COVID-19 Infections in Cancer Patients Were Frequently Asymptomatic: Description From a French Prospective Multicenter Cohort (PAPESCO-19)

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ABSTRACT

BACKGROUND: Cancer patients (CPs) are considered more vulnerable and as a high mortality group regarding COVID-19. In this analysis, we aimed to describe asymptomatic COVID (+) CPs and associated factors.

METHODS: We conducted a prospective study in CPs and health care workers (HCWs) in 4 French cancer centers (PAPESCO [*PAtients et PErsonnels de Santé des Centres de Lutte Contre le Cancer pendant l'épidémie de COvid-19*] study). This analysis used data recorded between June 17, 2020 and November 30, 2020 in CPs (first 2 waves, no variants). At inclusion and quarterly, CPs reported the presence of predefined COVID-19 symptoms and had a blood rapid diagnostic test; a reverse transcription polymerase chain reaction (RT-PCR) was done in case of suspected infection.

RESULTS: A total 878 CPs were included; COVID-19 prevalence was similar in both CPs (8%) and HCWs (9.5%); of the 70 CPs (8%) who were COVID (+), 29 (41.4%) were and remained asymptomatic; 241/808 of the COVID (–) (29.8%) were symptomatic. 18 COVID (+) were hospitalized (2% of CPs), 1 in intensive care unit (ICU) and 1 died (0.1% of CPs and 2.4% of symptomatic COVID [+] CPs). Only the inclusion center was associated with clinical presentation (in Nancy, Angers, Nantes, and Clermont-Ferrand: 65.4%, 35%, 28.6%, and 10% CPs were asymptomatic, respectively).

CONCLUSIONS: Seroprevalence of COVID-19 in CPs was similar to that observed in HCWs; mortality related to COVID-19 among CPs was 0.1%. More than 40% of COVID (+) CPs were asymptomatic and one third of COVID (–) CPs had symptoms. Only geographic origin was associated with the presence or absence of symptoms. Social distancing and protective measures must be applied in CPs at home and when hospitalized.

KEYWORDS: Cancer patients, COVID, asymptomatic

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Introduction

The COVID-19 outbreak began in early 2020, spread worldwide, and was responsible for more than 235 million cases and 4.8 million deaths by September 2021.[1]

Cancer patients (CPs) are considered a high mortality risk group,[2,3] and appeared to be more vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[4] In the first cohorts of CPs, the diagnosis of COVID-19 was made essentially in symptomatic hospitalized patients, with a bias toward more severe cases.[2,5-9] Prevalence of COVID-19 in asymptomatic CPs was low in initial studies testing with nasal swabs.[10-12] Serological tests are of major value, providing the cumulative prevalence of infection.[13] A French cross-sectional study observed low seropositivity, 1.7% and 1.8%, for SARS-CoV-2 in the two cohorts of healthcare workers (HCWs) and CPs, respectively, at the end of June, 2020.[14]

To better evaluate the impacts of COVID-19 in French cancer centers, we conducted a study analyzing two cohorts (CPs and HCWs). A first analysis (from data collected in January 2021) has shown that (1) COVID (+) prevalence was 8% in CPs and 9.5% in HCWs, (2) symptom combinations were only slightly different between these two cohorts, (3) 32.1% of CPs and 51.6% of HCW had symptoms, and (4) severe outcomes were mainly observed in CPs.[15] This article aims to describe the population of asymptomatic CPs infected by SARS-COV-2 and to better understand any patterns.

Materials and Methods

This multicenter cohort study recording data from CPs and HCWs during the COVID pandemic—PAPESCO-19 (*PAtients et PErsonnels de Santé des Centres de Lutte Contre le Cancer pendant l'épidémie de COvid-19*) took place in 4 comprehensive cancer centers from 3 different French regions (Pays de Loire: Angers, Nantes; Grand-Est: Nancy; Auvergne-Rhône-Alpes: Clermont-Ferrand). It consists of 4 work packages: (1) serology and clinic, (2) public health, (3) economics, and (4) psychology. The study is now closed for inclusions (June 21, 2021). For this analysis, data were collected until January 25, 2021 from participants enrolled between June 17, 2020 and November 30, 2020, approximately the end of the French second wave (no variants reported in France), allowing us to capture the effects of two epidemic waves.

Participation in the study was proposed to patients attending the centers for active treatment or for follow-up (only if treatment stopped for more than 1 year). It included CPs aged ⩾ 18 years, and attending cancer centers for treatment or monitoring. Participants were eligible irrespective of whether they had presented symptoms since the COVID-19 outbreak. The participation period was 1 year with visits planned every 3 months. All participants signed an informed consent form, and the study was 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. This study was registered at ClinicalTrials.gov Identifier: NCT04421625.

At baseline and quarterly, participants (1) reported the presence or not of 1 of 13 predefined COVID-19 symptoms (fever > 38°C, headache, anosmia, dysgeusia/ageusia, rhinorrhea, unusual cough, shortness of breath, muscle pain, intense fatigue, anorexia, red eyes [conjunctivitis], digestive disorders [diarrhea, vomiting, and abdominal pain], and chest pain)[16] observed from the beginning of the pandemic (at baseline) or in the 3 previous months (during follow-up), which the patients did not consider as related to any cancer treatment and (2) had blood sampling for a rapid diagnostic test done immediately (NG.TEST/SARS-CoV-2 IgG-IgM)[17,18]; aliquots were kept for antibody detection and measurement, to be performed at the end of the study. If CPs developed COVID-19 symptoms, they were required to perform an RT-PCR. Baseline demographic data, clinical details, and cancer history were recorded in the electronic case report forms. When analyzing symptoms, participants were considered symptomatic if they reported any of the listed symptoms. Those who did not report any symptoms were considered asymptomatic.[14,19] Participants with at least one positive serological test or RT-PCR result were considered to be COVID (+) and those with negative serological and RT-PCR results were COVID (–).

Statistical analysis

We first estimated the proportions of asymptomatic and symptomatic COVID (+) CPs. We further analyzed asymptomatic COVID (+) cases by factors *a priori* selected as potential risk factors. We described CP characteristics using median and range for continuous variables, and count or percentages for categorical variables. We assessed whether the asymptomatic proportion of COVID (+) CPs differed between the factors described above. To ensure consistency in our analyses, we used logistic regression for both the continuous and categorical independent variables. For categorical variables with more than two levels, we created dummy variables for each level and performed the analysis accordingly. Alternatively, we used Fisher's exact test when categories had a small number of individuals or included zero cell counts. In a sensitivity analysis, missing data were included separately to assess their potential bias. Finally, we used the Clopper–Pearson method to estimate the confidence interval (CI) of asymptomatic proportions. Based on cumulative normal distribution assumptions, we tested proportion differences between those from the literature and those from our study and reported the p-value. A P value $< .05$ was considered statistically significant. The Ennov Clinical system was used for data collection, and SAS 8.3 and STATA 14.2 software were used for statistical analysis.

Results

As previously reported, from June 17, 2020 to November 30, 2020, a total of 878 CPs were included (Table 1).[15]

In short, this population was composed of 68.7% women, median age was 62; 40.7% had comorbidities; 45% were treated for breast cancer; almost all (96.8%) were undergoing treatment and were ECOG performance status (PS) 0 (41.9%) or 1 (53.1%). Seventy CPs (8% of the included CPs) were COVID (+) (serological diagnosis: 59, positive RT-PCR: 26). The percentage of COVID (+) CPs was slightly different from one geographic area to another: Pays de Loire 7% in Nantes and 8.4% in Angers, Auvergne-Rhône-Alpes 6.3% in Clermont-Ferrand, and Grand-Est 9.3% in Nancy ($P = .66$). Forty-one percent (29/70, CI 95%: 30%-54%) of COVID (+) CPs never developed clinical symptoms and were thus considered asymptomatic. Predefined COVID-19 symptoms, observed in 282 CPs (32.1%), were more frequent in COVID (+) (41/70; 58.6%) than in COVID (–) (241/808; 29.8%) CPs ($P < .001$). Only 14.5% of symptomatic CPs (41/282) were COVID (+). Of the 878 CPs, 19 (2.2%) were hospitalized (1 in an intensive

Table 1. Characteristics of the cancer patient population included in this interim analysis.

CANCER PATIENTS (N = 878)	N (%)
Sex	
Men	275 (31.3)
Women	603 (68.7)
Age: Median (range)	62 (18-91)
Obesity (BMI > 30)	141 (19.9)
Missing data	170
Tobacco smoking status	
Non-smoker	299 (47.8)
Former smoker	228 (36.4)
Smoker	99 (15.8)
Missing data	252
No. of comorbidities	
0	481 (59.3)
1	241 (29.7)
> 2	89 (10.1)
Missing data	67
No. of co-medications	
0	575 (71)
> 1	235 (29)
Missing data	68
Center	
Angers	238 (27.1)
Clermont-Ferrand	159 (18.1)
Nancy	280 (31.9)
Nantes	201 (22.9)
Cancer location	
Breast	371 (45.7)
Uterine, endometrial, cervical	86 (10.6)
Digestive	58 (7.1)
Prostate	59 (7.3)
Urological	68 (8.4)
Lung	73 (9)
Miscellaneous	96 (11.8)
Missing data	67
Cancer stage	
Localized	215 (27.6)
Locally advanced	131 (16.8)
Metastatic	433 (55.6)
Missing data	99
ECOG-PS	
0	284 (41.6)
1	364 (53.4)
> 2	34 (5)
Missing data	196
Last treatment before inclusion	
Chemotherapy	462 (57.4)
Immunotherapy	123 (15.3)
Targeted therapy	155 (19.3)
Hormone therapy	95 (11.8)
Radiotherapy	43 (5.3)
Surgery	26 (3.2)
Missing data	73

Abbreviation: BMI, body mass index.

care unit) because of symptomatic COVID infection and 1 (0.1%) died. Of the COVID (+) patients, these figures were respectively 27% and 1.4%, and of the symptomatic COVID (+) CPs: 46.3% and 2.4%.

In the COVID (+) CPs (n = 70), we compared those totally asymptomatic (n = 29) with those who presented at least one symptom (n = 41; Table 2).

The proportion of asymptomatic men was slightly higher than women (50% vs 39%) though not significantly. Age, body mass index (BMI), and obesity rates were similar, as were comorbidities or co-medication rates. Amid the current smokers, about two-thirds were asymptomatic, but this was not significantly ($P = .11$) more frequent than in the former or never smoker populations. The influence of cancer location on symptomatology was difficult to assess (small numbers); 16/ 36 (44.4%) breast CPs were asymptomatic vs 2/8 (25%) lung CPs. While cancer stage had no influence on symptoms, asymptomatic CPs were non-significantly less frequent among ECOG PS 0 than PS 1 (6/21; 28.6% vs 16/31; 56.4%; $P = .10$). The last treatment had no major influence; treatments associated with the highest percentage of asymptomatic patients were hormone therapy (5/7; 71.4%) and systemic chemotherapy (16/37;

Table 2. Comparison of symptomatic and asymptomatic patients among COVID (+) cancer patients.

CHARACTERISTICS	COVID + PATIENTS (N = 70)			
	TOTAL, N = 70	ASYMPTOMATIC N = 29 (41.4%)	SYMPTOMATIC N = 41 (58.6%)	*P* VALUE*
Sex				.47
Men	14 (100/20)	7 (50/24.1)	7 (50/17.1)	
Women	56 (100/80)	22 (39.3/75.9)	34 (60.7/82.9)	
Age				.37
Median (range)	62 (27-84)	62 (34-83)	62 (27-84)	
Obesity				.86
Obese	13 (100/22)	6 (46.2/23.1)	7 (53.8/21.2)	
Missing data	11	3	8	.31
Tobacco smoking status				.28
Non-smoker	28 (100/51.9)	11 (39.3/47.8)	17 (60.7/54.8)	.61
Former smoker	15 (100/27.8)	5 (33.3/21.7)	10 (66.7/32.3)	.4
Smoker	11 (100/20.4)	7 (63.6/30.4)	4 (36.4/12.9)	.12
Missing data	16	6	10	.72
Center				.02
Nantes	14 (100/20)	4 (28.6/13.8)	10 (71.4/24.4)	.28
Angers	20 (100/28.6)	7 (35/24.1)	13 (65/31.7)	.49
Clermont-Ferrand	10 (100/14.3)	1 (10/3.4)	9 (90/22)	.06
Nancy	26 (100/37.1)	17 (65.4/58.6)	9 (34.6/22)	< .01
Cancer location				.84
Breast	36 (100/54.5)	16 (44.4/59.3)	20 (55.6/51.3)	.52
Uterine, endometrial, cervical	5 (100/7.6)	3 (60/11.1)	2 (40/5.1)	.38
Gastrointestinal	4 (100/5.7)	2 (50/6.9)	2 (50/4.9)	.4
Prostate	0 (—/0)	0 (—/0)	0 (—/0)	—
Urological	6 (100/9.1)	2 (33.3/7.4)	4 (66.7/10.3)	.69
Lung	8 (100/12.1)	2 (25/7.4)	6 (75/15.4)	.34
Skin	2 (100/3)	1 (50/3.7)	1 (50/2.6)	.79
Miscellaneous	5 (100/7.6)	1 (20/3.7)	4 (80/10.3)	.34
Missing data	4	2	2	.72
Treatment status				.38
Undergoing treatment	63 (100/90)	25 (39.7/86.2)	38 (60.3/92.7)	
Being monitored	7 (100/10)	4 (57.1/13.8)	3 (42.9/7.3)	
Cancer stage				.51
Localized	19 (100/31.7)	8 (42.1/33.3)	11 (57.9/30.6)	.82
Locally advanced	9 (100/15)	5 (55.6/20.8)	4 (44.4/11.1)	.31

(continued)

Table 2. (Continued)

CHARACTERISTICS	COVID + PATIENTS (N = 70)			
	TOTAL, N = 70	ASYMPTOMATIC N = 29 (41.4%)	SYMPTOMATIC N = 41 (58.6%)	*P* VALUE*
Metastatic	32 (100/53.3)	11 (34.4/45.8)	21 (65.6/58.3)	.34
Missing data	10	5	5	.55
ECOG				.26
0	21 (100/38.2)	6 (28.6/26.1)	15 (71.4/46.9)	.12
1	31 (100/56.4)	16 (51.6/69.6)	15 (48.4/46.9)	.1
⩾2	3 (100/5.5)	1 (33.3/4.3)	2 (66.7/6.3)	.77
Missing data	15	6	9	.9
Last treatment before inclusion				
Chemotherapy	37 (100/57.8)	16 (43.2/64)	21 (56.8/53.8)	.42
Immunotherapy	10 (100/15.6)	2 (20/8)	8 (80/20.5)	.19
Targeted therapy	16 (100/25)	4 (25/16)	12 (75/30.8)	.19
Hormone therapy	7 (100/10.9)	5 (71.4/20)	2 (28.6/5.1)	.82
Radiotherapy	2 (100/3.1)	0 (0/0)	2 (100/5.1)	.39
Surgery	4 (100/6.3)	2 (50/8)	2 (50/5.1)	.65
Missing data	6	4	2	.21

*$P < .05$.

43.2%); by contrast, only 20% of those treated with immunotherapy and 25% receiving targeted therapies were asymptomatic. Surprisingly, the center of inclusion was clearly of importance. In Angers, Nantes, and Clermont-Ferrand, respectively, 35%, 28.6%, and 10% of COVID (+) CPs were asymptomatic, while in Nancy 65.4% (17/26) did not have any symptoms (Nancy vs other centers; $P < .002$). Of the infections occurring in CPs under the age of 60 years (n = 32), 37.5% (12/32, 95% CI: 21.1%-56.3%) were asymptomatic; of those over the age of 60 years (n = 38), this proportion was 44.7% (CI: 28.6%-61.7%), higher than the former but without statistical significance ($P = .54$).

Discussion

In the French CP population studied (n = 878), 70 (8%) were COVID (+); 29 (41.4%) were asymptomatic; inversely 29.8% of the COVID (-) CPs (241/808) presented at least one symptom. The mortality related from COVID was low (0.1%) in the cohort, but 1.4% of COVID (+) CPs and 2.4% of symptomatic COVID (+) CPs died. No clinical factor was significantly associated with an asymptomatic infection, but there was a slight trend in favor of smokers and PS 1 CPs. Surprisingly, CPs from Nancy were significantly less frequently symptomatic (34.6%) than those from other cancer centers (65%-71.4%-90%). The Nancy area was the most severely hit by the first wave, with a peak of hospitalized COVID-19 patients 4-times higher in Nancy than in Nantes during the first epidemic wave. Perhaps CPs from Nancy considered that COVID-related symptoms needed to be more severe and censored themselves? In a French analysis of beliefs and risk perceptions during the first lockdown, in the region with the highest incidence (which included the Nancy area), individuals estimated their personal risk of catching COVID-19 as very high and increasing despite the lockdown.[20]

A recent meta-analysis of studies with long follow-up reported 35.1% (95% CI: 30.7%-39.9%) of asymptomatic CPs among laboratory confirmed COVID-19 cases, a figure which is in line with our findings of 41.4% (95% CI: 28.6%-61.7%). In this meta-analysis, only age was associated with the absence of symptoms, with a statistically significant trend toward a lower percentage of asymptomatic patients with increasing age (> 60 years: 19.7%; adults 19-59 years: 32.1% and children < 19 years: 46.7%).[21]

In an overall estimate of the burden of COVID-19 infection in France, it was estimated mid-May 2020 that 5.3% of the population had been infected.[22] By January 15, 2021, near the end of our interim analysis, 14.9% of the French adult population had been infected, ranging from 26.5% in Paris to 5.1% in Brittany; for those aged 50 to 70 years (like our CP population), this proportion was around 5% in Pays de Loire, 11% in Auvergne-Rhône-Alpes, and 13% in Grand Est.[23] The proportions of infected CPs we observed in our overall population

(8%) and by center (7% and 8.4% in Pays de Loire, 6.3% in Auvergne, and 9.3% in Lorraine?) were very similar. The seroprevalence observed in French CPs was thus similar to that obtained in the overall population and lower than reported in initial studies.[24,25]

Hospitalization and mortality rates due to COVID in our global cohort of CPs and among those who were COVID (+) were 2% to 0.1% and 27% to 1.4%, respectively; but, during this period, hospitalization was systematically proposed because of the fear of poor evolution. In the population of HCWs, 0.4% were hospitalized and none died.[15] In CPs, the "true" death rate was higher but we considered hospitalizations and deaths to be related to COVID if initial signs were not in relation to cancer or if there were treatment with demonstration of COVID infection (RT-PCR) within 28 days. In Dijon, of the 17 COVID (+) CPs, only 3 (0.3%) required hospitalization and none died.[14] In France, in May 2020, in the overall population, 2.9% of infected individuals were hospitalized and 0.5% of those infected died.[22] We confirm that the mortality rate among French CPs was higher than in the overall population.

In 2 other French studies, 1.4% to 4.8% of asymptomatic CPs were COVID (+).[14] Similar data were observed in Italy[12] and in New York (nasal swab; 3.75% positivity).[26] A systematic review of asymptomatic COVID-19 cases in the general population suggests that at least one-third of this population is asymptomatic; in longitudinal studies, three-fourth of asymptomatic people at the time of testing with a positive RT-PCR will remain asymptomatic.[27] In Iran, serologic evaluation before vaccination demonstrated that up to 20% of cancer patients had antibodies despite having no history of symptoms.[28,29] In PAPESCO, the incidence of COVID (+) was very similar in both CPs (8%) and HCWs (9.5%), but surprisingly 41% of the COVID (+) CPs and only 9% of the COVID (+) HCWs were asymptomatic.[15] The same figures (47% and 25% asymptomatic in CPs and HCWs, respectively) were observed in Dijon's study.[14] Half of French COVID (+) CPs thus remained asymptomatic.

One-third of CPs (282/878; 32.1%) developed COVID-19-like symptoms (CLSs), but most (241) were COVID (–). A large French survey analyzed the results of a self-administered questionnaire looking for incidence of CLS. The cumulative incidence of CLS was 7.2% and 10.1% on days 15 and 45 of the first lockdown. Incidence was lower in older age groups, and higher in participants from high-prevalence regions, large cities > 100 000 inhabitants, families with children, individuals who were overweight or obese or those with chronic diseases other than diabetes, cardiovascular diseases and cancer; individuals with "essential job positions," including HCWs, were at high risk of developing CLS.[30]

One can hypothesize that these asymptomatic COVID (+) CPs could contaminate family, other patients or HCWs, as well as symptomatic individuals. In asymptomatic individuals, viral clearance was achieved after a mean of 26 days (range 7-79 days), longer than in symptomatic cases.[31,32] These asymptomatic individuals may be the source of transmission, as demonstrated in the Diamond Princess cruise ship outbreak.[33] The proportion of asymptomatic patients with a high viral load is similar to that of symptomatic individuals,[34] and it was evaluated that, in the general population, 59% of all transmissions came from asymptomatic individuals, including 24% from those who remained asymptomatic.[35]

It has been demonstrated in HCWs that the presence of anti-spike or anti-nucleocapsid was associated with a reduced risk of reinfection in the ensuing 6 months.[36] In asymptomatic COVID (+) HCWs, all developed neutralizing antibodies lasting for at least 60 days.[37] In a longitudinal study in asymptomatic (n = 85) and symptomatic (n = 75) COVID-19 patients after seroconversion, the frequencies of SARS-CoV-2-specific T cells were similar between asymptomatic and symptomatic individuals; the former showed increased interferon-gamma (IFN-γ) and interleukin-2 (IL-2) production. This was associated with a proportional secretion of IL-10 and proinflammatory cytokines only in asymptomatic infections, while symptomatic individuals had disproportionate secretion of inflammatory cytokines. Asymptomatic COVID (+) individuals then mounted a highly functional virus-specific cellular immune response.[38] It is difficult to know whether these conclusions are also valid for CPs.

Our analysis of symptomatic and asymptomatic CPs in the PAPESCO-19 study has several strengths. This longitudinal study made long follow-up possible (at least 3 months) for all CPs; the diagnosis of COVID was based on "on demand" RT-PCR and on repeated serology. But antibody levels wane over time, and the average time from seroconversion to seroreversion is 3 to 4 months.[39] In our study, serology tests were repeated at a 3-month interval, so our estimated prevalence is only slightly underestimated. In this preliminary study, we used rapid lateral flow immunoassay tests (NG.TEST/SARS-CoV-2 IgG-IgM, NG Biotech Laboratoires, Guipry-Messac, France). This test has been approved by the French Ministry of Health (https://covid-19.sante.gouv.fr/tests). Performances asserted by the manufacturer were excellent, with sensitivity and specificity of. Respectively, 100% and 100% (if > 14 days after infection—NG.TEST/SARS-CoV-2 IgG-IgM). In academic studies, rapid lateral flow immunoassay tests were considered both reliable and accurate, particularly 15 or more days after the onset of symptoms.[17,18] A recent review of rapid, point-of-care antigen and molecular tests for diagnosis of SARS-CoV-2 infection concluded that assays with acceptable sensitivity (> 80%) and specificity (> 97%) can replace laboratory-based RT-PCR. The NG.TEST/SARS-CoV-2 IgG-IgM was not evaluated, however.[40]

Our study also has some weaknesses. First, regarding CLS, a recall bias is possible but the maximum delay between clinical signs and data collection was 9-10 months and during this period the disease and its symptoms were described daily in the media! Serology results were given to participants only after they filled in the symptom questionnaire, eliminating

reassessment of symptoms. This symptom questionnaire was predefined and composed of clinical signs considered to be of major value when the trial was designed; and this is still the case. As most signs were particularly frequent in CPs undergoing treatment (dysgeusia, fever, diarrhea, cough, . . .), it is likely that some considered as symptomatic, in fact, described signs related to treatment toxicity. It is also likely that some patients did not report these signs because they were usual after treatment.

Conclusions

In conclusion, in a French population of CPs tested in 2020, seroprevalence of COVID infection over a long period was 8%, similar to that observed in the general population. More than 40% of COVID (+) CPs remained asymptomatic, and almost 30% of COVID (–) CPs had symptoms. No factor was statistically associated with the fact of being asymptomatic. Hospitalization and mortality rates were, in the whole group and in COVID (+) CPs, 2% to 0.1% and 27% to 1.4%, respectively, higher than that observed in the general population. It seems that even asymptomatic CPs can contaminate family, HCWs, or other CPs, suggesting that social distancing and protective measures must be applied at home and when hospitalized.

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Author Contributions

KZ, J-LR, and MMB contributed to the conceptualization; KZ, MMB, AB-L, and VS contributed to the methodology; formal analysis was done by KZ.; investigation was done by J-LR, MB-C, MB, HM, AL, CM-B, and FB; writing—original draft preparation was done by J-LR, KZ, and MMB; writing—review and editing was done by all authors; funding acquisition was done by MC, TC, and FP-L. All authors have read and agreed to the published version of the article.

Informed Consent

Informed consent was obtained from all subjects involved in the study.

Institutional Review Board Statement

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

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