

## Article

# COVID-19-related symptoms among cancer patients and healthcare workers— First results from the PAPESCO-19 prospective cohort study.

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**Simple Summary:** COVID-19 has some similar clinical manifestations to the side effects of cancer treatments. Cancer patients may fail to distinguish COVID-19 symptoms from their treatment-related symptoms. The PAPESCO-19 study has investigated thirteen COVID-19-related symptoms and confirmed that, in combination with anorexia, fever, headache, and rhinorrhea, anosmia has a strong association with COVID-19 for cancer patients while dysgeusia/ageusia does not.

**Citation:** Last name, F.; Last name, F.; Last name, F. Title. *Cancers* **2021**, *13*, x. <https://doi.org/10.3390/xxxxx>

**Abstract: Background:** Cancer patients may fail to distinguish COVID-19 symptoms such as anosmia, dysgeusia/ageusia, anorexia, headache, and fatigue, which are frequent after cancer treatments. We aimed to identify symptoms associated with COVID-19 and to assess the strength of their association in cancer and cancer-free populations. **Methods:** The prospective multicenter cohort study PAPESCO-19 included 878 cancer patients and 940 healthcare workers (HCWs) systematically tested for SARS-CoV-2-specific antibodies. Participants reported the results of routine screening RT-PCR and thirteen COVID-19 symptoms. Backward logistic regression identified the symptom combinations significantly associated with COVID-19. **Results:** COVID+ proportions were similar in patients (8%) and HCWs (9.5%,  $p=0.26$ ), whereas symptomatic proportions were lower in patients (32%) than HCWs (52%,  $p<0.001$ ). Anosmia, anorexia, fever, headache, and rhinorrhea together accurately discriminated ( $c$ -statistic=0.7027) COVID-19 cases in patients. Anosmia, dysgeusia/ageusia, muscle pain, intense fatigue, headache, and chest pain better discriminated ( $c$ -statistic=0.8830) COVID-19 cases in HCWs. Anosmia had the strongest association in patients (OR=7.48, 95% CI: 2.96–18.89) and HCWs (OR=5.71, 95% CI: 2.21–14.75). **Conclusions:** COVID-19 symptoms and their diagnostic performance differ in cancer patients and HCWs. Anosmia is associated with COVID-19 for patients,

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while dysgeusia/ageusia are not. Cancer patients deserve tailored preventive measures due to their particular COVID-19 symptom pattern.

**Keywords:** cancer; COVID-19; symptoms; healthcare workers; anosmia; dysgeusia; ageusia; France; serological test ; RT-PCR

## 1. Introduction

The COVID-19 pandemic has affected the global population. The cancer population might be more susceptible to SARS-CoV-2 infection [1]. Patients who have had hematological malignancy, lung cancer or metastatic cancer, or undergone surgery or immunotherapy, are at higher risk of a severe clinical outcome (i.e. severe symptoms, admission to an intensive care unit, use of mechanical ventilation or death) [2–5]. Clinical factors, such as advanced cancer stage and cancer subtype, may be associated with poorer COVID-19 outcomes [1,2,5] alongside age, gender, and comorbidities [5–8]. As a result, cancer patients deserve particular attention when identifying the specific early symptoms of COVID-19 for further diagnosis and care.

The combination of specific symptoms, including anosmia, dysgeusia or ageusia, persistent cough, and fever, makes it possible to clinically identify individuals with COVID-19 [9–16]. A systematic review suggests anosmia as a frequent symptom (i.e. ranging from 22% to 68%) ahead of dysgeusia/ageusia (33% and 20%, respectively) in COVID-19 patients [17]. Studies reporting associations between seroprevalence and self-reported symptoms in healthcare workers (HCWs) have found that anosmia and ageusia, fever, malaise, and fatigue are especially common [18,19].

Smell and taste alteration are frequently observed in cancer patients during cancer treatments [20–25]. UK clinicians have raised concerns about anosmia and ageusia, recommended that oncology patients be carefully advised, and called for more evidence on this topic [26]. However, to the best of our knowledge, no study has investigated the predictive values of COVID-19-related anosmia or dysgeusia/ageusia in patients undergoing certain cancer treatments.

This paper hypothesizes that symptoms including anosmia and dysgeusia/ageusia are less likely to be associated with COVID-19 positivity in cancer patients than in cancer-free population.

We are conducting a French prospective cohort study involving cancer patients and HCWs, who are systematically tested for SARS-CoV-2 infection during the ongoing pandemic as described below. This paper aims to identify the symptoms associated with COVID-19 positivity and to investigate whether they differ between cancer patients and HCW populations. Our findings may serve to guide the COVID-19 diagnostic, screening, and prevention strategy for cancer patients.

## 2. Materials and Methods

### 2.1 Study design and Setting

We initiated a prospective multicenter cohort study involving patients and HCWs — PAPESCO-19 (*PAtients et PErsonnels de Santé des Centres de Lutte Contre le Cancer pendant l'épidémie de COvid-19*) — at comprehensive cancer centers located in three different French regions: in Western France, with the Nantes and Angers sites of the ICO Cancer Center; in Eastern France, with the Lorraine Cancer Center in Nancy; and in Central France, with the Jean Perrin Cancer Center in Clermont-Ferrand [27]. The three regions are of interest as the 2020 COVID-19 epidemic had different local impacts [28]. The PAPESCO-19 study consists of four work packages enabling different foci: i/ serological and clinical, ii/ public health, iii/ economic, and iv/ psychological. We planned to include 3,500 individuals.

The study is ongoing. For the current analysis based on the 'clinical work package', we therefore used data collected between June 17, 2020 for first enrollment and November 30, 2020, the approximate end of the second wave, allowing us to capture two epidemic wave effects.

### 2.2 Participants

We included patients aged  $\geq 18$  years attending cancer centers as part of their ongoing active treatment (such as radiotherapy, surgery, immunotherapy, and chemotherapy) or monitoring (i.e. treatment completed over a year ago). HCWs (nurses and clinicians as

well as other cancer center staff) informed by emails or on the cancer center intranet were voluntarily enrolled. Participants were eligible irrespective of whether they had presented with symptoms since the COVID-19 outbreak. There were no exclusion criteria. The inclusion period was one year with follow-up visits planned every three months. Participants signed an informed consent form. The study is being conducted in accordance with the Declaration of Helsinki. The Ethics Committee (CPP-IDF VIII, Boulogne-Billancourt) approved our study number 20.04.15 on May 15, 2020.

### *2.3 Data collection*

At baseline and follow-up, all participants completed questionnaires for sociodemographic and lifestyle-related characteristics, and for COVID-19-related history (including exposure to COVID-19-infected people, self-reported COVID-19 symptoms as detailed below, results of previous RT-PCR tests, and ambulatory care service use). For patients, baseline demographic data (age and sex), cancer history, and clinical details were recorded in electronic case report forms (CRFs). For HCWs, we collected demographics (age and sex), job, and occupation types (such as physician, nurse, assistant nurse, pharmacist, other healthcare professional), as well as clinical data (e.g. self-reported body weight and height, comorbidities, comedications) based on a self-completed questionnaire.

Rapid lateral flow immunoassay tests (NG Biotech®, SureScreen® Diagnostics) for SARS-CoV-2-specific antibodies were performed on blood samples collected at baseline and each follow-up [29,30].

Participants also reported the results of routine RT-PCR tests because of symptoms or possible contacts, independently of this study.

Participants reported symptoms since the beginning of the epidemic at baseline and since the previous visit for follow-up. In the CRF, any presence of COVID-19-related symptoms (Yes or No) and onset date were reported before blood sampling. In the questionnaire, we included detailed predefined symptoms said to be unrelated to any treatment with onset and end dates. They were: fever  $>38^{\circ}\text{C}$ , headache, anosmia, dysgeusia/ageusia, rhinorrhea, unusual cough, shortness of breath, body ache and muscle pain, intense fatigue, anorexia, red eyes (conjunctivitis), digestive disorders (including diarrhea, vomiting, and abdominal pain), and chest pain [31,32].

### *2.4 COVID-19 test outcomes and symptoms*

The main outcome was COVID-19 test results defined as follows. We considered participants with at least one positive serological test or RT-PCR result as SARS-CoV-2 infected (COVID+) and those with negative or uncertain serological results with a negative RT-PCR result as uninfected (COVID-).

In the analysis of symptoms, participants who had any of the thirteen listed symptoms were called symptomatic and those with none of the thirteen listed symptoms asymptomatic.

We then analyzed the association of COVID-19 positive tests with symptoms.

### *2.5 Statistical analysis*

We estimated the proportions of participants with positive serological tests or positive self-reported RT-PCR tests with a 95% confidence interval (CI). When relevant, we assessed the differences between the patient and personnel subpopulations using logistic regression for binary variables and the Kruskal-Wallis test for continuous variables.

In univariable analysis, we estimated the proportion of symptoms in COVID+ and COVID- participants and the association of COVID-19 test outcomes with symptoms in logistic regression to estimate the Odds Ratio (OR) of the association. We also estimated the sensitivity (Se), specificity (Sp), and OR for every single symptom. All the diagnostic performance indicators were reported with a 95% CI.

We further investigated the symptom pattern associated with a positive COVID-19 test in a multivariable model. Backward logistic regression was performed, starting with a full model including the thirteen symptoms with a variable entry and removal threshold of  $p=0.20$ . We used the Akaike information criterion (AIC) for model selection. The model was developed independently in the patient and HCW subpopulations.

We reported the models' Se, Sp, and accuracy values. C-statistic was used to evaluate the models' performance and discrimination ability [33,34]. We validated the models within datasets of 75% random samples and 25% random samples of each subpopulation. We also evaluated the models' performance within the subgroups of defined gender, median age for patients and HCWs, and cancer features (only for patients). To account for differences in epidemic exposure at the cancer centers, we included Nantes and Angers simultaneously in the model, and the Nancy and Clermont-Ferrand centers together.

Of note, we reported the number of missing data in the descriptive tables and calculated percentages by excluding them. No imputation was made since the missing data were not included as covariates in the regression analysis.

The Ennov Clinical® system was used for data collection, and SAS® 8.3 and STATA® 14.2 were used for statistical analysis.

### 3. Results

#### 3.1 Population characteristics

878 patients and 940 HCWs were enrolled. The median age was 62 years (range: 18–91 years) for patients and 40 years for HCWs (range: 19–66 years). Women represented more than two-thirds of patients (69%) and three-quarters of HCWs (81%). Forty-one percent (330/811) of patients and 13 % (123/940) of HCWs had at least one comorbidity. A public-facing role was observed in 42% (204/487) of patients and 81% (740/917) of HCWs (Table 1).

Ninety percent (845/878) of patients were undergoing cancer treatments, of whom 55.6% (433/878) had metastatic cancer. Almost half of the patients (371/811=46%) had breast cancer, followed by uterine, endometrial, and cervical cancer (86/811=11%). Among male patients, prostate cancer was the most prevalent type (59/262=23%), followed by urological cancer (56/262=21%). Fifty-nine percent (462/788) of patients received chemotherapy as the last treatment before their inclusion in this study (Table 2).

#### 3.2 COVID-19 outcomes

Seventy patients (8%, 95% CI: 6%–10%) and 89 HCWs (9.5%, 95% CI: 8%–12%) tested positive for COVID-19 ( $p=0.26$ ) (Table 1). Systematic serological tests detected 6.7% (95% CI: 5%–9%) COVID-19 cases for patients and 7.8% (95% CI: 6%–10%) for HCWs (Table 1). Of the one in five participants (16.7% in patients and 23.5% in HCWs,  $p<0.001$ ) having routine screening RT-PCR, 3% (95% CI: 2%–4%) were positive for patients and 5% (95% CI: 4%–7%) for HCWs (Table 1). Eighteen patients (2.1%) and four HCWs (0.4%) were hospitalized, one patient was admitted to the intensive care unit, and another died from COVID-19.

In cancer patients, the highest proportion of COVID+ was observed in Nancy (9.3%) and the lowest in Clermont-Ferrand (6.3%) (Table A1), though no differences were observed among the centers ( $p=0.27$ ). Despite being from the same region (i.e. distant less than 100 km), HCWs in Nantes had more than double the proportion of positive tests for COVID-19 than in Angers (11.7% versus 5.0% respectively,  $p=0.01$ ) (Table A1).

Table 1. Population characteristics

Characteristics	Patients N (%) N=878	Healthcare workers N (%) N=940
<b>Sex</b>		
Male	275 (31.3)	177 (18.8)
Female	603 (68.7)	763 (81.2)
<b>Age</b>		
Median (Range)	62 (18–91)	40 (19–66)
[18–50]	171 (19.5)	706 (80.4)
[50–65]	334 (38.0)	233 (26.5)
[65–75]	264 (30.1)	1 (0.1)
≥75	109 (12.4)	0 (0)
<b>BMI</b>		
Median (Range)	25 (17–43)	23 (18–36)
Obesity (BMI≥30)	141 (19.9)	71 (7.8)
missing data	170	33
<b>Tobacco smoking status</b>		
Non-smoker	299 (47.8)	672 (73.6)
Former smoker	228 (36.4)	93 (10.2)
Current smoker	99 (15.8)	149 (16.3)
missing data	252	26
<b>Public-facing role <sup>1</sup></b>		
No	283 (58.1)	177 (19.3)
Yes	204 (41.9)	740 (80.7)
missing data	391	23
<b>No. of Comorbidities <sup>2</sup></b>		
≥1	330 (40.7)	123 (13.1)
missing data	67	0 (N/A)
<b>No. of Comedications <sup>3</sup></b>		
≥1	235 (29.0)	206 (21.9)
missing data	68	0 (N/A)
<b>Centers of inclusion</b>		
Nantes	201 (22.9)	307 (32.7)
Angers	238 (27.1)	240 (25.5)
Clermont-Ferrand	159 (18.1)	344 (36.6)
Nancy	280 (31.9)	49 (5.2)
<b>Symptoms <sup>4</sup></b>		
Symptomatic	282 (32.1)	485 (51.6)
Asymptomatic	596 (67.9)	455 (48.4)
<b>COVID-19 tests <sup>5</sup></b>		
Any positive test	70 (8.0)	89 (9.5)
Positive serological test	59 (6.7)	73 (7.8)
Positive RT-PCR test	26 (3.0)	51 (5.4)

<sup>1</sup> Public-facing role: The question asked to patients was: "Does your job involve contact with the public?" For health professionals, the question was: "Does your job involve contact with patients?"; <sup>2</sup> Comorbidities included: Hypertension, Diabetes, Chronic respiratory failure, Chronic kidney failure, Chronic heart failure, Weight loss, Autoimmune disease, Surgery under general anesthesia in the last twelve months; <sup>3</sup> Comedications included: Corticosteroids, NSAIDs (Nonsteroidal anti-inflammatory drugs), Immunosuppressive drugs, and Immunomodulatory drugs; <sup>4</sup> Symptomatic: Having at least one COVID-19 symptom; Asymptomatic: Having no COVID-19 symptoms; <sup>5</sup> Positive test results: Any positive result from M0 to M3 follow-ups

Table 2. Cancer features of patients

Cancer Features	COVID- N (%) N=808	COVID+ N (%) N=70	Total N (%) N=878
<b>Location</b>			
Breast	335 (45)	36 (54.5)	371 (45.7)
Uterine. Endometrial. Cervical	81 (10.9)	5 (7.6)	86 (10.6)
Colorectal	32 (4.3)	3 (4.5)	35 (4.3)
Gastrointestinal	22 (3)	1 (1.5)	23 (2.8)
Prostate	59 (7.9)	0 (0)	59 (7.3)
Urological	62 (8.3)	6 (9.1)	68 (8.4)
Lung	65 (8.7)	8 (12.1)	73 (9)
Miscellaneous <sup>1</sup>	89 (11.9)	7 (10.6)	96 (11.8)
missing data	63	4	67
<b>Treatment status</b>			
Undergoing treatment	782 (96.8)	63 (90.0)	845 (96.2)
Being monitored	26 (3.2)	7 (10.0)	33 (3.8)
<b>Stage</b>			
Localized	196 (27.3)	19 (31.7)	215 (27.6)
Locally advanced	122 (17.0)	9 (15.0)	131 (16.8)
Metastatic	401 (55.8)	32 (53.3)	433 (55.6)
missing data	89	10	99
<b>ECOG PS</b>			
0	263 (41.9)	21 (38.2)	284 (41.6)
1	333 (53.1)	31 (56.4)	364 (53.4)
>=2	31 (4.9)	3 (5.5)	34 (5)
missing data	181	15	196
<b>Years since the first cancer diagnostic</b>			
>=1 year	467 (62.9)	44 (66.7)	511 (63.2)
missing data	65	4	69
<b>Last treatment before inclusion</b>			
Chemotherapy	425 (58.7)	37 (57.8)	462 (58.6)
Immunotherapy	113 (15.6)	10 (15.6)	123 (15.6)
Targeted therapy	139 (19.2)	16 (25.0)	155 (19.7)
Hormone therapy	88 (12.2)	7 (10.9)	95 (12.1)
Radiotherapy	41 (5.7)	2 (3.1)	43 (5.5)
Surgery	22 (3.0)	4 (6.3)	26 (3.3)
Miscellaneous	23 (3.2)	0 (0)	23 (2.9)
missing data	67	6	73

<sup>1</sup> Including: Upper Respiratory Tract, Brain, Endocrine Gland Neoplasms, Connective and Soft Tissue Neoplasms, Skin, and unidentified cancers



### 3.3 Symptoms

A total of 282 (282/878=32%) patients and 485 (485/940=52%) HCWs were symptomatic (Table 1). The reported symptom prevalence was higher in HCWs than in patients ( $p<0.001$ ). Among all COVID+ participants, 29 patients (29/70=41%) and 8 HCWs (8/89=9%) had no symptoms ( $p<0.001$ ).

In HCWs, we observed that after the 30–40-year age range, reported symptom prevalence decreased with increasing age ( $p=0.004$ ). Between cancer centers, we noted differences in the reported symptom prevalence for patients ( $p<0.001$ ), with 16.1% in Nancy (from an Eastern region badly affected by the epidemic) and 46.3% in Nantes (from a less-affected region). Symptoms in HCWs were less prevalent in Angers than in Nantes (44.6% and 54.7% respectively,  $p=0.019$ ) and overall differences among centers were significant ( $p=0.018$ ) (Table A1).

In univariable analysis, in both the patient and HCW subpopulations, anosmia and dysgeusia/ageusia showed statistical significance ( $p<0.001$ ) on COVID-19 test outcome (Table 3).

Figure 1a shows the OR of the association between each symptom and a positive COVID-19 test. Among patients, anosmia had the highest OR (12.69, 95% CI: 6.02–26.76). However, dysgeusia/ageusia had a lower OR (4.93, 95% CI: 2.53–9.62) than fever (OR=5.69, 95% CI: 3.32–9.76) and anorexia (OR=6.02, 95% CI: 3.10–11.70). Among HCWs, anosmia and dysgeusia/ageusia had similar and the highest OR (46.25, 95% CI: 25.79–82.93; 45.35, 95% CI: 25.69–80.04, respectively).

The Se and Sp of each symptom are presented in Figure 1b. Anosmia was the most specific symptom for patients (Sp=0.98, 95% CI: 0.97–0.99). Anosmia and dysgeusia/ageusia were the most specific symptoms for HCWs (anosmia Sp=0.97, 95% CI: 0.96–0.98; dysgeusia/ageusia Sp=0.97, 95% CI: 0.95–0.98). Rhinorrhea was the most sensitive symptom, though not very high, for patients (Se=0.39, 95% CI: 0.27–0.51), and headache was the most sensitive symptom for HCWs (Se=0.78, 95% CI: 0.67–0.86).

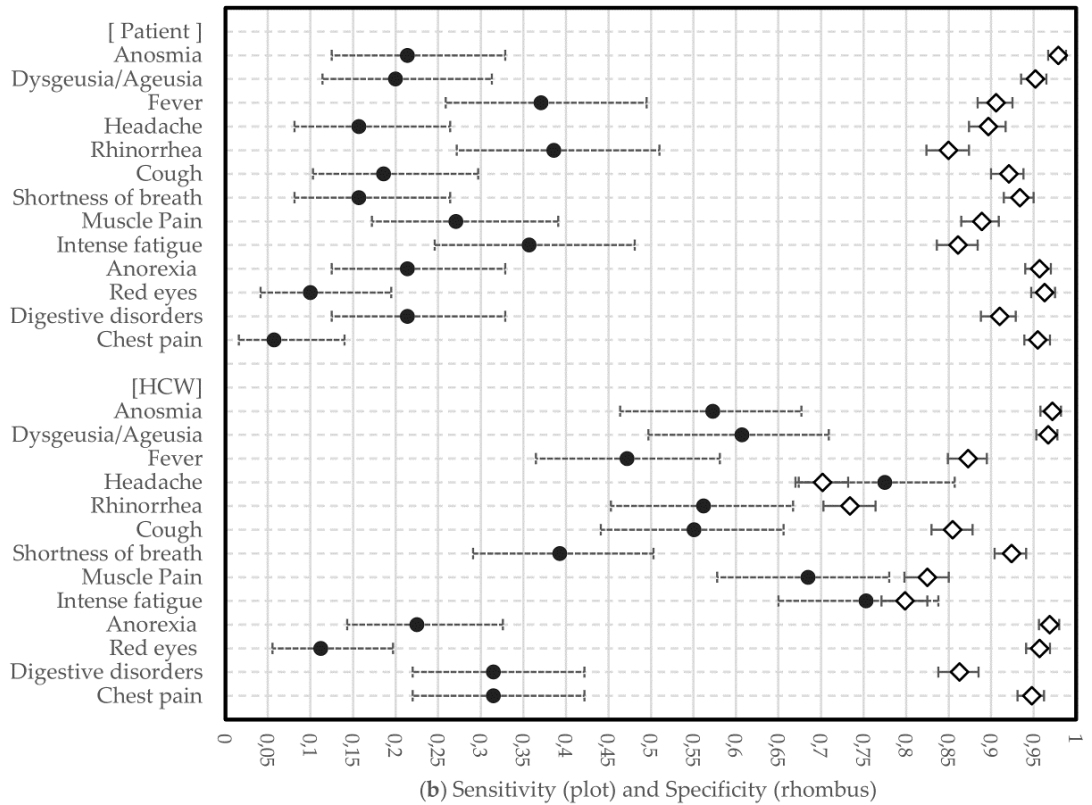
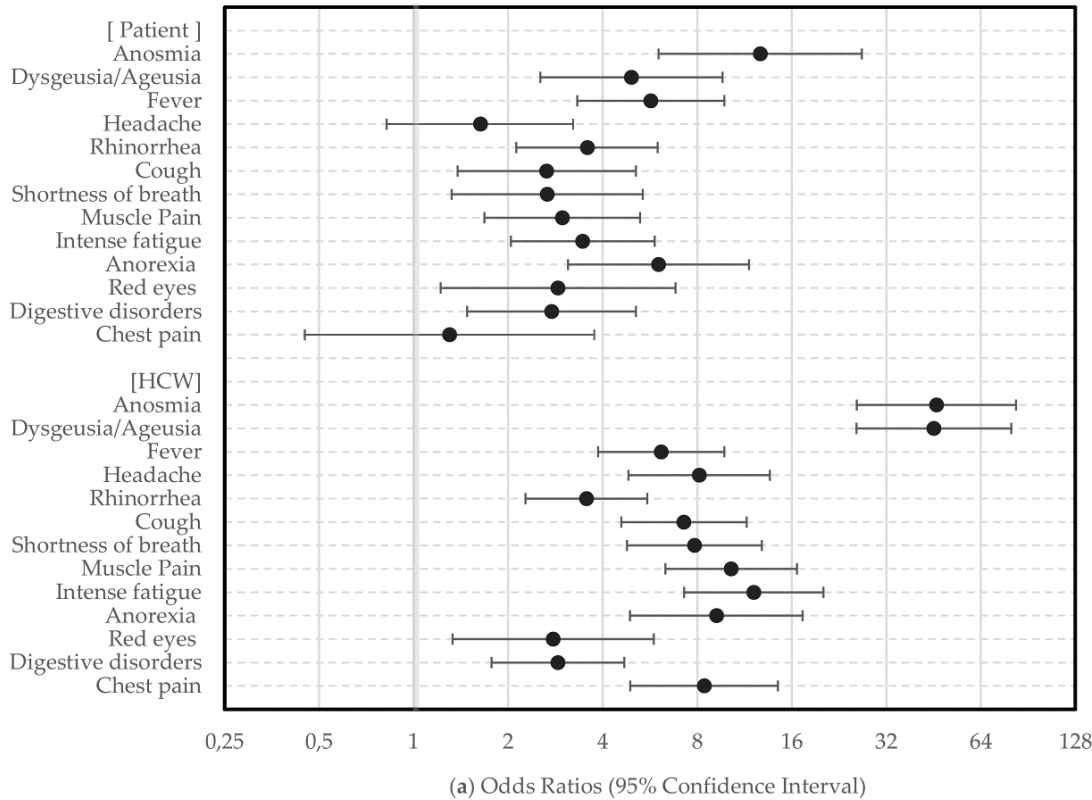


Table 3. Univariable analysis of symptoms

Symptoms	COVID- N (%)	COVID+ N (%)	Total N (%)	p-value
Patients	N=808	N=70	N=878	
Anosmia <sup>1</sup>	17 (2.1)	15 (21.4)	32 (3.6)	<0.001
Dysgeusia/Ageusia <sup>2</sup>	39 (4.8)	14 (20)	53 (6)	<0.001
Fever >38°C	76 (9.4)	26 (37.1)	102 (11.6)	<0.001
Headache	83 (10.3)	11 (15.7)	94 (10.7)	0.161
Rhinorrhea <sup>3</sup>	121 (15)	27 (38.6)	148 (16.9)	<0.001
Cough	64 (7.9)	13 (18.6)	77 (8.8)	0.003
Shortness of breath	53 (6.6)	11 (15.7)	64 (7.3)	0.006
Muscle pain	90 (11.1)	19 (27.1)	109 (12.4)	<0.001
Intense fatigue	112 (13.9)	25 (35.7)	137 (15.6)	<0.001
Anorexia <sup>4</sup>	35 (4.3)	15 (21.4)	50 (5.7)	<0.001
Red eyes (conjunctivitis)	30 (3.7)	7 (10)	37 (4.2)	0.016
Digestive disorders <sup>5</sup>	73 (9)	15 (21.4)	88 (10)	0.001
Chest pain	36 (4.5)	4 (5.7)	40 (4.6)	0.629
Symptomatic <sup>6</sup>	241 (29.8)	41 (58.6)	282 (32.1)	<0.001
Asymptomatic <sup>7</sup>	567 (70.2)	29 (41.4)	596 (67.9)	-
Healthcare workers	N=851	N=89	N=940	
Anosmia <sup>1</sup>	24 (2.8)	51 (57.3)	75 (8.0)	<0.001
Dysgeusia/Ageusia <sup>2</sup>	28 (3.3)	54 (60.7)	82 (8.7)	<0.001
Fever >38°C	108 (12.7)	42 (47.2)	150 (16.0)	<0.001
Headache	254 (29.8)	69 (77.5)	323 (34.4)	<0.001
Rhinorrhea <sup>3</sup>	226 (26.6)	50 (56.2)	276 (29.4)	<0.001
Cough	123 (14.5)	49 (55.1)	172 (18.3)	<0.001
Shortness of breath	65 (7.6)	35 (39.3)	100 (10.6)	<0.001
Muscle pain	149 (17.5)	61 (68.5)	210 (22.3)	<0.001
Intense fatigue	171 (20.1)	67 (75.3)	238 (25.3)	<0.001
Anorexia <sup>4</sup>	26 (3.1)	20 (22.5)	46 (4.9)	<0.001
Red eyes (conjunctivitis)	37 (4.3)	10 (11.2)	47 (5.0)	0.006
Digestive disorders <sup>5</sup>	117 (13.7)	28 (31.5)	145 (15.4)	<0.001
Chest pain	44 (5.2)	28 (31.5)	72 (7.7)	<0.001
Symptomatic <sup>6</sup>	404 (47.5)	81 (91)	485 (51.6)	<0.001
Asymptomatic <sup>7</sup>	447 (52.5)	8 (9)	455 (48.4)	-

<sup>1</sup> Anosmia: smell blindness. In the questionnaire, the description was "loss of smell"; <sup>2</sup> Dysgeusia: distortion of the sense of taste. Ageusia: loss of the sense of taste. In the questionnaire, the description was "alteration or even loss of taste"; <sup>3</sup> Rhinorrhea: free discharge of a thin nasal mucus fluid, runny nose; <sup>4</sup> Anorexia: Eating disorder; <sup>5</sup> Digestive disorders: including diarrhea, vomiting, and abdominal pain; <sup>6</sup> Symptomatic: Having at least one of the symptoms; <sup>7</sup> Asymptomatic: Having no symptoms

Figure 1. Forest plot. **(a)** The Odds Ratio (OR) of the association between each symptom and a positive COVID-19 test. **(b)** Sensitivity (Se) and specificity (Sp) of each symptom.



### 3.4 Backward logistic regression

Table 4 reports the results of the backward variable selection logistic regression. For patients, in the final model, anosmia was the most significant symptom (OR=7.48, 95% CI: 2.96–18.89,  $p<0.001$ ). A patient, holding all other factors constant, is 7.5 times more likely to have a positive test than a patient who did not report anosmia. Among the four other selected symptoms, anorexia, fever, and headache were the most significant ( $p<0.05$ ). Surprisingly, headache had an OR of less than 1. It is worth noting that dysgeusia/ageusia had not been selected as a significant predictor of COVID-19 positive test outcome among cancer patients.

For HCWs, anosmia and dysgeusia/ageusia were significant symptoms with the largest ORs for the COVID-19 positive test outcome (anosmia OR=5.71, 95% CI: 2.21–14.75; dysgeusia/ageusia OR=5.14, 95% CI: 2.01–13.14) in the final model. Muscle pain, intense fatigue, headache, and chest pain ( $p<0.05$ ) were also selected symptoms.

Overall, the selected symptoms better classified COVID-19 test outcome for HCWs than for patients (c-statistic=0.8830 versus 0.7027) (Table A2).

The equations used to estimate the probability of a COVID-19 positive test outcome are reported in Appendix B.

### 3.4 Model validation

In the patient model, less than 10% variation in the c-statistics was observed within the 75% and 25% sub-datasets, and sub-datasets stratified by gender, median age, and cancer-related variables, compared to the original dataset. Sub-datasets stratified by centers of inclusion resulted in smaller variation in performance measurements. Cancer treatment types, such as chemotherapy and immunotherapy, did not influence the model's validity given the very limited change in the c-statistics of these sub-datasets.

In the HCW model, the c-statistics ranged from 0.7989 to 0.9241. The final model had relatively stable performance measurement values through 75% and 25% sub-datasets and sub-datasets stratified by gender and median age (Table A2). The validation performed for two cancer centers simultaneously yielded closer estimates accordingly.

Finally, when comparing sub-datasets stratified with the same factors, the HCW model consistently performed better than the patient model.

Table 4. Result of the backward logistic regression

Predictors	OR (95% CI)	Wald	p-value <sup>1</sup>
<b>Patients' Full Model (N=878)</b>			
Anosmia	9.71 (2.99–31.57)	14.3	<0.001
Dysgeusia/Ageusia	0.77 (0.26–2.35)	0.21	0.651
Fever	3.23 (1.54–6.78)	9.57	0.002
Headache	0.33 (0.12–0.90)	4.75	0.029
Rhinorrhea	1.98 (0.95–4.10)	3.36	0.067
Cough	0.61 (0.23–1.59)	1.02	0.313
Shortness of breath	1.34 (0.48–3.72)	0.32	0.575
Muscle pain	1.15 (0.50–2.67)	0.11	0.738
Intense fatigue	1.17 (0.46–2.99)	0.11	0.738
Anorexia	4.52 (1.69–12.09)	9.03	0.003
Red eyes	1.16 (0.35–3.91)	0.06	0.809
Digestive disorders	0.65 (0.25–1.66)	0.82	0.366
Chest pain	0.42 (0.11–1.67)	1.50	0.221
<b>Patients' Final Model (N=878)</b>			
Anosmia	7.48 (2.96–18.89)	18.12	<0.001
Anorexia	3.82 (1.66–8.76)	9.99	0.002
Fever	3.07 (1.53–6.17)	9.90	0.002
Headache	0.30 (0.12–0.76)	6.49	0.011
Rhinorrhea	1.81 (0.93–3.51)	3.08	0.079
<b>Healthcare Workers' Full Model (N=940)</b>			
Anosmia	6.11 (2.26–16.49)	12.76	<0.001
Dysgeusia/Ageusia	5.30 (1.96–14.34)	10.78	0.001
Fever	0.65 (0.30–1.41)	1.18	0.276
Headache	2.08 (0.96–4.48)	3.47	0.062
Rhinorrhea	0.67 (0.33–1.34)	1.29	0.256
Cough	1.26 (0.57–2.79)	0.32	0.570
Shortness of breath	0.90 (0.37–2.20)	0.05	0.825
Muscle pain	2.01 (0.91–4.41)	3.01	0.083
Intense fatigue	2.05 (0.89–4.73)	2.87	0.090
Anorexia	1.25 (0.47–3.30)	0.20	0.654
Red eyes	0.91 (0.31–2.65)	0.03	0.866
Digestive disorders	0.78 (0.38–1.60)	0.47	0.494
Chest pain	2.61 (1.07–6.35)	4.49	0.034
<b>Healthcare Workers' Final Model (N=940)</b>			
Anosmia	5.71 (2.21–14.75)	12.93	<0.001
Dysgeusia/Ageusia	5.14 (2.01–13.14)	11.68	0.001
Muscle pain	1.75 (0.82–3.75)	2.08	0.149
Intense fatigue	1.78 (0.85–3.72)	2.34	0.126
Headache	1.88 (0.86–4.11)	2.53	0.111
Chest pain	2.42 (1.11–5.27)	4.95	0.026

<sup>1</sup>Variable entry and removal threshold fixed at p=0.20

#### 4. Discussion

Based on the PAPESCO-19 prospective multicenter cohorts, the current study assessed the symptoms associated with SARS-CoV-2 infection in 878 cancer patients and 940 oncology HCWs enrolled over about six months and two pandemic waves.

Proportions of COVID+ cases were similar in the two subpopulations (8% and 9.5%). Nevertheless, more cancer patients than HCWs had severe outcomes (hospitalized: 2.1% versus 0.4%,  $p<0.01$ ; for both ICU and death: 1 vs. 0). Symptoms considered to be associated with COVID-19 were significantly lower in prevalence in cancer patients (32%) than in HCWs (52%). Almost all COVID+ HCWs (91%) experienced symptoms while about half (49%) of COVID+ cancer patients reported one or more. In contrast, 5% of asymptomatic patients and 2% of asymptomatic HCWs were COVID+ ( $p<0.01$ ).

In cancer patients, one immediate finding is that single symptoms had weak relationships with COVID-19 test outcomes. It is worth noting that cancer patients usually suffer from diverse symptoms, perhaps meaning that they fail to notice additional symptoms of SARS-CoV-2 infection. Nevertheless, combining several symptoms, i.e. anosmia, fever, headache, rhinorrhea, and anorexia, discriminates COVID-19 positivity quite well. This held consistently within different sub-datasets such as cancer treatment or cancer type. Negative association with headache may serve as a differential diagnosis criterion and improve diagnostic accuracy. With the other symptoms, headache is more likely to suggest health conditions other than COVID-19, whereas its absence raises the possibility of COVID-19. Cancer patients deserve tailored preventive measures irrespective of the absence of symptoms.

In HCWs, single symptoms had a strong association with COVID-19 test outcomes. We identified several common symptom combinations validated in previous studies. They were anosmia, dysgeusia/ageusia, muscle pain, and intense fatigue [11,15]. Our study further included headache and chest pain, which differed from other symptoms in the previous studies' models.

Anosmia, as a single symptom or combined with others, remained strongly associated with COVID-19 positivity. While dysgeusia was also found to be a 'good predictor' for identifying individuals with COVID-19, though less frequent than anosmia [9–17], this was not the case in cancer patients, but only in HCWs.

Our findings from the PAPESCO-19 study were strengthened by the study period covering two main waves of COVID-19 pandemic in France and different geographical locations with varying epidemic impact levels [28,35]. That diversity reinforced the robustness and extrapolability of our final models, since symptom diagnostic performance depends on the prevalence of symptomatic and COVID+ cases. Recruiting cancer and cancer-free subpopulations in the same geographical areas made it possible to compare the symptoms between them. In addition, a particular feature of our study design enabled us to capture COVID-19 cases comprehensively, with systematic testing of all participants irrespective of symptoms.

The overall COVID-19 prevalence we observed was, to a certain extent, comparable to a French survey covering only the first wave and in which 7% of participants were COVID-19 positive [36]. There were significant regional differences in symptom prevalence and in the proportion of COVID+ cases in HCWs but not in patients. The effect of self-protection measures in cancer patients should be investigated in future studies.

Severe COVID-19 cases might be underrepresented in our study. Only 1.2% of participants were hospitalized due to the infection and only one death was reported, versus 23 cancer-related deaths. It was more likely that individuals with SARS-CoV-2 infections would have been admitted into COVID-19-specialized hospitals and were not attending cancer centers during the PAPESCO-19 recruitment period.

We recognize limitations in our study.

Self-report bias may have affected the collected data, especially the self-declared symptoms, as observed in previous studies [11,37]. Symptoms might be overreported or

underreported. In addition, recall bias was inevitable due to the time gap between the first wave of the Covid-19 pandemic in France (mid-March 2020) and the study's inclusion period (mid-June 2020).

Participants experiencing symptoms onset less than 8-15 days before blood sampling might have a false negative serological result [29,38]. Thanks to the longitudinal design of this study, an infected participant with negative result at baseline (M0) was likely to have a positive result at three-month follow-up (M3) due to the sufficient time interval resulting in a quasi perfect sensitivity of the serological test used in our study [29]. As we considered participants with any positive result at M0 and M3 as COVID+, the participant was recorded as COVID+ in our data.

The self-reported RT-PCR test was performed as part of the general screening practice, leading to a substantial number of under-detected cases [35]. Only one in five study participants were tested. Potential reasons for that small proportion may include the lack of testing resources during the first wave, the national health system's limited testing capacity, and the limited implementation of the test-trace-isolate strategy.

## 5. Conclusion

The combination of symptoms, including anosmia, anorexia, fever, headache, and rhinorrhea, accurately identifies cancer patients with COVID-19. Specifically, our results demonstrate that some symptoms, such as headache, dysgeusia, and ageusia, have completely different expressions between cancer and cancer-free populations. Accurately predicting COVID-19 from identified symptoms in cancer patients would be helpful for the diagnosis, screening, and prevention of SARS-CoV-2 infection.



**Supplementary Materials:** The following are available online at [www.mdpi.com/xxx/s1](http://www.mdpi.com/xxx/s1). Table A1. Symptom prevalence and COVID-19 positive proportion by centers of inclusion; Table A2. Model validation; Appendix B: Equations for calculating the estimated probability of a positive COVID-19 test outcome.

**Author Contributions:** Conceptualization, M.M.B., J.-L.R., M.B.-C., F.B., A.B.-L., V.S., M.B.; methodology, K.Z., M.M.B., A.B.-L., V.S.; validation, M.M.B., J.-L.R., A.B.-L., V.S.; formal analysis, K.Z.; investigation, H.M., A.L., M.C.; writing—original draft, K.Z., M.M.B., J.-L.R.; writing—review and editing, all authors; visualization, K.Z.; supervision, M.M.B., M.C.; funding acquisition, M.C., M.M.B., J.-L.R., A.B.-L., V.S., M.B.-C., All authors have read and agreed to the published version of the manuscript.

**Funding:** The Nantes Metropolis financed partially the study (10% of total budget). However, the PAPESCO-19 is an independent study and the ideas and opinions expressed in this work are those of the authors.

**Acknowledgments:** We thank all staff from the study investigating centers and especially Valerie Pacteau, Marine Tigreat and Dahlia Bateta for their support in setting the study and the data collection and management.

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki. The study was approved by the Ethics Committee (Ref: CPP-IDF VIII, Boulogne-Billancourt) approved our study number 20.04.15 on May 15, 2020).

**Informed Consent Statement:** All participants provided signed informed consent to participate in the study.

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author (K.Z.).

**Conflicts of Interest:** The authors have no conflicts of interest. The study was registered at ClinicalTrials.gov Identifier: NCT04421625.

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