms associated with a positive test could have been higher if, for example, RT-PCR tests had been combined with serological tests in our study.

Comparison with existing literature

The majority of patients with COVID-19 are thought to have mild to moderate disease and do not require hospitalization. However, it is of utmost importance to screen them in order to reduce the spread of the epidemic. Unfortunately, only a few studies described the clinical characteristics of these patients treated on an outpatient basis. [12–14] In the future, our results should help GPs to triage patients with infectious symptoms, especially in the winter period when the influenza virus is circulating.

We found that the three most frequently reported ENT and non-ENT symptoms in COVID-19 patients were dry throat (42%), loss of smell (36%) and loss of taste (31%), respectively fever (58%), cough (52%) and headache (45%). These prevalence data are quite different from those from a study conducted by ENT specialists in ambulatory patients recruited in French, Italian, Spanish, Belgian and Swiss hospitals (n=1566). [14] In this recently published study, the most frequent symptoms were headache (70%), loss of smell (70%), nasal obstruction (68%) and asthenia (63%). The data from our study also differed from those from studies conducted in China, which mainly involved hospitalized patients with severe infections. [7–11] For example, in the study by Huang et al (n=41 patients hospitalized in Wuhan), the most frequently reported symptoms were fever (98%), cough (76%) and dyspnea (55%), [11] while in the study by Wang et al (n=138 patients hospitalized in Wuhan), the most prevalent symptoms were fever (99%), fatigue (70%) and cough (59%). [10] The differences observed between these studies are likely explained by population differences. For the studies conducted in China, the patients were inpatients with severe infections (vs. outpatients with mild to moderate infections in our study). For the European study, a large proportion of these patients were included either following a consultation with a specialist (cardiologist, ENT, etc.) or following admission to the hospital emergency department. By contrast, our data came from patients who had consulted GPs, and self-referred health professionals. They thus likely represent a population of patients with milder presentations of SARS-CoV2 infection, typical of those in whom early identification through primary care will be of essence at the wake of the next epidemic wave.

As already suggested in our preliminary study, [16] we confirm that the two symptoms most strongly associated with a positive test were loss of taste and smell. Interestingly, the combination of these two symptoms results in an even stronger association. The adjusted OR was 6.5 for patients complaining of loss of taste and smell, while it was 6.7 for those complaining of either symptom. Several other authors have recently published similar results, particularly on European outpatient populations. [13–15,18,21] SARS-CoV-2 has been shown to have a particular tropism for the nerves of the ear, nose and throat system. [22] This is probably the reason why the proportion of patients with taste and smell disorders is higher in COVID-19 patients than in patients with other respiratory tract infections. The fact that in our study COVID-19 patients complained less frequently about stuffy nose than other patients (23% vs. 34%) is consistent with this hypothesis.

While the presence of a stuffy nose decreased the likelihood of a positive test, the presence of a dry nose increased it. These results are potentially interesting because, in combination with loss of taste and smell, they could theoretically increase the diagnostic performance of the ENT clinical evaluation.

We found that patients who tested positive were less likely to complain of dyspnea and diarrhea than patients who tested negative. This result is rather counter-intuitive as several authors showed that these two symptoms were relatively common in patients infected with CoV-2-SARS. [7–10,12,13] However, these were mainly data from hospital-based studies. The clinical pictures presented by these patients are not necessarily similar to those presented by outpatients with mild to moderate symptoms. For example, patients often require hospitalization because of oxygen desaturation due to lung involvement. Its high prevalence among inpatients certainly explains why they have more dyspnea than our community-based sample.

Implications for research and/or practice

The results of this study should be confirmed and refined in future studies, involving patients from various primary care context, to extend the external validity of these findings.

As explained above, we showed that taste and smell disorders were the most specific symptoms of CoV-2-SARS infection in our sample, and the specificity increased further when these two symptoms were combined. However, their diagnostic performance was not sufficient to confirm infection with sufficient safety in affected patients. Indeed, the positive predictive value (i.e. the probability of testing positive) was only 53% in patients with loss of taste, 50% in patients with loss of smell, 57% in the presence of both symptoms and 49% in the presence of at least one of the two symptoms. Furthermore, these diagnostic performances are expected to decrease as the prevalence of infection decreases.

Theoretically, it would be interesting to use the clinical characteristics of patients to promote targeted screening for CoV-2 SARS infection. However, our results suggesting a high risk of false positives do not encourage this approach across the board. This screening strategy could be used in cases of high prevalence of infection (e.g. typical symptoms in a second epidemic wave context) or in certain patients with a high probability of infection (e.g. typical symptoms and notion of close contact with an infected patient).

Conclusion

In conclusion, we found that dry nose, loss of taste and/or smell and muscle pain were more frequent in patients with a positive test, while sore throat, stuffy nose, dyspnea and diarrhea were more frequent in patients with a negative result. We confirmed that the two symptoms most strongly associated with a positive test were loss of taste and loss of smell, and that the combination of these two symptoms resulted in an even stronger association. These results could further inform triage and targeted screening in primary care.

Abbreviations

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Ethical approval: The research protocol has been approved by the ethics committee of CNGE (Collège National des Généralistes Enseignants).

Competing interests: none

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Tables

Table 1. Sociodemographic characteristics and medical conditions of 1543 patients included in the study

Characteristics	N (%) or median (IQR)
Female gender (n=1543)	964 (62.5)
Median age (n=1543)	44 (27)
Health care provider (n=1543)	434 (28.1)
Medical conditions (n=1225)	
Asthma	154 (12.6)
Hypertension	132 (10.8)
Immunosuppression	73 (6.0)
Diabetes	58 (4.7)
Lung disease ¹	45 (3.7)
Pregnancy	38 (3.1)
Stroke or ischemic heart disease ²	29 (2.4)
Heart failure	27 (2.2)
Obesity	26 (2.1)
Cancer	16 (1.3)

¹ number of available data: 1224

² number of available data: 1223

Table 2. Proportion of symptoms reported by patients with negative and positive SARS-CoV-2 RT-PCR test (N=1543)

Symptoms	Patients with negative test, N (%)	Patients with positive test, N (%)	p-value ¹
ENT symptoms			
Dry throat (n=1476)	506 (41.3)	106 (42.1)	0.76
Dry nose (n=1475)	225 (18.4)	67 (26.6)	<0.001
Sore throat (n=1517)	97 (7.7)	10 (4.0)	<0.001
Stuffy nose (n=1477)	410 (33.5)	59 (23.4)	0.02
Loss of taste (n=1543)	71 (5.5)	79 (31.2)	<0.001
Loss of smell (n=1543)	90 (7.0)	90 (35.6)	<0.001
Loss of taste and smell (n=1543)	42 (3.3)	56 (22.1)	<0.001
Loss of taste or smell (n=1543)	119 (9.2)	113 (44.7)	<0.001
Other symptoms			
Chest pain (n=1478)	264 (21.5)	43 (17.1)	<0.001
Fever (n=1497)	556 (44.7)	145 (57.5)	0.04
Fatigue (n=1517)	214 (16.9)	33 (13.2)	0.08
Headache (n=1487)	653 (52.9)	114 (45.2)	<0.001
Cough (n=1517)	563 (44.5)	130 (51.8)	0.27
Muscle pain (n=1517)	207 (16.4)	64 (25.5)	0.001
Dyspnea (n=1517)	200 (15.8)	23 (9.2)	<0.001
Diarrhea (n=1480)	358 (29.2)	48 (19.1)	0.04

¹ univariate logistic regression (adjusted for clustering within labs)

Table 3. Association between various symptoms, and positivity of the SARS-CoV-2 RT-PCR test (unadjusted and adjusted analysis)

Symptoms	Crude OR (95% CI)	p-value ¹	Adjusted OR (95%CI)	Adjusted p-value ²
ENT symptoms				
Dry throat	1.0 (0.9-1.2)	0.76	0.9 (0.6-1.2)	0.41
Dry nose	1.6 (1.6-1.6)	<0.001	1.3 (1.1-1.6)	0.01
Sore throat	0.5 (0.4-0.7)	<0.001	0.6 (0.4-0.8)	0.003
Stuffy nose	0.6 (0.4-0.9)	0.02	0.7 (0.6-0.7)	<0.001
Loss of taste	7.8 (6.2-9.9)	<0.001	3.8 (3.3-4.4)	<0.001
Loss of smell	7.4 (5.8-9.4)	<0.001	3.0 (1.9-4.8)	<0.001
Loss of taste and smell	8.5 (4.3-16.7)	<0.001	6.5 (3.9-10.8)	<0.001
Loss of taste or smell	8.0 (7.2-8.8)	<0.001	6.7 (5.9-7.5)	<0.001
Other symptoms				
Chest pain	0.8 (0.7-0.8)	<0.001	0.9 (0.7-1.1)	0.32
Fever	1.7 (1.0-2.8)	0.04	2.1 (0.7-5.9)	0.18
Fatigue	0.7 (0.5-1.0)	0.08	0.7 (0.4-1.1)	0.11
Headache	0.7 (0.6-0.9)	<0.001	1.0 (1.0-1.1)	0.46
Cough	1.3 (0.8-2.3)	0.27	1.0 (0.7-1.3)	0.81
Muscle pain	1.8 (1.3-2.5)	0.001	1.6 (1.2-2.0)	0.001
Dyspnea	0.5 (0.4-0.8)	<0.001	0.5 (0.3-0.7)	<0.001
Diarrhea	0.6 (0.3-1.0)	0.04	0.6 (0.5-0.6)	<0.001

¹ univariate logistic regression (adjusted for clustering within labs)

² multivariate logistic regression (adjusted for clustering within labs, gender, age group, patient population (health care provider vs. other), RT-PCR date (March, April or May), and all symptoms listed in the table)