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Epidemiology

Self-reported symptoms in French primary care SARS-CoV-2 patients: association with gender and age group

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Abstract

Introduction: The early identification of COVID-19 patients is of outmost importance in the current pandemic. As with other pathogens, presenting symptoms of SARS-CoV-2 may vary, depending on sociodemographic factors. We aimed to describe the clinical characteristics of COVID-19 patients by age/gender and to assess whether the diagnostic performance of these symptoms varied according to these variables.

Methods: We analysed data from a cross-sectional study involving primary care patients undergoing RT-PCR testing in Lyon, France. Among patients who tested positive, we examined whether there was an association between age/gender and various symptoms. In addition, we calculated the diagnostic performance of the most specific symptoms (smell/taste disorder).

Results: Among 1543 consecutive patients, 253 tested positive (16%). There were significant age/gender-related differences in symptoms. In middle-aged women, the diagnostic performance of smell/taste disorders were AUC = 0.65 [95%CI 0.59–0.71] and PPV = 72% [95%CI 53–87%], that is higher than in the entire sample (smell/taste disorders: AUC = 0.59 [95%CI 0.57–0.62] and PPV = 57% [95%CI 47–67%]. In contrast, the negative predictive values of smell/taste disorders were similar in both groups (85% [95%CI 81–89%] for middle-age women and 86% [95%CI 85–88%] for the entire sample).

Conclusion: We found significant age/gender-related differences in the clinical characteristics of COVID-19 patients. Screening strategies based on smell/taste disorders performed better in middle-aged women, but could not ensure a diagnosis of COVID-19 in any subgroup of patients. Future diagnostic strategies should use age/gender differentiated approaches.

Key words: Age, COVID-19, France, gender, primary care, symptoms

Background

The current COVID-19 pandemic is unprecedented. Depending on the severity of pneumonia and associated respiratory failure, four degrees of severity are described: mild, moderate, severe and critical disease (1). Patients with mild or moderate disease are generally screened as outpatients and often followed up in primary care. Documenting the diagnostic performance of the various symptoms experienced by these patients can inform targeted screening

Key Messages

- We identified that COVID-19 presenting symptoms differ by age and gender
- Women and middle-aged patients tended to have more symptoms
- Future prediction scores should use age and gender differentiated approaches

strategies. To the best of our knowledge, there is currently no screening test that can be used by general practitioners (GPs) examining patients suspected of having COVID-19.

We hypothesize that there are significant differences in COVID-19 clinical presentations between gender and age groups. This could lead to variations in the diagnostic performance of the symptoms experienced by patients. Unfortunately, most of the literature on the clinical features of COVID-19 is limited to inpatients (2–5), or patients presenting to hospital or outpatient clinics (6,7). Only a few studies were conducted with primary care patients (8,9), but, to the best of our knowledge, none of them evaluated the clinical manifestations of patients by gender and/or age group. Note that several other descriptive studies were carried out in outpatient settings, but they focused on a specific population (e.g. patients in nursing homes) (10) or a selected symptom (e.g. patients with smell and/or taste disorder) (11–16). Smell and taste disorders have been found to be a typical symptom of COVID-19 and two reviews recently updated the knowledge on this subject (17,18).

The aim of the present study was to describe, by gender and age group, the clinical characteristics of primary care COVID-19 patients. We also aimed to compute in the same subgroups of patients the diagnostic performance of smell and taste disorders (the most specific symptoms of COVID-19 in our study).

Methods

Study site and study population

This study was part of a larger project to describe the clinical characteristics of COVID-19 ambulatory patients. In the current paper, we present, by gender and age group, the prevalence of various symptoms and the diagnostic performance of smell and taste disorders (the most specific symptoms of COVID-19 in our study). We conducted this cross-sectional study between 24 March and 7 May 2020 in two clinical laboratories in Lyon (France) equipped to receive patients suspected of being infected with SARS-CoV-2. GPs in the region refer their patients to these two laboratories to perform a nasopharyngeal smear for RT-PCR. Following the screening policy in France, patients were either referred by their GP or came spontaneously (healthcare professionals).

Data collection

Before being tested, patients referred to the laboratory were asked to complete a paper questionnaire. This questionnaire included questions about their gender, age and medical conditions (whether or not they had hypertension, diabetes, obesity, ischemic heart disease, stroke, heart failure, asthma, lung disease, immunosuppression, pregnancy and cancer). They were also asked whether or not they had a number of symptoms according to a predetermined list based on the literature and expert opinion (2,19). One part of the symptoms concerned the ear–nose–throat area (dry throat, dry nose, sore throat, nasal congestion, loss of taste, loss of smell), a second part concerned other systems (fever, fatigue, headaches, muscle pain, chest pain, palpitations, cough, dyspnea, diarrhea, nausea). There were no exclusion criteria. All patients were eligible, regardless of their age.

Confidentiality and ethical approval

All information collected for the study were anonymous. The names of the patients participating in the study were not known to the study investigators. The study received ethics approval from the Ethics Committee of the *Collège National des Généralistes Enseignants* (ref: 200423163).

Diagnosis of COVID-19

Patients were diagnosed as having COVID-19 if they were positive on a real-time RT-PCR test (RT-qPCR) carried out on a respiratory sample obtained by nasopharyngeal swab. We used two diagnostic kits for the test. Cobas SARS-CoV-2 Assay (ROCHE) detects the *ORFlab* gene (specific for SARS-CoV-2) and the *E* gene (not specific). Allplex 2019-nCoV Assay (SEEGENE) detects *RdRP* and *N* genes (specific for SARS-CoV-2) and *E* gene (not specific).

Statistical analyses and sample size

We used chi-square tests to compare the proportion of positive RT-PCR tests, health care providers and medical conditions between groups. In the subgroup of COVID-19 patients, we used univariate logistic regressions adjusted for clustering within the laboratories to assess the association between patients' symptoms, and gender and age group. We excluded symptoms that were reported by <5% of patients: sore throat, nausea and palpitations. Using multivariate logistic regressions, we adjusted the data for gender, age group (<40 years, 40–60 years, >60 years), patient population (health care provider versus other), RT-PCR date (March, April or May) and medical conditions. The age groups in our study were chosen to be consistent with a study conducted by an ENT group on outpatients examined in 18 European hospitals (20). We calculated the diagnostic performance (sensitivity, specificity, ROC area (Area Under Curve, AUC), positive predictive value and negative predictive value) of two ENT symptoms (anosmia and ageusia), taken separately and combined, first for the complete sample, then for subgroups of patients (by gender and age group). We chose these symptoms because in our original study these symptoms showed the strongest association with RT-PCR positivity (21).

We calculated the required sample size for our primary study using the formula for proportions estimated with a given precision and found that the minimum required sample size ranged from 553 (for symptoms with 10% prevalence) to 1537 (for symptoms with 50% prevalence). For the current study, we calculated that a sample of COVID-19 patients from 35 (for symptoms with 10% prevalence) to 96 (for symptoms with 50% prevalence) would be sufficient to obtain prevalence estimates with a precision of ±10%. With an estimated proportion of positive tests at 15%, our sample of 1537 patients met these requirements. Statistical significance was set at a

two-tailed *P*-value ≤0.05. We carried out all statistical analyses using STATA version 15.1 (College Station, USA).

Results

Socio-demographic characteristics, medical conditions and RT-PCR positivity according to gender and age group

The study was proposed to 1561 consecutive patients. Of these, 1543 agreed to participate. Table 1 presents their sociodemographic characteristics and medical conditions, as well as the proportion of patients with RT-PCR positivity, overall and then by gender and age group (<40 years, 40–60 years, >60 years). Patients were predominantly female (63%) and relatively young (only 24% of patients were over 60 years of age). More than a quarter were health professionals. The two most frequently encountered medical problems (by more than 10% of patients) were asthma (13%) and hypertension (11%). There were 253 positive RT-PCR tests (16%). Compared to men, women were younger (<40 years: 44% versus 35% in men), were more likely to be health professionals and were in better health (only immunosuppression was statistically more prevalent among women). As expected, younger patients were in better health. Finally, the proportion of patients with RT-PCR positivity was similar in all subgroups.

Association between symptoms reported by patients with RT-PCR positivity, and gender and age groups

Table 2 shows the proportion of symptoms reported by patients who tested positive for SARS-CoV-2 (women: 62%, men: 38%), the following two tables show the unadjusted and adjusted association between gender (Table 3) and age group (Table 4), and the symptoms reported by these patients. In summary, women and middle-aged patients (40–60 years) tended to have more symptoms than men and younger or older patients. Men reported muscle pain more frequently than women. Compared to middle-aged patients, those under 40 years of age more frequently reported fever and muscle pain. Compared to middle-aged patients, those over 60 years of age more frequently reported anosmia and dyspnea.

Diagnostic performance of smell and taste disorders (the most specific symptoms of COVID-19 in our study)

Table 5 shows the diagnostic performance of smell and taste disorders, taken alone and combined, first in the entire sample, then in the subgroup of patients showing the strongest association with positive RT-PCR (women aged 40–60 years). The results for the six patient subgroups (men/women <40 years, men/women 40–60 years, men/women >40 years) are presented as supplementary material. The table allows a comparison of the diagnostic performance of smell and taste disorder by gender and age group.

Restricting the sample to only women aged 40–60 years resulted in improved diagnostic performance for these two symptoms (larger ROC area) as well as improved prediction of COVID-19 (higher positive predictive values). For example, these middle-aged women had a 72% probability of COVID-19 if both ENT symptoms were present (versus 57% for the full sample). In contrast, negative predictive values (i.e. the probability that patients without these symptoms truly did not have COVID-19) were similar. For example, the negative predictive value of the combination anosmia or ageusia was

Table 1. Sociodemographic characteristics and medical conditions of 1543 patients included in the study, overall and stratified by gender and age group

Characteristic	Overall, *N* (%)	Women, *N* (%)	Men, *N* (%)	*P*[a]	<40 years, *N* (%)	40–60 years, *N* (%)	>60 years, *N* (%)	*P*[a]
Positive RT-PCR test (*N* = 1543)	253 (16.4)	157 (16.3)	96 (16.6)	0.88	89 (14.1)	97 (18.1)	67 (17.9)	0.12
Female gender (*N* = 1543)	964 (62.5)	NA	NA	NA	428 (67.6)	321 (60.0)	215 (57.3)	**0.002**
Age group (*N* = 1543)				**0.002**				NA
<40 years	633 (41.0)	428 (44.4)	205 (35.4)		NA	NA	NA	
40–60 years	535 (34.7)	321 (33.3)	214 (37.0)		NA	NA	NA	
>60 years	375 (24.3)	215 (22.3)	160 (27.6)		NA	NA	NA	
Health care provider (*N* = 1543)	434 (28.1)	346 (44.2)	88 (19.9)	**<0.001**	240 (50.1)	162 (38.2)	32 (9.9)	**<0.001**
Medical conditions (*N* = 1225)								
Asthma	154 (12.6)	99 (12.6)	55 (12.4)	0.92	74 (15.5)	55 (13.0)	25 (7.8)	**0.01**
Hypertension	132 (10.8)	68 (8.7)	64 (14.5)	**0.002**	4 (0.8)	53 (12.5)	75 (23.3)	**<0.001**
Diabetes	58 (4.7)	25 (3.2)	33 (7.5)	**0.001**	7 (1.5)	17 (4.0)	34 (10.6)	**<0.001**
Immunosuppression	73 (6.0)	55 (7.0)	18 (4.1)	**0.04**	22 (4.6)	40 (9.4)	11 (3.4)	**0.001**
Lung disease	45 (3.7)	20 (2.6)	25 (5.7)	**0.01**	8 (1.7)	20 (4.7)	17 (5.3)	**0.01**
Pregnancy	38 (3.1)	38 (4.9)	NA	NA	35 (7.3)	3 (0.7)	0	**<0.001**
Stroke or ischemic heart disease	29 (2.4)	12 (1.5)	17 (3.9)	**0.01**	4 (0.8)	11 (2.6)	14 (4.4)	**0.01**
Heart failure	27 (2.2)	13 (1.7)	14 (3.2)	0.08	3 (0.6)	8 (1.9)	16 (5.0)	**<0.001**
Obesity	26 (2.1)	13 (1.7)	13 (2.9)	0.14	11 (2.3)	12 (2.8)	3 (0.9)	0.19
Cancer	16 (1.3)	11 (1.4)	5 (1.1)	0.69	3 (0.6)	7 (1.7)	6 (1.9)	0.24

[a]Chi-square tests.

Table 2. Proportion of symptoms reported by patients with positive SARS-CoV-2 RT-PCR test, stratified by gender and age group ($N = 253$)

Symptom	Women, *N* (%)	Men, *N* (%)	*P*[a]	<40 years, *N* (%)	40–60 years, *N* (%)	>60 years, *N* (%)	*P*[a,b]	*P*[a,c]
Overall	157 (62.1)	96 (37.9)	NA	89 (35.2)	97 (38.3)	67 (26.5)	NA	NA
ENT symptoms								
Dry throat[d]	66 (42.3)	40 (41.7)	0.94	34 (38.2)	46 (47.9)	26 (38.8)	0.27	0.39
Dry nose[d]	44 (28.2)	23 (24.0)	0.17	25 (28.1)	28 (29.2)	14 (20.9)	0.77	**<0.001**
Stuffy nose[d]	44 (28.2)	15 (15.6)	**<0.001**	22 (24.7)	27 (28.1)	10 (14.9)	**<0.001**	**<0.001**
Ageusia (loss of taste)	56 (35.7)	23 (24.0)	**<0.001**	32 (36.0)	37 (38.1)	10 (14.9)	0.73	**<0.001**
Anosmia (loss of smell)	62 (39.5)	28 (29.2)	**<0.001**	31 (34.8)	36 (37.1)	23 (34.3)	0.71	0.18
Ageusia and anosmia	43 (27.4)	13 (13.5)	**<0.001**	23 (25.8)	25 (25.8)	8 (11.9)	0.91	**<0.001**
Ageusia or anosmia	75 (47.8)	38 (39.6)	**<0.001**	40 (44.9)	48 (49.5)	25 (37.3)	**<0.001**	**<0.001**
Other symptoms								
Chest pain[d]	28 (18.0)	15 (15.6)	0.69	15 (16.9)	19 (19.8)	9 (13.4)	0.78	0.42
Fever[d]	83 (53.2)	62 (64.6)	0.34	53 (59.6)	48 (50.0)	44 (65.7)	**<0.001**	0.33
Fatigue[e]	21 (13.5)	12 (12.6)	0.83	7 (8.0)	16 (16.7)	10 (14.9)	**0.01**	0.87
Headache[d]	82 (52.6)	32 (33.3)	**<0.001**	45 (50.6)	51 (53.1)	18 (26.9)	0.83	**<0.001**
Cough[e]	73 (46.8)	57 (60.0)	**<0.001**	44 (50.0)	50 (52.1)	36 (53.7)	0.81	0.87
Muscle pain[e]	39 (25.0)	25 (26.3)	0.13	29 (33.0)	27 (28.1)	8 (11.9)	0.66	**<0.001**
Dyspnea[e]	18 (11.5)	5 (5.3)	0.44	5 (5.7)	11 (11.5)	7 (10.5)	**<0.001**	**<0.001**
Diarrhea[d]	37 (23.7)	11 (11.5)	**0.01**	13 (14.6)	23 (24.0)	12 (17.9)	0.05	**<0.001**

[a]Univariate logistic regression (adjusted for clustering within labs).

[b] *P*-value for comparison between patients aged 40–60 years and those under 40 years.

[c]*P*-value for comparison between patients aged 40–60 years and those over 60 years.

[d]Number of missing data = 1.

[e]Number of missing data = 2.

Table 3. Association between gender and symptoms reported by patients with positive SARS-CoV-2 RT PCR test

Symptom	Crude OR (95%CI)[a]	*P*[b]	Adjusted OR (95%CI)[a]	Adjusted *P*[c]
ENT symptoms				
Dry throat	1.0 (0.5–2.0)	0.94	0.8 (0.4–1.4)	0.34
Dry nose	1.3 (0.9–1.7)	0.17	1.1 (0.8–1.7)	0.56
Stuffy nose	2.1 (1.4–3.1)	**<0.001**	2.1 (1.7–2.7)	**<0.001**
Ageusia (loss of taste)	1.8 (1.3–2.4)	**<0.001**	1.2 (0.5–2.9)	0.65
Anosmia (loss of smell)	1.6 (1.3–2.0)	**<0.001**	1.4 (1.1–1.9)	**0.02**
Ageusia and anosmia	2.4 (2.3–2.6)	**<0.001**	1.7 (1.0–3.0)	0.06
Ageusia or anosmia	1.4 (1.4–1.4)	**<0.001**	1.1 (0.9–1.3)	0.26
Other symptoms				
Chest pain	1.2 (0.5–2.7)	0.69	0.9 (0.4–2.4)	0.86
Fever	0.6 (0.2–1.7)	0.34	0.7 (0.3–1.8)	0.43
Fatigue	1.1 (0.6–2.1)	0.83	1.1 (0.8–1.5)	0.62
Headache	2.2 (2.0–2.4)	**<0.001**	1.4 (1.4–1.4)	**<0.001**
Cough	0.6 (0.5–0.8)	**<0.001**	0.6 (0.4–1.1)	0.08
Muscle pain	0.9 (0.9–1.0)	0.13	0.6 (0.5–0.7)	**<0.001**
Dyspnea	2.4 (0.3–20.4)	0.44	2.3 (0.2–25.5)	0.50
Diarrhea	2.4 (1.2–4.7)	**0.01**	2.3 (1.3–4.3)	**0.01**

[a]Reference group: men.

[b]Univariate logistic regression (adjusted for clustering within labs).

[c]Multivariate logistic regression (adjusted for clustering within labs, age group, patient population (health care provider versus other), RT-PCR date (March, April or May), and all medical conditions listed in Table 1).

89% for the overall sample and 88% for the middle-aged subgroup of women.

Discussion

Our sample consisted of 1543 patients tested in two laboratories in the Lyon area (France), with 253 positive tests for SARS-CoV-2 (16%). We found that women and middle-aged patients (40–60 years) generally had more symptoms than men and younger or older patients. We also found that no symptom was specific enough to ensure a diagnosis of SARS CoV-2 infection in any subgroup of patients.

Comparison with existing literature

Gender differences in symptoms reported by patients with RT-PCR positivity

On the theme of COVID-19, there is obviously a large and growing amount of literature available to researchers. However, most publications on the clinical features of COVID-19 are limited to inpatients (2–5), or patients presenting to hospital or outpatient clinics (6,7). To the best of our knowledge, none of the studies conducted in primary care settings were designed to provide a picture of the clinical manifestations of patients by gender and/or age group. However, several studies that focused on ENT symptoms in ambulatory patients showed a higher prevalence or incidence of smell and/or taste disorders in women compared to men (11,16). A European ENT group published an article in which hospital physicians recruited COVID-19 outpatients in 18 European hospitals (20). This study found higher prevalence in women for anosmia, headache, nasal obstruction, sore throat and fatigue, and higher prevalence in men for cough and fever ($P < 0.001$).

Our results were relatively similar to these studies. In general, we found higher prevalence of symptoms in women compared to men. Interestingly, we also found higher prevalence of cough in men (60% versus 47%), but the difference was only statistically significant in the univariate analysis. Fever was also slightly more prevalent in men, but the difference was not statistically significant.

Further research is needed to explain these gender differences. With regard to ENT symptoms, it seems that women are more prone to develop olfactory disorders in case of viral infection, including infection with coronaviruses other than SARS-CoV-2 (20,22). In addition, researchers have shown that women were less prone to complications from viral infections, possibly due to protective factors related to sex chromosomes (20,23). In particular, it seems that women generally have a lower viral load and less inflammation than men. This may be the reason certain symptoms in our study were less prevalent in women, such as cough and muscle pain.

Age-related differences in symptoms reported by patients with RT-PCR positivity

As in our study, Lechien *et al*. also showed significant differences according to age (20). However, in contrast to the results for gender, those for age were very different between the two studies despite identical age groups (<40, 40–60, >60). In the study by Lechien *et al*., patients under 40 years of age were more likely to have ENT symptoms, while elderly patients were more likely to have non-ENT symptoms (mainly fever, fatigue, lack of appetite and diarrhea). The population of the two studies was not the same, which may explain at least part of these differences. Lechien *et al*.'s study was led by ENT researchers, COVID-19 patients were recruited by hospital physicians, and a number of patients were referred by cardiologists, respiratory physicians and ENT specialists. In contrast, our study included mainly patients referred to the laboratory by GPs.

Our results are consistent with other studies in infectiology, which show that elderly people often have fewer symptoms (or possibly atypical symptoms, such as delirium or falls at home) in, for example, lung or urinary tract infections (24–26). Our results are also partly consistent with several ambulatory studies on ENT symptoms that showed a lower prevalence or incidence of smell and/or taste disorder in elderly patients (11,12,16,27). In our study, elderly patients were less likely to report loss of taste as well as loss of taste and smell, but slightly more likely to report loss of smell.

Table 4. Association between age group and symptoms reported by patients with positive SARS-CoV-2 RT PCR test

Symptom	Crude OR (95% CI) for patients <40 years[a]	*P*[b]	Crude OR (95%CI) for patients >60 years[a]	*P*[b]	Adjusted OR (95% CI) for patients <40 years[a]	Adjusted *P*[c]	Adjusted OR (95%CI) for patients >60 years[a]	Adjusted *P*-value[c]
ENT symptoms								
Dry throat	0.7 (0.3–1.4)	0.27	0.7 (0.3–1.6)	0.39	0.8 (0.4–1.9)	0.65	0.7 (0.3–1.4)	0.31
Dry nose	1.0 (0.7–1.4)	0.77	0.6 (0.5–0.8)	**<0.001**	0.8 (0.5–1.3)	0.27	0.6 (0.5–0.9)	**0.002**
Stuffy nose	0.8 (0.8–0.9)	**<0.001**	0.5 (0.4–0.6)	**<0.001**	0.6 (0.4–1.1)	0.09	0.7 (0.2–2.2)	0.55
Ageusia (loss of taste)	0.9 (0.5–1.6)	0.73	0.3 (0.2–0.5)	**<0.001**	0.8 (0.3–2.1)	0.59	0.3 (0.2–0.4)	**<0.001**
Anosmia (loss of smell)	0.9 (0.5–1.5)	0.71	0.9 (0.7–1.1)	0.18	0.8 (0.7–0.9)	**<0.001**	1.2 (1.1–1.4)	**0.001**
Ageusia and anosmia	1.0 (1.0–1.1)	0.91	0.4 (0.3–0.5)	**<0.001**	0.8 (0.8–0.9)	**<0.001**	0.5 (0.3–0.6)	**<0.001**
Ageusia or anosmia	0.8 (0.8–0.9)	**<0.001**	0.6 (0.6–0.7)	**<0.001**	0.7 (0.3–1.7)	0.45	0.6 (0.3–1.2)	0.14
Other symptoms								
Chest pain	0.8 (0.2–3.2)	0.78	0.6 (0.2–2.0)	0.42	0.9 (0.1–6.0)	0.90	0.8 (0.4–1.4)	0.35
Fever	1.5 (1.4–1.6)	**<0.001**	1.9 (0.5–7.0)	0.33	1.6 (1.5–1.8)	**<0.001**	1.4 (0.4–4.7)	0.55
Fatigue	0.4 (0.2–0.9)	**0.01**	0.9 (0.2–4.4)	0.87	0.5 (0.2–1.5)	0.23	0.9 (0.2–4.1)	0.90
Headache	0.9 (0.4–2.4)	0.83	0.3 (0.2–0.5)	**<0.001**	1.1 (0.4–2.8)	0.85	0.6 (0.3–1.2)	0.13
Cough	0.9 (0.5–1.8)	0.81	1.1 (0.5–2.4)	0.87	0.9 (0.6–1.3)	0.56	0.8 (0.5–1.6)	0.61
Muscle pain	1.3 (0.5–3.4)	0.66	0.4 (0.2–0.5)	**<0.001**	2.0 (1.7–2.4)	**<0.001**	0.3 (0.2–0.4)	**<0.001**
Dyspnea	0.5 (0.4–0.6)	**<0.001**	0.9 (0.9–0.9)	**<0.001**	0.6 (0.2–1.3)	0.18	1.8 (1.5–2.2)	**<0.001**
Diarrhea	0.5 (0.3–1.0)	0.05	0.7 (0.6–0.8)	**<0.001**	0.5 (0.2–1.1)	0.07	1.0 (0.4–2.4)	0.96

[a]Reference group: patients aged 40–60 years.

[b]Univariate logistic regression (adjusted for clustering within labs).

[c]Multivariate logistic regression (adjusted for clustering within labs, gender, patient population (health care provider versus other), RT-PCR date (March, April or May), and all medical conditions listed in Table 1).

Table 5. Diagnostic performance of smell and/or taste disorders in the total sample (N = 1543) and in women aged 40–60 years (N = 321)

Symptom	Sensitivity, % (95%CI)	Specificity, % (95%CI)	ROC area (95%CI)	Positive predictive value, % (95%CI)	Negative predictive value, % (95%CI)
Total sample					
Anosmia (loss of smell)	35.6 (29.7–41.8)	93.0 (91.5–94.4)	0.64 (0.61–0.67)	50.0 (42.5–57.5)	88.0 (86.2–89.7)
Ageusia (loss of taste)	31.2 (25.6–37.3)	94.5 (93.1–95.7)	0.63 (0.60–0.66)	52.7 (44.4–60.9)	87.5 (85.7–89.2)
Anosmia and ageusia	22.1 (17.2–27.8)	96.7 (95.6–97.6)	0.59 (0.57–0.62)	57.1 (46.7–67.1)	86.4 (84.5–88.1)
Anosmia or ageusia	44.7 (38.4–51.0)	90.8 (89.1–92.3)	0.68 (0.65–0.71)	48.7 (42.1–55.3)	89.3 (87.5–90.9)
Women aged 40–60 years					
Anosmia (loss of smell)	42.2 (29.9–55.2)	93.0 (89.2–95.8)	0.68 (0.61–0.74)	60.0 (44.3–74.3)	86.6 (82.0–90.4)
Ageusia (loss of taste)	42.2 (29.9–55.2)	94.2 (90.6–96.7)	0.68 (0.62–0.74)	64.3 (48.0–78.4)	86.7 (82.2–90.5)
Anosmia and ageusia	32.8 (21.6–45.7)	96.9 (94.0–98.6)	0.65 (0.59–0.71)	72.4 (52.8–87.3)	85.3 (80.7–89.1)
Anosmia or ageusia	51.6 (38.7–64.2)	90.3 (86.0–93.6)	0.71 (0.65–0.77)	56.9 (43.2–69.8)	88.2 (83.7–91.8)

Diagnostic performance of smell and taste disorders (the most specific symptoms of COVID-19 in our study)

Our results may be useful for GPs examining patients with potential COVID-19. The presence of very specific symptoms of the infection, such as anosmia and ageusia, does not ensure a diagnosis of SARS-CoV-2 infection. The positive predictive value of the combination of anosmia and ageusia was only 57% in our study, meaning that 43% of patients complaining of anosmia and ageusia had a negative RT-PCR test. If we consider only middle-aged women (the subgroup of patients with the highest diagnostic performance for these ENT symptoms), the positive predictive value was higher (72%). Yet even in this subgroup of patients, the performance of these very specific symptoms was insufficient to allow targeted screening based on symptoms alone (28% of middle-aged women with anosmia and ageusia tested negative for SARS-CoV-2). In addition, the absence of these symptoms did not rule out COVID-19 with sufficient safety. The negative predictive value of the combination anosmia or ageusia was 89% for the overall sample (88% for the middle-aged subgroup of women). In other words, 11% of patients were infected despite the absence of both symptoms. Thus, even in middle-aged women, using anosmia and ageusia as a guide to decide about testing would be unreliable. The number of uninfected patients who are referred to RT-PCR testing would not be sufficiently reduced, and a large number of patients would be misdiagnosed as not having COVID-19.

Yet our results suggest that COVID-19's diagnostic strategy could be differentiated by gender and age group. Screening policies could differ, for example, in terms of the priority given to patients for screening tests, particularly in contexts in with limited or delayed access to such tests. These results may also be useful to researchers seeking to build a predictive score for COVID-19. Score development should consider different subpopulations based on gender and age. Such a screening tool would allow GPs to appropriately refer patients with few symptoms to RT-PCR screening or to avoid testing patients with a relatively high probability of COVID-19 when testing resources become scarce in an epidemic setting (28).

Limitations

Patients were recruited in only one region in France (the Lyon region). Therefore, our results are not necessarily generalizable to other regions of France or to other countries. Due to the heavy workload of the SARS-CoV-2 screening laboratories, no data were collected on patients who refused to participate. For the same reason (time constraint), we do not have complete data on the sociodemographic characteristics of the participants (e.g. their socio-economic level was not recorded). Similarly, we did not collect information about the severity or timing of the different symptoms. In the future, it could be important to investigate whether these elements are informative in predicting the probability of COVID-19. Finally, the results of our study are also limited by the diagnostic performance of the RT-PCR test, but we found no evidence suggesting that the diagnostic performance of the test differs according to gender or age.

Conclusion

In conclusion, we found that women and middle-aged patients (40–60 years) tended to have more symptoms than men and younger or older patients. We also found that no symptoms, even those that were very specific to the infection (such as smell and taste disorders) ensured a diagnosis of SARS CoV-2 infection in any subgroup of

patients. These results could help improve the triage of patients suspected of having COVID-19 in primary care medicine. In addition, they could inform the further development and validation of clinical scores for GPs.

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Declarations

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