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# Diagnosis of COVID-19 Based on Symptomatic Analysis of Hospital Healthcare Workers in Belgium

## Observational Study in a Large Belgian Tertiary Care Center During Early COVID-19 Outbreak

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**Objective:** To identify early symptoms allowing rapid appraisal of infection with SARS-CoV-2 among healthcare workers of a large Belgian hospital. **Methods:** Healthcare workers with mild symptoms of an acute respiratory tract infection were systematically screened on clinical characteristics of corona virus disease 2019 (COVID-19). A nasopharyngeal swab was taken and analyzed by real-time Reverse-Transcription-Polymerase-Chain-Reaction (rRT-PCR). **Results:** Fifty percent of 373 workers tested COVID-19 positive. The symptoms cough (82%), headache (78%), myalgia (70%), loss of smell or taste (40%), and fever more than or equal to 37.5 °C (76%) were significantly higher among those infected. **Conclusion:** Where each individual symptom contributes to the clinical evaluation of possible infection, it is the combination of COVID-19 symptoms that could allow for a rapid diagnostic appraisal of the disease in a high prevalence setting. Early transmission control is important at the onset of an epidemic.

**Keywords:** clinical diagnosis, COVID-19, hospital healthcare workers, rapid diagnostic appraisal, SARS-CoV-2

In Belgium, the first confirmed case of SARS-CoV-2 was reported on February 2, 2020; an asymptomatic person repatriated from Wuhan, China. The Italian authorities reported on February 22 clusters of cases in northern Italy. During the following 2 weeks, several European countries, including Belgium, increasingly reported new cases of COVID-19 in travelers from the affected areas in Italy, as well as cases without epidemiological links to Italy, China or other countries with ongoing transmission. In Belgium, the province of Limburg in the eastern part of Flanders became the epicenter of the

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Clinical significance: First Belgian study among suspected COVID-19 healthcare workers. Rapid symptomatic appraisal found early warning symptoms of SARS-CoV-2 infection. Fever is not the first symptom to look at. Cough, myalgia and loss of smell/taste are of critical importance. More research is needed to control virus-spread among professionals fighting it.

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### Learning Objectives

- Discuss the importance of early transmission control at the onset of an epidemic, with special reference to healthcare workers (HCWs) caring for patients with COVID-19.
- Summarize the new findings on clinical characteristics of COVID-19 among HCWs in a Belgian hospital early in the course of the pandemic.
- Discuss the implications for design of diagnostic strategies for HCWs at risk of COVID-19.

Belgian outbreak with the highest incidence across the country.<sup>1</sup> In a large non-academic tertiary hospital (Jessa) with 981 beds located in Hasselt, the provincial capital, the first patient with COVID-19 was admitted on March 11. At the start of the surge of the COVID-19 epidemic, the Belgian government canceled all elective admissions to general hospitals. The large majority of patients admitted to the Jessa hospital were diagnosed with COVID-19 thereafter. Until now, May 1, 490 patients have been admitted of which 322 were discharged, 88 died, and 80 are still being hospitalized.

At this point, evidence indicates that SARS-CoV-2 is mainly transmitted from human to human by infectious droplets<sup>2</sup> and that direct contact, rather than airborne spread, is the main transmission route as supported by evidence from contact tracing.<sup>3,4</sup> The average incubation period—period between infection and onset of symptoms—is about 4 to 6 days while 95% of individuals will develop symptoms within 14 days from infection.<sup>5–7</sup> Viral load in the upper respiratory tract is highest 1 day before and the first days after onset of symptoms.<sup>8–11</sup> Since coughing and sneezing increase the number of droplets that are expelled in the air or on surfaces, symptomatic individuals represent the highest transmission potential (in absence of containment measures) with a risk of infecting other people. A large spectrum of possible clinical manifestations is reported in COVID-19 patients, including symptoms and signs of neurological involvement (ie, chemosensory dysfunction, viral encephalitis, stroke), cardiac disease like myocarditis and cutaneous lesions (ie, erythematous rash, widespread urticaria).<sup>12–15</sup> Most SARS-CoV-2 infected people experience mild to moderate respiratory illness and recover without requiring hospital admission. The most common symptoms reported at the onset of illness are fever, cough, myalgia, fatigue, and headache.<sup>16–18</sup>

In this study, clinical characteristics suggestive for SARS-CoV-2 infection are compared with results from laboratory analysis of nasopharyngeal samples. The data in this study permit an early assessment of the clinical characteristics of COVID-19 in hospital healthcare workers in Belgium. However this study was not designed to look at the prevalence of different symptoms in COVID-19 patients. Rather, it enables us to look at the predictive value of certain symptoms suggestive for COVID-19. The aim was to assess symptoms that are most likely to contribute to a fast appraisal of potential

infected hospital healthcare workers and to provide early warning information that could slow down uncontrolled transmission.

## MATERIALS AND METHODS

### Case Study Descriptions

Early during the outbreak of COVID-19 in Belgium, all hospital healthcare workers self-reporting mild symptoms of an acute upper- or lower respiratory tract infection were tested in a large non-academic hospital with a high number of admitted COVID-19 patients. In the period March 9 to April 17 a total of 373 symptomatic healthcare workers were tested at the onset of illness. To limit sampling technique errors across patients, a deep nasopharyngeal swab was taken by a single occupational health nurse from the occupational health service Mensura. When laboratory analysis was inconclusive a second or third sample was taken within 48 hours of the previous one. Based on the anamnesis performed by the occupational health service Mensura, we scored 11 clinical manifestations possibly related to SARS-CoV-2 infection: temperature (highest measured within 24 hours before testing without the use of antipyretic medication), cough, headache, myalgia, sore throat, shortness of breath (dyspnea), runny or stuffy nose, sneezing, fatigue, diarrhea, and loss of smell/taste (anosmia and dysgeusia). Following the national guidelines of Sciensano, based on those of the CDC, positive tested healthcare workers were isolated at home for 7 days or longer until at least 24 hours after resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (eg, cough, shortness of breath). Return to work was only allowed after approval of the occupational health physician.<sup>19</sup>

### Definitions Used

#### Suspected Case

Hospital healthcare workers presenting with mild symptoms of an acute respiratory infection.

#### Probable Case

A suspected case where real-time Reverse-Transcription-Polymerase-Chain-Reaction (rRT-PCR) testing for SARS-CoV-2 was inconclusive.

#### Confirmed Case

A suspected case with laboratory confirmation of SARS-CoV-2 by rRT-PCR testing.

### Screening Criteria during Early Onset of the Epidemic in Belgium

Healthcare workers with respiratory complaints and fever, according to the national guidelines for PCR-testing for SARS-CoV-2 by Sciensano, based on those of the World Health Organization (WHO) and the European Center for Disease Control (ECDC). Because fever was not well-defined and is not always present in the early onset of infection, it was not included as one of the criteria for screening in our hospital but was scored as one of the suggestive symptoms for SARS-CoV-2 infection.<sup>19</sup>

### Typical Cold Symptoms

The CDC defines “typical cold symptoms” as sneezing, stuffy nose, sore throat, and mild to moderate cough and/or chest discomfort.

### rRT-PCR for SARS-CoV-2 on Nasopharyngeal Swabs

A deep nasopharyngeal swab was taken from all symptomatic hospital healthcare workers (Nasopharyngeal FLOQSwab, 1 mL in Liquid Amies Medium, 482CE, Copan) and sent to laboratory for detection of SARS-CoV-2 by rRT-PCR. A total of 383 nasopharyngeal

swabs were analyzed from 373 hospital workers (nine probable cases were tested a second time, one a third time). For each sample a lysis step was performed by adding Maxwell Lysis Buffer (Promega, Southampton, UK) and proteinase K (Qiagen, Hilden, Germany). An extraction and amplification control (Phocine Distemper Virus, kindly provided by the Department of Viroscience, Erasmus Medical Centre, Rotterdam, The Netherlands) was added to each sample. Nucleic acid extraction was done with the Maxwell RSC Viral TNA kit (Promega) on the Maxwell RSC Instrument (Promega) according to the manufacturers' instructions. An in-house rRT-PCR, based on the CDC oligonucleotide primers and probes for detection of the viral nucleocapsid (N) gene of 2019-nCoV (2019-nCoV\_N1), was performed on the Quantstudio 7 flex (ThermoFisher, Waltham, MA).<sup>20</sup> Our real-time reverse transcriptase PCR was extensively validated, limit of detection was 50 viral copies/mL, analytical specificity was 100%.

### Statistical Analysis

Descriptive data are presented as frequencies and percentages. Only the first rRT-PCR test was used in further analysis because of the focus on early symptoms of COVID-19 in this study. The continuous variable fever is presented as mean and standard deviation (SD). To present differences in prevalence of symptoms between COVID-19 positive and COVID-19 negative tested hospital workers in a radar chart, the variable fever was dichotomized (more than or equal to 37.5 °C). The chi-square test was used to test differences between groups for discrete data, the *t* test for continuous data. To identify associated factors of COVID-19, logistic regression was used. Variables with a *P*-value < 0.20 were entered simultaneously in a multivariate logistic regression model to test the associations' independency. A correlation analysis was used to test for multicollinearity between the independent variables (Spearman's  $\rho$  < 0.60). SPSS 26.0 (SPSS Inc., Chicago, IL) was used for the statistical analyses. The significance was set at *P* < 0.05.

## RESULTS

In our sample group of 373 hospital healthcare workers, the majority were women (77.8%). Most healthcare workers that consulted the occupational health service were in their 30s or 40s (Table 1).

### Prevalence of Covid-19

Figure 1 shows the daily number of COVID-19 positive and COVID-19 negative tested hospital workers, together with the cumulative numbers. In total, 49.9% (*n* = 185) tested COVID-19 positive, with peaks in the period from March 23 to April 6, 2020. In two cases out of 373, the test was inconclusive and therefore excluded for further analysis.

### General Characteristics and Symptoms

An overview of general characteristics and symptoms of COVID-19 positive and COVID-19 negative tested hospital workers are presented in Table 1. Significant differences (*P* < 0.05) between COVID-19 negative and COVID-19 positive tested hospital workers were found for the symptoms cough, sore throat, headache, myalgia, loss of smell/taste, and fever. Significant higher prevalence among COVID-19 positive tested hospital workers were found for cough (82.2% vs 65.6%), headache (78.4% vs 62.4%), myalgia (70.3% vs 51.6%), loss of smell/taste (39.7% vs 10.3%), and fever more than or equal to 37.5 °C (75.7% vs 67.1%) (Fig. 2). A significant (*P* < 0.05) higher proportion of men tested COVID-19 positive (60.2% vs 46.9% women). A significant difference (*P* < 0.05) between COVID-19 positive tested men and women was found for the symptom fatigue (90.0% vs 71.9% respectively). The highest prevalence of COVID-19 was observed in the age group less than 30 (60.5%). Loss of smell/taste was highest among the youngest group of hospital workers (50.0%, 37.8%, 41.9%, 32.3%, and 0.0% or age groups less than 30, 30 to 39, 40 to 49, 50 to 59, more than 60 respectively). Myalgia was

**TABLE 1.** Characteristics and Symptoms of COVID-19 Positive Versus COVID-19 Negative Hospital Workers

	<i>N</i>	COVID-19 Negative <i>n</i> (%)	COVID-19 Positive <i>n</i> (%)	<i>P</i> -Value
Gender				0.032
Male	83	–	50 (60.24%)	
Female	288	–	135 (46.88%)	
Age				0.043
<30	76	–	46 (60.53%)	
30–39	112	–	46 (41.44%)	
40–49	102	–	50 (49.51%)	
50–59	65	–	37 (56.92%)	
≥60	18	–	6 (33.33%)	
Symptoms				
Cough	371	122/186 (65.59%)	152/185 (82.16%)	<0.001
Sore throat	371	117/186 (62.90%)	93/185 (50.27%)	0.014
Runny or stuffy nose	370	108/185 (58.38%)	94/185 (50.81%)	0.144
Headache	371	116/186 (62.37%)	145/185 (78.38%)	<0.001
Myalgia	371	96/186 (51.61%)	130/185 (70.27%)	<0.001
Diarrhea	371	48/186 (25.81%)	36/185 (19.46%)	0.144
Fatigue	371	126/186 (67.74%)	142/185 (76.76%)	0.053
Shortness of breath	371	77/186 (41.40%)	74/185 (40.00%)	0.784
Sneezing	371	76/186 (40.86%)	66/185 (35.68%)	0.304
Loss of smell	312	16/156 (10.26%)	62/156 (39.74%)	<0.001
		<b>Mean (SD)</b>	<b>Mean (SD)</b>	
Fever	318	37.55 (.78)	37.85 (.76)	0.001

highest in the age group 50 to 59 (78.4%), followed by age group 40 to 49 (78.0%) and lowest in the age group < 30 (58.7%). Typical cold symptoms were highest in the age group less than 30. 69.6% of tested hospital workers in this age group presented with a runny or stuffy nose, 63.0% reported a sore throat, and 43.5% reported sneezing.

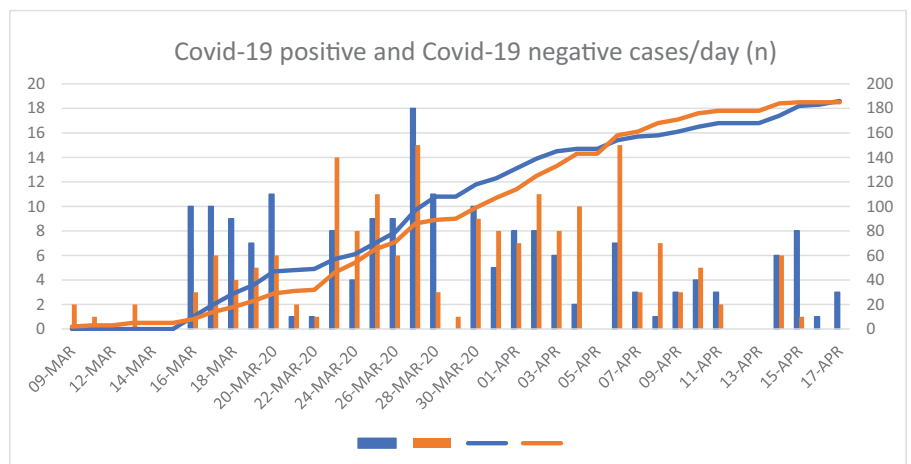
**Associated Factors**

Univariate analysis showed that fever, cough, headache, myalgia, and loss of smell/taste were independently associated with a higher prevalence of COVID-19 infection; a sore throat was found to be negatively associated (Table 2). The multivariate model demonstrated no significant association for headache. No multicollinearity was observed between the independent factors.

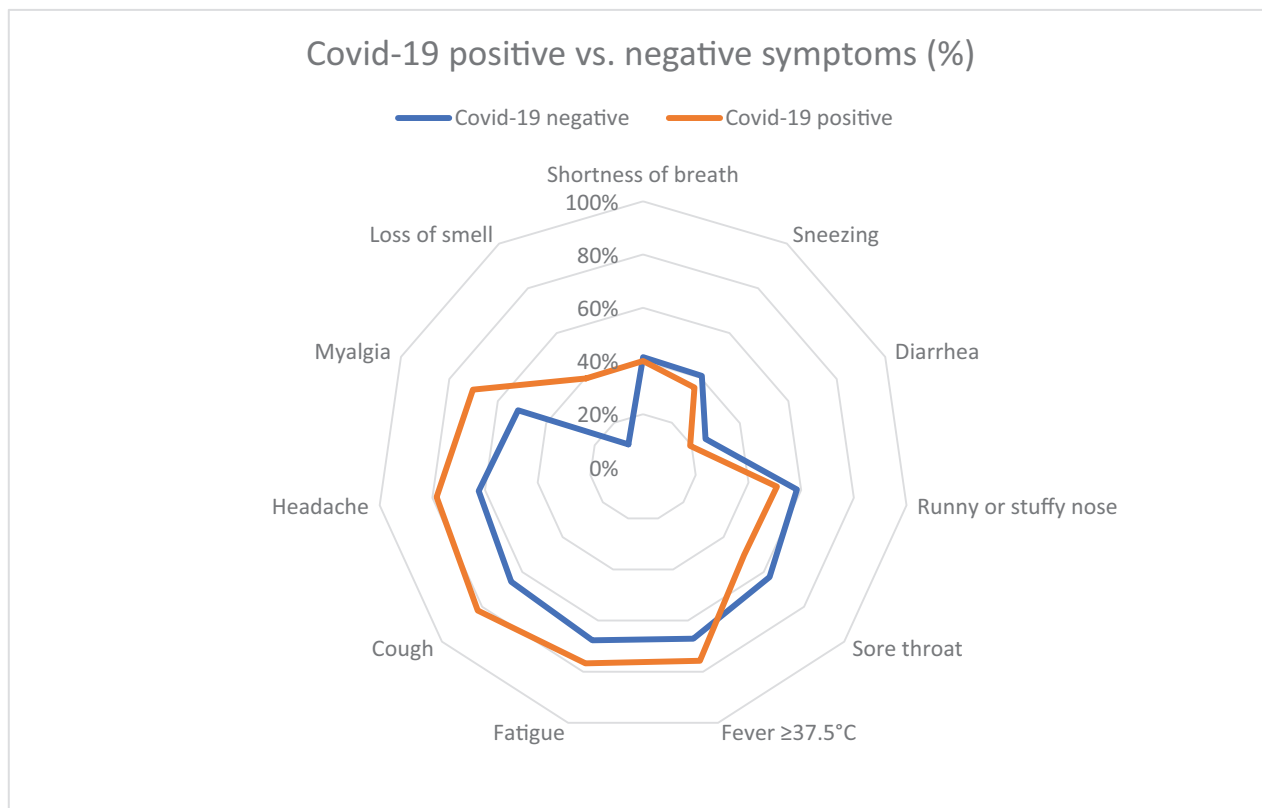
**DISCUSSION**

In concert with recent studies<sup>21,22</sup> we know that the clinical presentation of COVID-19 mimics those of the Asian severe acute

respiratory syndrome coronavirus (SARS-CoV). Since gastro-intestinal symptoms are less common than when infected with SARS-CoV and the seasonal influenza virus, SARS-CoV-2 suggests a difference in viral tropism.<sup>17</sup> The absence of fever in COVID-19 is more frequent than in infections caused by other coronaviruses<sup>23</sup> so afebrile patients may be missed if the surveillance case definition focuses on fever detection according to the WHO guidelines.<sup>24</sup> We found that cough, headache, myalgia, loss of smell and fever (more than or equal to 37.5 °C) were more common among COVID-19 positive versus COVID-19 negative tested cases. Our results confirm or in part contradict previous findings in patient groups, without any specific emphasis to the subpopulation of healthcare workers.<sup>7,16,17</sup> These findings were confirmed by Tian et al<sup>18</sup> who described the characteristics of COVID-19 at the illness onset in 133 hospitalized patients from more than 20 families in Beijing. Interestingly, chemosensory dysfunction, such as loss of smell (anosmia) and taste (dysgeusia), either isolated or in combination with other symptoms, are increasingly reported in the clinical presentation of COVID-19 in relation to mild-to-moderate forms of the disease—



**FIGURE 1.** Number of daily COVID-19 positive and COVID-19 negative tested hospital workers.



**FIGURE 2.** Symptoms of COVID-19 positive versus COVID-19 negative hospital workers.

including in a European multicenter study.<sup>25,26</sup> Meanwhile, loss of smell/taste was also added to the list of COVID-19-like symptoms by the WHO. Notably, loss of smell has been reported after infection with other respiratory- or coronaviruses.<sup>27</sup> Increasingly, self-assessment apps for COVID-19 diagnosis based on self-reported symptoms, are being promoted to the public. A recent study based on the data registered by the COVID Symptom Tracker smartphone app in the UK, showed that of all participants who tested positive for COVID-19, 59% reported losing their sense of smell, compared with 18% of those

who tested negative.<sup>28</sup> To our knowledge, there are no data published yet of the results of self-assessment in healthcare workers. It would be worthwhile to analyze this type of data in the subset of healthcare workers since presumably different transmission types of SARS-CoV-2 RNA, coming from close contacts with patients with a much higher viral load, can occur.

Our study suffers from the usual limitations of initial investigations of infections with an emerging novel pathogen, particularly during the early phase, when little is known about any aspect of the

**TABLE 2.** Univariate and Multivariate Binary Logistic Regression With COVID-19 Positive as Dependent Variable and Symptoms and Gender as Independent Variables

	Univariate			Multivariate		
	β (SE)	OR [95% CI]	P-Value	β (SE)	OR [95% CI]	P-Value
Symptoms						
Fever	0.51 (0.15)	1.67 [1.23–2.26]	<0.001	0.49 (0.19)	1.62 [1.12–2.35]	0.01
Cough*	0.88 (0.25)	2.42 [1.49–3.92]	<0.001	1.27 (0.34)	3.56 [1.84–6.89]	<0.001
Sore throat*	−0.52 (0.21)	0.60 [0.39–0.90]	0.014	−0.77 (0.31)	0.47 [0.26–0.85]	0.012
Runny or stuffy nose*	−0.31 (0.21)	0.74 [0.49–1.11]	0.144	−0.24 (0.30)	0.79 [0.44–1.41]	0.419
Headache*	0.78 (0.23)	2.19 [1.38–3.46]	<0.001	0.52 (0.35)	1.68 [0.85–3.35]	0.137
Myalgia*	0.80 (0.22)	2.22 [1.45–3.40]	<0.001	0.67 (0.32)	1.96 [1.05–3.66]	0.035
Diarrhea*	−0.36 (0.25)	0.70 [0.43–1.13]	0.145	−0.55 (0.34)	0.58 [0.30–1.13]	0.110
Fatigue*	0.45 (0.23)	1.57 [0.99–2.45]	0.053	−0.18 (0.34)	0.83 [0.43–1.61]	0.590
Shortness of breath*	−0.06 (0.21)	0.94 [0.62–1.43]	0.784	–	–	–
Sneezing*	−0.22 (0.21)	0.80 [0.53–1.22]	0.305	–	–	–
Loss of smell*	1.75 (0.31)	5.77 [3.14–10.61]	<0.001	2.22 (0.40)	9.21 [4.21–20.13]	<0.001
Gender†	0.54 (0.25)	1.72 [1.05–2.82]	0.033	0.17 (0.37)	1.19 [0.58–2.43]	0.006

CI, confidence interval; OR, Odds ratio; SE, Standard Error.

\*Reference category is no.

†Reference category is female.

outbreak. To increase the sensitivity for early detection and diagnosis, epidemiology history has been continually modified once more information has become available. This study focuses on healthcare workers presenting with mild symptoms. Therefore not all healthcare workers were tested—only symptomatic ones. This may have biased up estimates of symptom prevalence. Further, because of design, the sensitivity or specificity of symptom-based definitions cannot be tested—only the positive and negative predictive value (which are dependent upon the prevalence of the population). Whereas the initial focus of case detection was on patients with fever, we now understand that infected cases can present with mild respiratory symptoms without fever. Early infections with atypical presentations may have been missed.

Similar to the Symptom Tracker app in the UK, we think different innovative actions could optimize public health. Developing an appropriate digital diagnostic strategy for healthcare workers such as an institutionalized real time data evaluation of suggestive symptoms for COVID-19 could allow for a rapid diagnostic appraisal. A personalized early warning system based on adequate detection of changes in several clinical parameters is crucial to mitigate further spread at the onset of the disease. The working case definitions may also need to be refined as more is learned about the clinical characteristics and outbreak dynamics. The characteristics of cases should continue to be monitored to identify any changes in epidemiology. Future studies could include forecasts of the epidemic dynamics and special studies of person-to-person transmission in healthcare workers, and sero-surveys to determine the incidence of the subclinical infections would be valuable.

## CONCLUSIONS

Early transmission control is crucial to mitigate the risks of fast spreading of SARS-CoV-2. Certainly among healthcare workers who have an increased risk of high viral load exposure and a higher risk of infecting other patients at work. Considering that the viral loads in the upper respiratory tract are highest in the day prior but also the initial days of symptom onset, a more rapid clinical diagnosis could prevent further transmission of the virus by isolating the victim in an early stage of infection. Prior to the identification of SARS-CoV-2 RNA by rRT-PCR testing, the clinical assessment contributes to speed up the diagnostic process of COVID-19. Based on the type and combination of symptoms, an infection with SARS-CoV-2 can be predicted more accurately and allow for a rapid diagnostic appraisal of the disease in a high prevalence setting. The presence of cough, myalgia, loss of smell/taste in combination with fever more than 37.5 °C has a high positive predictive value for SARS-CoV-2 infection. Further research is needed to support this type of early healthcare worker appraisal based on the prevalence of clinical manifestations and in a more automated preventative strategy, including future self-assessment and monitoring tools.

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