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Original article

COVID-19 outpatient management: Shorter time to recovery in Healthcare workers according to an electronic daily symptoms assessment

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ABSTRACT

Objectives: Our aim is to compare the course of the disease between healthcare workers (HCWs) and non-HCWs suffering from covid-19 and eligible for outpatient management.
Methods: Single-center prospective cohort of outpatients with covid-19, diagnosed between the 10th March and the 2nd April, 2020 with a daily collection of symptoms by an on-line auto-questionnaire.
Results: A total of 186 patients were included (median age, 41 years [interquartile range, 19–78 years]; 74.2% female), of whom 132 (71%) were HCWs. The median follow-up after symptom onset was 14 (min 4–max 24) days. HCWs were significantly younger than non-HCWs (median age 40.3 years vs. 47.2 years [$P < 0.005$]), and 81.8% were women. Four patients (2.2%) were hospitalized including one HCW. The median time to recovery was 9 days after symptom onset (95% CI 8-11) in the global population and respectively 8 (95% CI 8–9) and 13 (95% CI 11–15) days in HCWs and in non-HCWs ($P < 0.005$). After adjusting for age, co-morbidities, and gender, the instantaneous risk ratio for symptom absence in HCWs was 1.76 compared with non-HCWs (95% CI [1.16–2.67], $P = 0.037$).
Conclusion: HCWs suffering from covid-19 had favorable outcomes and had a shorter time to recovery than non HCWs.

1. Introduction

Coronavirus Disease 2019 (COVID-19) has now become a global pandemic [1]. At of September 4th 2020, 300,181 cases of confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections called COVID-19 have been declared in France, including 30,706 related deaths [2]. Considering the data, the case-fatality rate of confirmed COVID-19 in France could be assumed to be around 10.2%. However, in France, during the epidemic peak, screening recommendations for SARS-CoV-2 infections focused on symptomatic healthcare workers (HCWs), people who met hospitalization criteria and at-risk individuals for a severe disease [3,4]. Therefore, many people, notably asymptomatic or pauci-symptomatic cases, were not screened for SARS-CoV-2 infection, leading to an overestimated case fatality rate.

Worldwide, among infected people, HCWs account for a large number of COVID-19 cases, representing for example 19% of infected people in the USA [5]. In Italy, 20% of exposed HCWs were infected [6]. In France, Santé Publique France reported 31,171 infections and 16 deaths in staff of healthcare facilities [7].

Much of the knowledge on COVID-19s course is based either on clinical data and the severity of the disease or on prognosis from hospitalized patients' data [8,9]. However, a Chinese study of 72,314 cases shows that 81% infected patients initially suffered from only mild symptoms (i.e. without pneumonia or with mild pneumonia) [10]. Descriptions of the characteristics and the evolution of mild COVID-19 are lacking and focus mainly on specific clinical signs such as anosmia [11,12].

Our objective is therefore to describe the spontaneous evolution of SARS-CoV-2 infected individuals experiencing mild symptoms

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requiring outpatient follow-up by analyzing individual trajectories through a daily web-based questionnaire lasting at least 14 days from the symptom onset, in order to better understand the natural evolution of this new infection.

2. Methods

2.1. Study design and participants

Between the 10th March and the 2nd April, 2020, all symptomatic people with a notable clinical history and symptoms suggestive of SARS-CoV-2 infection screened at the University Hospital of Saint-Etienne and eligible for outpatient management were included in this prospective cohort. All people with a negative SARS-CoV-2 RT-PCR on respiratory samples (mainly nasopharyngeal swabs) and those under the age of eighteen were excluded. Cases of SARS-CoV-2 infections confirmed by RT-PCR [13] were symptomatic healthcare workers (HCWs) and symptomatic people with risk factors for severe COVID-19 without hospitalization criteria seen at the ambulatory COVID-19 clinic.

After screening, all patients with a SARS-CoV-2 infection without hospitalization criteria were included on the basis of outpatient follow-up (LIFEN®, Paris, France). They were offered a daily outpatient monitoring service with a web-based auto questionnaire sent by text message. Outcomes were followed up until the 14th April, 2020. We extracted the data from the base.

2.2. Data collection

Patient demographics, co-morbidities, clinical signs, symptoms and laboratory tests were collected at the time of SARS-CoV-2 infection diagnosis. Follow-up data reported in this study was collected by web-based auto questionnaire sent by text message every morning for at least 14 days from the day after the symptom onset. RT-PCR results were obtained within 24 h after the nasopharyngeal sampling. Each patient had to fill in a daily follow-up questionnaire including clinical data such as sensation of dyspnea (evaluated by the Borg scale) [14], temperature, respiratory rate, heart rate, presence of chills and chest pain. Based on the data collected via the application, patients were contacted by phone and offered a course of action depending on their clinical condition: continue remote monitoring, contact a general practitioner or call the emergency medical service for hospital admission. We focused on 3 symptoms: fever (> 37.8 °C in the morning) dyspnea (Borg scale > 1) and chest pain. We considered that a patient was cured when none of these symptoms were reported after the last known symptoms [15].

2.3. Statistical analysis

Variables were described as frequency and percentage for qualitative variables; mean, median (min-max) for quantitative variables. Relationships between the variables were explored using Student and Wilcoxon–Mann–Whitney tests for quantitative variables, Pearson Chi^2 tests or Fisher exact tests for qualitative variables.

The general time to recovery was described using medians of survival, and modelled as survival curves by the Kaplan–Meier method, with 95% confidence intervals and annotation of censored events. Regarding the survival curve, the overall symptomatic state was evaluated per day for all the people responding on the day-to-day application. As soon as a patient stopped responding to the application, this data was considered to be censored.

The comparison of the general survival function between HCWs and non-HCWs was performed using the non-parametric Logrank test, with verification of the hypothesis of risk proportionality. It was then analyzed with the Cox model by adjusting for age, sex, SARS-CoV-2 RT-PCR cycle threshold and comorbid status, after verification of the hypothesis of proportional instantaneous risks. We applied the Bonferroni correction to the p-values.

The statistical analyses were carried out using software R, version 3.5.1. The significance threshold was set at 5%. The tests were bilateral.

3. Results

3.1. Characteristics of the global study population

The characteristics of the cohort are described in Table 1. The mean age was 42.3 years ± 12.6, 138 individuals (74.2%) were women. One hundred and thirty-two (70.9%) were HCWs. The SARS-CoV-2 infection rate was 34% (132/389) in HCWs and 51.4% (54/105) in non-HCWs ($P = 0.03$). The Diagnosis of SARS-CoV-2 infection was confirmed with a mean delay of 5.6 ± 3.3 days after the symptoms onset. Forty-six individuals (24.7%) had at least one comorbidity. Median follow-up after symptom onset was 14 (4–24) days. Individuals answered the daily follow-up questionnaire for a median of 8 days (3–14) after their inclusion (day after the diagnosis). The Mean cycle threshold for SARS-CoV-2 RT-PCR was 25.1 ± 7.0 (Table 1). Cycle thresholds were correlated to the duration of symptoms before the screening for SARS-CoV-2 infection ($R^2 = 0.4$, $P < 0.005$).

At the time of diagnosis, we obtained data on the clinical manifestations for 102 individuals (54.8% of the cohort). Among them, the most present symptoms were coughing in 71 people (70%) and myalgia in 63 people (61.7%). Fever was observed in only 20 (19.6%) individuals at the time of screening (see Table 2).

3.2. Outcomes in the global study population

During the follow-up, four patients (2.2%) were hospitalized, of whom two (1.1%) required oxygen therapy and one (0.5%) required intensive care intubation and died. The median time to recovery was 9 days after symptom onset (95% CI 8–11) (Fig. 1). Concerning the evolution of symptoms, Fig. 2 represents the number of symptoms felt daily per patient. Seventy-six (41%) people reported dyspnea at least once with a mean duration of four days.

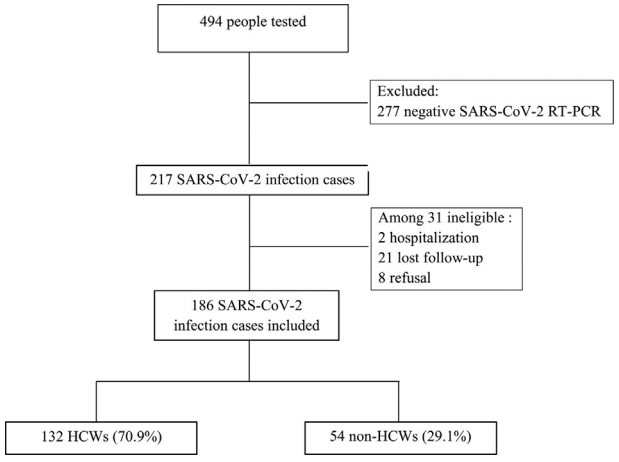

Fig. 1. depicts the flowchart of the people included in our outpatient cohort. Four hundred and ninety-four individuals were screened for SARS-CoV-2 infection during the study period. Two hundred and seventeen people (43.93%) had a positive RT-PCR for SARS-CoV-2. Among the positive individuals, 31 were excluded because of their inability to perform the ambulatory follow-up by telephone application (people who did not have a mobile phone or were unable to complete the questionnaires were followed up at home with daily telephone calls.). Overall, 186 individuals with COVID-19 were included in this study.

Table 1
Demographic and clinical characteristics of people infected with SARS-CoV-2.

	Total health care workers (n = 132)	Total non-health care workers (n = 54)	Total (n = 186)	P-values
Demographic parameters				
Age, mean, SD (years)	40.3 ± 11.4	47.2 ± 14.2	42.3 ± 12.6	< 0.005
Males, n (%)	24 (18.2)	24 (44.4)	48 (25.8)	< 0.005
Females, n (%)	108 (81.8)	30 (55.6)	138 (74.2)	< 0.005
Comorbidities, n (%)				
People with ≥ 1 comorbidity	31 (23.5)	15 (28.7)	46 (24.7)	NS
Chronic heart disease	3 (2.3)	7 (13)	10 (5.4)	< 0.05
Hypertension	8 (6.1)	5 (9.3)	13 (7)	NS
Chronic lung disease	1 (0.8)	2 (3.7)	3 (1.6)	NS
Asthma	11 (8.3)	1 (1.8)	12 (6.4)	NS
Kidney disease	1 (0.8)	0 (0)	1 (0.5)	NS
Hepatic disease	1 (0.8)	1 (1.8)	2 (1.1)	NS
Neurological disorders	0 (0)	0 (0)	0 (0)	NS
Neoplasia	3 (2.3)	3 (5.6)	6 (3.2)	NS
Hematologic disease	2 (1.5)	2 (3.7)	4 (2.1)	NS
HIV	0 (0)	0 (0)	0 (0)	NS
Obesity	3 (2.3)	0 (0)	3 (1.6)	NS
Diabetes	2 (1.5)	5 (9.3)	7 (3.8)	NS
Rheumatologic disease	2 (1.5)	0 (0)	2 (1.1)	NS
Clinical diagnosis				
Delay between disease onset and diagnosis, mean, SD (day)	5 ± 3	7 ± 3.3	5.6 ± 3.3	< 0.005
Virological diagnosis				
RT-PCR Cycle threshold, mean, SD	24.2 ± 6.7	27.2 ± 7.5	25.1 ± 7.0	0.009
Vital signs at diagnosis, mean ± SD (n)				
Temperature (°C)	38 ± 0.7 (16)	38.6 ± 0.6 (9)	38.2 ± 0.7 (25)	NS
Saturation (%)	98.1 ± 1.6 (63)	97.8 ± 2.1 (25)	98 ± 1.8 (88)	NS
Respiratory rate	18.4 ± 5.1 (42)	19.7 ± 3.5 (16)	18.8 ± 4.7 (58)	NS
Systolic blood pressure (mmHg)	139.1 ± 16.7 (63)	136.9 ± 22.4 (22)	138.6 ± 18.4 (85)	NS
Diastolic blood pressure (mmHg)	89.0 ± 9.6 (63)	81.4 ± 13.1 (22)	87.1 ± 10.9 (85)	NS
Cardiac frequency (bpm)	91 ± 13.8 (11)	86.1 ± 17.8 (16)	88.1 ± 15.4 (27)	NS
Symptoms over illness course, mean ± SD (n)				
Symptomatic state				
Onset (day)	6.0 ± 2.6 (83)	8.3 ± 2.7 (36)	6.7 ± 2.8 (119)	< 0.005
Duration (day)	3.6 ± 3.2 (83)	4.1 ± 3.2 (36)	3.7 ± 3.1 (119)	NS
Number of recurrences	1.2 ± 0.5 (83)	1.3 ± 0.5 (36)	1.2 ± 0.5 (119)	NS
Fever				
Onset (day)	5.8 ± 2.4 (26)	8.7 ± 2.3 (20)	7.1 ± 2.8 (46)	< 0.005
Duration (day)	3 ± 2.4 (26)	2.2 ± 1.5 (20)	2.7 ± 2.1 (46)	NS
Number of recurrences	1.3 ± 0.6 (26)	1.3 ± 0.6 (20)	1.3 ± 0.6 (46)	NS
Dyspnea				
Onset (day)	6.6 ± 2.6 (51)	8.6 ± 2.9 (25)	7.2 ± 2.8 (76)	< 0.005
Duration (day)	3.8 ± 3.3 (51)	4.2 ± 3.3 (25)	3.9 ± 3.3 (76)	NS
Number of recurrences	1.2 ± 0.4 (51)	1.2 ± 0.4 (25)	1.2 ± 0.4 (76)	NS
Chest pain				
Onset (day)	6.1 ± 2.6 (46)	7.7 ± 1.9 (21)	6.6 ± 2.5 (67)	NS
Duration (day)	2.7 ± 2.4 (46)	3.2 ± 2.8 (21)	2.9 ± 2.5 (67)	NS
Number of recurrences	1.4 ± 0.7 (46)	1.2 ± 0.4 (21)	1.3 ± 0.6 (67)	NS
Outcomes, n (%)				
Hospitalization	1 (0.8)	3 (5.5)	4 (2.2)	NS
Death	0	1 (1.6)	1 (0.5)	NS
Number of days of response on the mobile application				
Mean	8.3	7.3	8.0	NS
Median (range)	9 (1–14)	7.5 (1–14)	8 (3–14)	
Delay from symptoms onset to the last response on the mobile application				
Mean	13.7	14.6	13.9	NS
Median (Interquartile range)	14 (6–24)	14 (4–22)	14 (4–24)	
Days from symptom onset to resolution of all symptoms, Median (Interquartile range)	8 (8–9)	13 (11–15)	9 (8–11)	< 0.005

For quantitative parameters, data is expressed by means and standard deviations if normally distributed and by median and interquartile ranges if not. For qualitative parameters, data in numbers and percentages. NS: not significant.

Dyspnea was the most frequently reported symptom during follow-up (Table 1).

3.3. Characteristics of COVID-19 in outpatient HCWs compared with non-HCWs

Among the 132 HCWs, 108 (81.82%) were women. HCWs were significantly younger than non-HCWs, median age 40.3 vs 47.2 years-old (P < 0.005). Mean delay between the symptom onset and the SARS-CoV-2 infection diagnosis was 5 days ± 3.0 days in HCWs and 7.0 ± 3.3 days in non-HCWs (P < 0.005). The mean of the RT-PCR for SARS-CoV-2 cycle threshold value was lower (24.3 ± 6.7) for HCWs than for non-HCWs (27.2 ± 7.5; P = 0.009) (see Table 1).

Median time to recovery from symptoms onset was 8 (IQR 8–9) days in HCWs and 13 (IQR 11–15) days in non-HCWs (P < 0.005). This difference remains significant after adjustment on age, gender, comorbidities and SARS-CoV-2 RT-PCR cycle threshold (Fig. 3). After adjustment for age, comorbidities, gender, and SARS-CoV-2 RT-PCR cycle threshold, the instantaneous risk ratio of being

Table 2
Main manifestations at diagnosis.

	Total health care workers ($n = 72$)	Total non-health care workers ($n = 30$)	Total ($n = 102$)	*P*-values
Manifestations at diagnosis, *n* (%)				
Fever	11 (15.3)	9 (30)	20 (19.6)	NS
Dyspnea	9 (12.5)	10 (33.3)	19 (18.6)	NS
Asthenia	43 (59.7)	12 (40)	55 (53.9)	NS
Cough	53 (73.6)	18 (60)	71 (69.6)	NS
Myalgia	48 (66.7)	15 (50)	63 (61.7)	NS
Headache	38 (52.8)	10 (34.3)	48 (47.1)	NS
Abnormal lung auscultation	2 (2.8)	2 (6.7)	4 (3.92)	NS
Diarrhea	22 (30.6)	10 (33.3)	32 (31.4)	NS
Anosmia	24 (33.3)	4 (13.3)	28 (27.4)	NS

Data in raw values and percentages. NS: not significant.

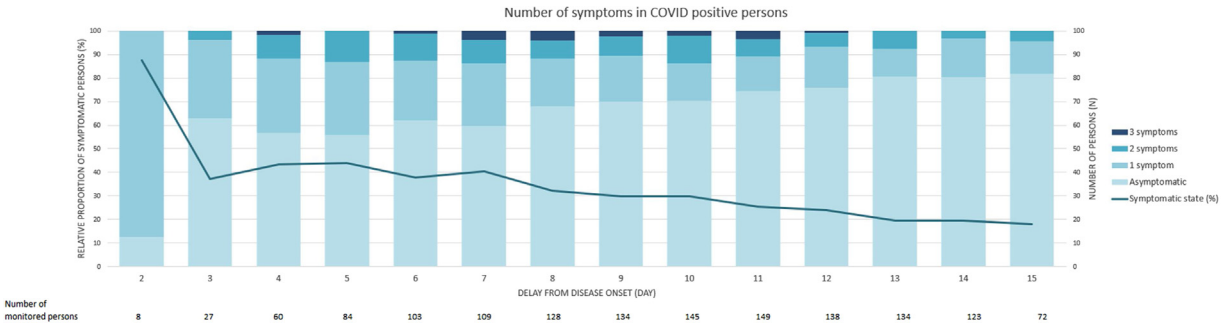

Fig. 2. Number of symptoms in COVID-19 positive persons.

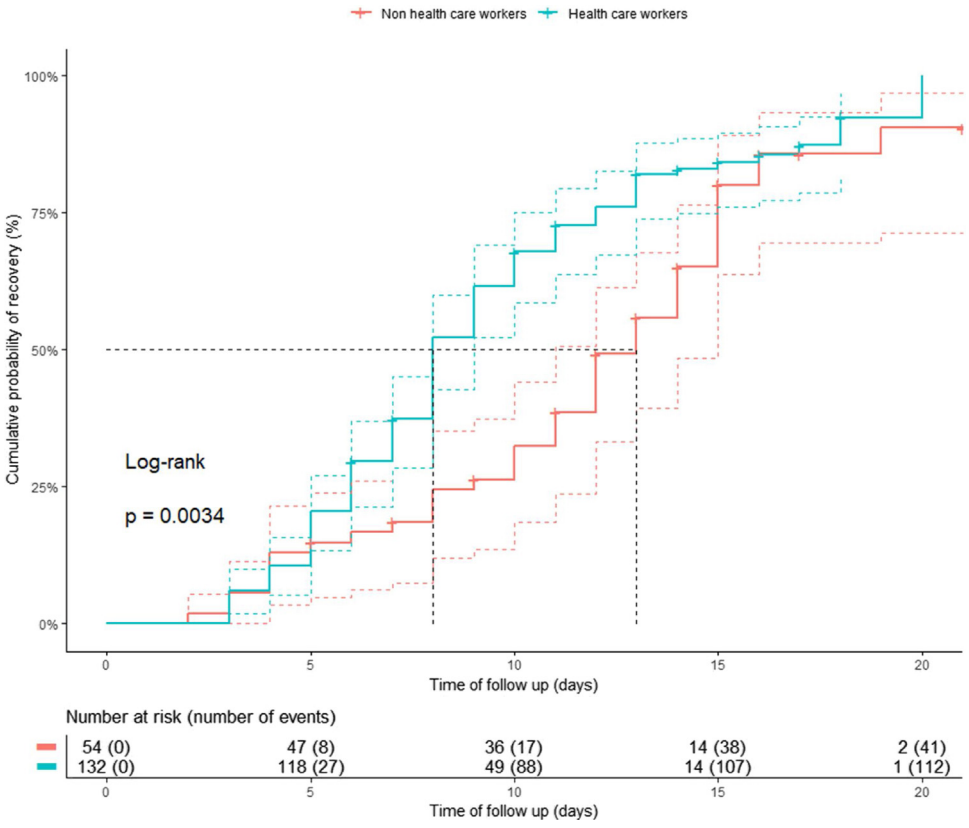

Fig. 3. Kaplan Meier curve of cumulative probability of recovery in healthcare workers and non-healthcare workers.

symptom-free among HCWs was 1.76 compared to non-HCWs (95% CI [1.16–2.67], $P = 0.037$).

4. Discussion

This prospective case series reports the clinical features of 186 people with a laboratory-confirmed SARS-CoV-2 infection, mild symptoms and eligible for outpatient management reporting epidemiologic features and clinical course in detail. To our knowledge, this is the first study reporting individual trajectories with a daily follow-up in outpatient care. Our results suggest that a spontaneous outcome is favorable in 98% of individuals with SARS-CoV-2 infection eligible for outpatient care. We observed one death but retrospectively the patient should not have been considered for outpatient management as he suffered from severe neutropenia, lymphopenia and thrombopenia. The median time to recovery was nine days. The median time to recovery was significantly lower than observed in a prospective cohort of 391 COVID-19 cases in China [16] where median time to recovery was 20.1 days, but only 26% of the cohort experienced mild symptoms of COVID-19. The authors highlight that time to recovery was probably inflated as a negative SARS-CoV-2 RT-PCR was necessary for isolation cessation, and the RT-PCR was performed after 14 days of isolation [17].

Our results confirmed that, as recommended by the World Health Organization, individuals with mild symptoms of COVID-19 could be treated at home [17]. To our knowledge, no individuals in this prospective cohort had received a possible specific treatment for COVID-19. The percentage of patients with favorable outcomes is quite similar to that in the cohort of individuals treated with the combination of Hydroxychloroquine and Azythromycin [18]. Our observation confirmed that COVID-19 cases with mild symptoms and eligible for outpatient care had favorable outcomes since eligibility criteria for outpatient care are followed as recommended in the French National Guidelines [15]. The majority of individuals in this case series were asymptomatic at the end of the 14-day outpatient follow-up.

In addition to a favorable outcome in the global study population, we observed a very favorable outcome in HCWs, and time to recovery was significantly shorter in HCWs than in non-HCWs. We had the opportunity to follow infected HCWs because, during the epidemic peak in France, screening for SARS-CoV-2 infection mainly concerned HCWs and hospitalized patients. Our cohort included more than 70% of HCWs, and outcome was favorable in 99% of them. Furthermore, most of the HCWs in our cohort had no longer any symptoms on the 7th day after symptom onset. According to the recommendations of the French High Council for Public Health (HCSP), they were able to resume their work as soon as the fever and possible dyspnea disappeared at the 8th day after the onset of symptoms, keeping a surgical mask on for seven days (fourteen days if they are immunocompromised). In a study conducted in the USA, the authors observed that 90% of the HCWs were treated on an outpatient basis [5]. Our observations are quite similar; their study population included 73% of women, and median age was 42 years in SARS-Cov-2 infected HCWs. During Middle East Respiratory Syndrome Coronavirus epidemics, HCWs had also more favorable outcomes than non-HCWs [19]. The difference of prognosis between HCWs and non-HCWs might be due to younger age and a lower prevalence of comorbidities in HCWs [20]. However, in our study cohort the difference remained significant after adjustment for age, gender, comorbidities and viral load. We have different hypotheses to explain the observed difference in the course of mild COVID-19 in HCWs and in non-HCWs. First, HCWs consider their role to be essential, notably during the current health crisis, and may underestimate their symptoms. However, we evaluated three main symptoms: dyspnea, fever and chest pain. Dyspnea was evaluated with Borg scale considered as reproductive [14]. At diagnosis, HCWs reported more fatigue and less often dyspnea than non-HCWs. HCWs were particularly encouraged for screening since the first symptoms, they might suffer from more benign form of COVID-19 than non-HCWs. During the study period, screening for SARS-CoV-2 infection was limited and individuals with mild symptoms or asymptomatic SARS-CoV-2 infections were not systematically tested, this point may in part explain the differences observed between HCWs who were concerned by screening and non-HCWs. Secondly, we cannot rule out a memory bias regarding the date of symptom onset, HCWs felt themselves at risk for COVID-19 and are more prone to give a precise date than non-HCWs. In fine, we hypothesized that innate immunity may play a role in the observed difference, COVID-19 being characterized by alteration in peripheral lymphocyte subset, with decreased Natural Killers (NK) cells count [20,21]. HCWs, often exposed to pathogens, might have a stronger innate immunity than non-HCWs. In the same vein, in Hepatitis C Virus infection, innate immunity and NK cells were described as protective for HCWs exposed to HCV infection [22]. Furthermore, a T-cell response to SARS-CoV-2 was observed in unexposed individuals suggesting a cross immune response with other coronaviruses [23], HCWs might be frequently exposed to other coronaviruses.

4.1. Limitations

This study has several limitations. First, although this was a prospective study of individuals followed on an outpatient basis, the data studied are observational and declarative only. However, the compliance rate for answering daily questionnaire was estimated at 69% (data not shown), and reached 80% in individuals aged from 30 to 50 years. Secondly, information about symptoms between the symptom onset and the start of the outpatient monitoring was assessed in only 55% of individuals. Lastly, some people stopped answering the questionnaire before the end of the follow-up period. However, the majority of people who prematurely ended the follow-up no longer had any symptoms at the time of the last questionnaire they answered. While this study was carried out in a context of limited access to testing, our results could be confirmed in a further study carried out in a context of large screening.

5. Conclusions

In this series of individuals diagnosed with SARS-CoV-2 infection with mild symptoms and eligible for outpatient management, only 4 people (2.2%), including one HCW, were admitted to hospital and one patient died. Thanks to the outpatient follow-up of people for at least 14 days after the symptoms onset, we were able to observe that the great majority of these individuals suffering from mild symptoms at the time of diagnosis recovered spontaneously in 9 days. Short-term outcomes in HCWs suffering from COVID-19were favorable, and time to recovery was shorter in HCWs than in non-HCWs.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments. The institutional review board of the University Hospital of Saint-Etienne approved this study in April 2020 (number IRBN472020).

Disclosure of interest

The authors declare that they have no competing interest.

Contribution of authors

A.G.B., E.B.N, E.B. conceived the research.
E.B., H.T., A.F. F.S., A.G.B., R.L. collected the data.
H.T., S.P., F.L., P.B., E.B. analyzed the data.
A.G.B., E.B.N., E.B. wrote the article.
All authors approved the final version.

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