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COVID-19 symptoms: a case–control study, Portugal, March–April 2020

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Short Paper

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Abstract

COVID-19, although a respiratory illness, has been clinically associated with non-respiratory symptoms. We conducted a negative case–control study to identify the symptoms associated with SARS-CoV-2-positive results in Portugal. Twelve symptoms and signs included in the clinical notification of COVID-19 were selected as predictors, and the dependent variable was the RT-PCR test result. The χ^2 tests were used to compare notified cases on sex, age group, health region and presence of comorbidities. The best-fit prediction model was selected using a backward stepwise method with an unconditional logistic regression. General and gastrointestinal symptoms were strongly associated with a positive test ($P < 0.001$). In this sense, the inclusion of general symptoms such as myalgia, headache and fatigue, as well as diarrhoea, together with actual clinical criteria for suspected cases, already updated and included in COVID-19 case definition, can lead to increased identification of cases and represent an effective strength for transmission control.

Introduction

COVID-19, the illness caused by SARS-CoV-2 virus, has a range of flu-like clinical manifestations, including cough, fever, fatigue, myalgia and shortness of breath [1]. Although resembling a common cold, this infection can cause serious respiratory illness, such as pneumonia and acute respiratory distress syndrome, especially in high-risk individuals [2]. Diagnosis of COVID-19 is usually based on the detection of SARS-CoV-2 by a reverse transcription polymerase-chain reaction (RT-PCR) testing of oropharyngeal or nasopharyngeal swabs, tracheal aspirate or bronchoalveolar lavage samples [3]. Patients with moderate or severe COVID-19 are usually hospitalised for observation and supportive care, since there is currently no specific treatment [4]. Early in the pandemic, the presence of non-respiratory symptoms, such as gastrointestinal and smell and taste disorders, was widely reported [5, 6]. Due to this, attention to COVID-19 patients with non-classic symptoms has been heightened, as well as their predictive value for test positivity [5, 7, 8].

The Portuguese National Epidemiological Surveillance System (SINAVE) is an electronic epidemiological surveillance system of all nationally notifiable diseases [9]. Notification is exclusively and compulsorily online, where clinicians and laboratories report each suspect case in a clinical and laboratorial disease-specific form, respectively [10]. The COVID-19 case report form was created in January 2020, and includes a clinical section with symptoms and signs for inquiry, based on international guidelines. The first diagnosed case of COVID-19 in Portugal was on 1 March, a symptomatic male with fever, cough and myalgia, and a recent travel history to a country with an active COVID-19 outbreak [11].

This study aims to better understand the clinical presentation of COVID-19 cases at the time of notification in Portugal, in order to update surveillance components. We aimed to identify which symptoms, at the time of notification, were associated with a positive RT-PCR result for SARS-CoV-2 among suspected cases in mainland Portugal between 1 March and 1 April 2020.

Case definition

For surveillance purposes, the national case definition aligned with guidance from the World Health Organization and the European Centre for Disease Control and Prevention (ECDC) [12, 13]. The criteria for testing until 8 March were: the presence of fever and/or cough and/or shortness of breath, in addition to an epidemiological link with a confirmed case or recent travel history to an affected country (the list of countries was frequently updated by

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the Portuguese Directorate-General of Health (DGS), according to the COVID-19 risk of transmission). On 9 March, the criteria for SARS-CoV-2 testing were widened to include hospitalised cases with severe pneumonia and no other apparent cause. On 26 March, Portugal entered the mitigation phase, and the criteria for testing were further expanded to include all cases of acute respiratory distress syndrome with cough or fever [13].

Methods

We extracted retrospective surveillance data on all COVID-19 suspected cases notified to SINAVE until 1 April 2020. Socio-demographic data were collected from each case report form, being automatically fed by the National Patient Record System. Data on clinical symptoms and signs were reported by clinicians on each case report form. An automatised procedure using structured query language algorithm was used to clean and merge both clinical and laboratory SINAVE databases. Posteriorly, a team of clinicians and epidemiologists cleaned, deduplicated, reviewed and cross-checked the data on each suspect case notification. Because completeness of the symptom variables ranged from 33.7% to 46.6%, we selected only those notifications with complete information on symptom variables for analysis.

Cases were defined as individuals with an RT-PCR-positive test result for SARS-CoV-2 virus and compared to controls, defined as all notifications on individuals with an RT-PCR-negative test result for SARS-CoV-2. Controls were chosen as we wanted to better understand the clinical presentation of COVID-19 cases compared to those with similar clinical presentation. No matching methods were used. All suspected cases that met the test criteria and were in mainland Portugal during the study period were tested and included in this study, since COVID-19 suspected cases notification in SINAVE is compulsory nationally. All 12 symptoms and signs included in the clinical notification of COVID-19 were selected as predictors (fever as tympanic temperature equal or above 38 °C, cough, shortness of breath, headache, myalgia, joint pain, fatigue, sore throat, chest pain, diarrhoea, nausea and abdominal pain). The dependent variable was the RT-PCR test result. The χ^2 tests were used to compare notified cases on sex, age group, health region and presence of comorbidities, defined as a binary variable on having a prior diagnosed chronic medical condition. Symptoms were first analysed using unconditional univariate logistic regression, assessed by calculating odds ratios and 95% confidence intervals. For model selection, a backward stepwise method was performed. To correct for possible confounding, we started with all variables of the study, a multiple adjustment and carried out a multivariate logistic regression. Variables with a P-value <0.001 in univariate analysis were included in the initial model. The best-fit prediction model was selected by choosing the one with the lowest Bayesian Information Criterion (BIC) score. Analyses were performed using STATA v.16 (Statacorp, Texas, USA).

Aggregated data were collected in the scope of national epidemiological surveillance, requiring no supplementary ethical clearance. Confidentiality and anonymity were protected, as no individual cases are identifiable in this analysis.

COVID-19 suspected cases

From 51 726 COVID-19 suspected cases notifications, 11 442 had sufficiently complete symptom data for analysis: 2031 (15.96%) tested positive for SARS-CoV-2. Among all COVID-19 suspected cases, 56.98% were female (Table 1), although this proportion was slightly lower among cases (52.1%, $P < 0.001$). Median age of controls was 43 years (s.d. ± 22.6), while among cases was 50 years (s.d. ± 19.8). The North region was the most affected area, with circa 50% of test-positive cases. A larger proportion of individuals in the SARS-CoV-2 test-positive group had comorbid conditions ($P < 0.001$).

Cases and controls differed significantly on age group, sex, health region and presence of comorbidities. Because cases and controls were not matched, we included these variables in further analysis of symptoms for multiple adjustment.

COVID-19 symptoms

Among test-positive cases, cough (73.0%, $n = 1483$), fever (59.7%, $n = 1212$), myalgia (43.9%, $n = 891$), headache (40.0%, $n = 812$) and fatigue (38%, $n = 771$) were most frequently reported (Table 2).

At the time of notification, the presence of general symptoms such as fever, myalgia, arthralgia, headache and fatigue, as well as gastrointestinal symptoms (diarrhoea and nausea or vomiting) was positively associated with COVID-19. Symptoms of chest pain, shortness of breath and abdominal pain were not associated with a positive test result in the univariate analysis.

For symptoms included in the case definition (presence of fever or cough or shortness of breath), only cases presenting with fever (alone or in combination with other symptoms) were strongly associated with a positive test for SARS-CoV- 2 (crude odds ratio (OR) 2.29, 95% CI 2.08–2.53). Those presenting with cough, alone or in combination with other symptoms, were 20% less likely to test positive for SARS-CoV-2 virus (95% CI 0.72–0.89) and for those presenting only with shortness of breath, the association with positive test outcome was not statistically significant (crude OR 0.94, 95% CI 0.84–1.05).

After multiple adjustment for symptoms, as well as age group, sex and health region, the best-fit model did not retain nausea or vomiting, arthralgia and presence of comorbidities (Table 3). In this multivariate model, the presence of fever, myalgia, headache, fatigue or diarrhoea was strongly associated with the outcome of positive SARS-CoV-2 test result.

General symptoms on this model were strongly associated with a positive test. Those who had fever were almost twice as likely to have a positive test as those presenting without fever (adjusted OR (aOR) 1.96, 95% CI 1.76–2.17). For respiratory symptoms, the presence of cough or sore throat was negatively associated with COVID-19 test positivity ($P < 0.001$). Diarrhoea increased by 42% the odds of testing positive (aOR 1.42, 95% CI 1.22–1.65). Running the same model only with multiple adjustment for symptoms, without including age, sex, health region and presence of comorbidities (possible cofounders), led to the same conclusions within groups of symptoms (Supplementary Table S1).

Discussion

Based on the results presented, symptoms most prevalent in SARS-CoV-2-positive cases were cough and fever, demonstrating testing criteria previously described in case definition. Nevertheless, we acknowledge also that myalgia, fatigue and headache, classified as general symptoms, were presented each in more than one-third of COVID-19 cases. Indeed, ECDC last updated case definition criteria on 29 May 2020, acknowledging additional less specific symptoms to be considered in clinical criteria. Headache, chills, myalgia, fatigue, vomiting and/or diarrhoea were described as to be considered [14].

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Table 1. Description of COVID-19 notifications with complete data, as of date of notification, by SARS-CoV-2 test result, Portugal, March–April 2020 ($n = 11\,442$)

	Total, $n = 11\,442$		SARS-CoV-2-positive, $n = 2031$		SARS-CoV-2-negative, $n = 9411$		
	n	%	*n*	%	*n*	%	*P* value (χ^2 test)
Sex							
Male	4922	43.0	973	47.0	3949	42.0	<0.001
Female	6520	57.0	1058	52.1	5462	58.0	
Age group (years)							
0–9	869	7.6	35	1.7	834	8.9	<0.001
10–19	625	5.5	75	3.7	550	5.8	
20–29	1275	11.1	204	10.0	1071	11.4	
30–39	1939	17.0	336	16.5	1603	17.0	
40–49	2073	18.1	348	17.1	1725	18.3	
50–59	1776	15.5	391	19.3	1385	14.7	
60–69	1219	10.7	288	14.2	931	9.9	
70–79	791	6.9	185	9.1	606	6.4	
80+	875	7.7	169	8.3	706	7.5	
Health region							
North	5007	43.8	1033	50.9	3974	42.2	<0.001
Centre	1636	14.3	261	12.9	1375	14.6	
Lisbon and Tagus Valley	3262	28.5	563	27.7	2699	28.7	
Alentejo	398	3.5	28	1.4	370	3.9	
Algarve	944	8.3	96	4.7	848	9.0	
Madeira	115	1.0	25	1.2	55	0.6	
Azores	80	0.7	25	1.2	90	1.0	
Comorbidities							
No	7030	61.4	1141	56.2	5889	62.6	<0.001
Yes	4412	38.6	890	43.8	3522	37.4	

In our study, non-respiratory symptoms, including general and gastrointestinal symptoms (diarrhoea), were strongly associated with a positive test for SARS-CoV-2. Based on 12 symptoms analysed, the most parsimonious model retained nine symptoms with the strongest association. Presence of fever, myalgia, headache, fatigue or diarrhoea was associated with a COVID-19 laboratory confirmation. Compared with other respiratory viruses, fatigue, headache and myalgia were more common among human coronavirus-infected patients [15]. This study highlights the predictive value of general non-respiratory symptoms as a differential tool to distinguish COVID-19 cases in the universe of respiratory symptoms patients.

This is not the first study where respiratory symptoms in COVID-19 cases played a minor role in predicting laboratory test results for SARS-CoV-2 [5, 8]. Although respiratory symptoms, such as cough, are frequent among COVID-19 cases and other human coronavirus infections, in our study, COVID-19 cases report less cough comparing to other respiratory viruses and less shortness of breath than other human coronaviruses [15]. Furthermore, some symptoms initially not diagnosed or not associated with this virus are being reported, such as smell and taste disorders [6]. In consequence, the addition of general and gastrointestinal symptoms proven to be strongly associated with a positive test for SARS-CoV-2 is an asset on cases identification and resource-saving. In fact, this study contributes to the evidence that supports last updates on COVID-19 case definitions, highlighting reported less specific symptoms [14].

This study has some limitations, as it reflects the clinical presentation of suspected and confirmed cases of COVID-19 at the time of notification. This means that we were assessing early symptoms in some cases, and several days of symptoms in others. Although methods exist to deal with missing data, completeness of data was a major issue in this analysis: due to poor completeness, we opted to analyse complete case reports to improve confidence in our results, though we cannot exclude the presence of a selection bias. In this sense, we compared our sample with all COVID-19 suspected cases regarding age, sex, presence of comorbidities and health region. Our sample was younger, had higher female proportion and reported less comorbidities at the time of notification ($P < 0.001$) (further details in Supplementary material S2). Although there is evidence on sex differences regarding COVID-19 mortality, the effect of sex on disease presentation and diagnosis is still not clear [16, 17]. There is also evidence on older age groups having a higher risk of atypical disease presentation (asthenia, delirium, fall), which is likely related to the higher

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Table 2. Frequency and univariate association of COVID-19 symptoms with test outcome, among SINAVE notified cases, Portugal, March–April 2020 ($n = 11\,442$)

	Total ($n = 11\,442$)		SARS-CoV-2-positive ($n = 2031$)		SARS-CoV-2-negative ($n = 9411$)					
Symptoms	*n*	%	*n*	%	*n*	%	OR (95% CI)	*P* value	aOR (95% CI)[a]	*P* value
General										
Fever	4902	42.8	1212	59.7	3690	39.2	**2.29** (2.08–2.53)	<0.001	**2.36** (2.14–2.61)	<0.001
Myalgia	3399	29.7	891	43.9	2508	26.7	**2.15** (1.95–2.37)	<0.001	**2.19** (1.98– 2.42)	<0.001
Arthralgia	449	3.9	124	6.1	325	3.5	**1.82** (1.47–2.25)	<0.001	**1.85** (1.49–2.30)	<0.001
Headache	3545	31.0	812	40.0	2733	29.0	**1.62** (1.47–1.80)	<0.001	**1.83** (1.65–2.03)	<0.001
Fatigue	3105	27.1	771	38.0	2334	24.8	**1.50** (1.39–1.61)	<0.001	**1.75** (1.58–1.94)	<0.001
Chest pain	1598	14.0	262	12.9	1336	14.2	0.90 (0.78–1.03)	0.127	0.90 (0.78–1.04)	0.169
Respiratory										
Shortness of breath	2834	24.8	483	23.8	2351	25.0	0.94 (0.84–1.05)	0.256	**0.79** (0.70–0.89)	<0.001
Cough	8738	76.4	1483	73.0	7255	77.1	**0.80** (0.72–0.89)	<0.001	**0.82** (0.73–0.92)	<0.001
Sore throat	3322	29.0	500	24.6	2822	30.0	**0.76** (0.68–0.85)	<0.001	**0.85** (0.76–0.95)	0.004
Gastrointestinal										
Diarrhoea	1144	10.0	290	14.3	854	9.1	**1.70** (1.45–1.93)	<0.001	**1.76** (1.53–2.04)	<0.001
Nausea or vomiting	907	7.9	202	10.0	705	7.5	**1.36** (1.16–1.61)	<0.001	**1.43** (1.21–1.69)	<0.001
Abdominal pain	670	5.9	134	6.6	536	5.7	1.17 (0.96–1.42)	0.117	1.22 (1.00–1.48)	0.054

Bold significants $P<0.05$.
[a]Symptoms, age group, sex, health region and comorbidities adjusted.

Table 3. Multivariate model on COVID-19 symptoms among SINAVE notified cases, Portugal, March–April 2020 ($n = 11\,442$)

Symptoms	aOR[a] (95% CI)	*P* value
General		
Fever	**1.96** (1.78–2.18)	<0.001
Myalgia	**1.64** (1.46–1.84)	<0.001
Headache	**1.44** (1.29–1.62)	<0.001
Fatigue	**1.24** (1.11–1.39)	<0.001
Respiratory		
Cough	**0.75** (0.67–0.85)	<0.001
Sore throat	**0.71** (0.63–0.80)	<0.001
Gastrointestinal		
Diarrhoea	**1.42** (1.22–1.65)	<0.001

[a]Symptoms, age group, sex and health region adjusted.

prevalence of comorbidities, being one of the variables that we adjusted for in our analysis [18]. Furthermore, due to the younger mean age in this sample, it is expected that the occurrence of SARS-CoV-2-positive test is higher in this group due to higher probability of typical clinical presentation, possibly overestimating the reported magnitude of the association. Individuals in our sample had a lower prevalence of comorbidities, leading to a likely underestimation of the association between having a prior medical precondition and a positive test result, since having the first increases the risk for SARS-CoV-2 infection [19]. In this comparison, variables presented small statistically significant differences, in both directions, and not surprisingly due to correspondent population and sample sizes. Due to the study design, identification of symptoms was dependent on accurate clinical documentation on SINAVE predefined questionnaire. Moreover, we acknowledge that some symptom misclassification likely exists, but expect that it is non-differential, as test outcomes were unknown at the time of their documentation.

Our results can be compared with the settings using the same case definition and similar surveillance system, due to comprehensiveness of detection and reporting of patients.

Conclusion

These results highlight that general and gastrointestinal symptoms, at the time of notification, are strongly associated with a positive test for SARS-CoV-2. In contrast, the presence of respiratory symptoms was less likely to lead to a positive test for SARS-CoV-2. Based on our findings, respiratory symptoms, such as cough, although frequent among cases, are negatively associated with COVID-19 case status. In this sense, the inclusion of general symptoms such as myalgia, headache and fatigue, as well as diarrhoea, together with actual clinical criteria for suspected cases, already updated and included in COVID-19 case definition, can lead to increased identification of cases and represent an effective strength for transmission control.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S095026882100042X

Data availability statement. The data that support the findings of this study are available from the Portuguese Directorate-General of Health

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(DGS). Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from the authors with the permission of DGS.

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Author contributions. MPD, RSM, HL, CC and RM conceived the study. MPD wrote the manuscript. RSM supervised the overall study. RM was responsible for data acquisition. MPD and CC did data cleaning and MPD analysed the data. RSM, DA and LH critically revised the manuscript.

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