Characteristics and outcomes of asthmatic outpatients with COVID-19 who receive home telesurveillance

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Shareable abstract (@ERSpublications)
Asthma appears independently associated with clinical worsening in outpatients receiving ambulatory care for #COVID19 using the Covidom telesurveillance solution for home monitoring but no death was reported among asthmatics https://bit.ly/3vMTzpZ

Cite this article as: Beurnier A, Yordanov Y, Dechartres A, *et al*. Characteristics and outcomes of asthmatic outpatients with COVID-19 who receive home telesurveillance. *ERJ Open Res* 2022; 8: 00012-2022 [DOI: 10.1183/23120541.00012-2022].

Received: 7 Jan 2022
Accepted: 24 July 2022

Abstract

Background The prognosis of asthmatic outpatients with COVID-19 needs to be clarified. The objectives of this study were: 1) to investigate the characteristics and outcomes of asthmatic patients receiving initial ambulatory care and home monitoring for COVID-19 with Covidom, a telesurveillance solution; and 2) to compare the characteristics and outcomes between asthmatic and non-asthmatic patients.

Methods Inclusion criteria were age ⩾18 years, suspected or confirmed COVID-19 diagnosis allowing initial ambulatory care, registration in Covidom between March 2020 and April 2021 and completion of the initial medical questionnaire. We compared clinical characteristics and outcomes between asthmatic and non-asthmatic patients, and we evaluated whether asthma was independently associated with clinical worsening (hospitalisation or death) within 30 days follow-up using a multivariate logistic regression model.

Results 33 815 patients met the inclusion criteria. Asthma was reported in 4276 (12.6%). The main comorbidities among asthmatic patients were obesity (23.1%), hypertension (12.7%) and diabetes (4.5%). As compared with non-asthmatic patients, asthmatic patients were more often female (70.0 *versus* 62.1%, p<0.001), of younger age (42.2 *versus* 43.8 years, p<0.001) and obese (23.1 *versus* 17.6%, p<0.001). The rate of hospitalisation did not differ significantly (4.7 *versus* 4.2%, p=0.203) and no asthmatic patient died during follow-up (*versus* 25 non-asthmatic patients, 0.1%; p=0.109). In multivariate analysis, asthma was independently associated with higher risk of clinical worsening (OR 1.23, 95% CI 1.04–1.44, p=0.013).

Conclusion In a large French cohort of patients receiving initial ambulatory care and home monitoring for COVID-19, asthma was independently associated with higher risk of clinical worsening although no asthmatic patient died within the 30 days follow-up.

Introduction

Asthma is a chronic respiratory condition characterised by variable airflow obstruction, airway hyperresponsiveness and bronchial inflammation that results in a heavy burden for individuals and health

services worldwide [1]. Exacerbations of asthma are potentially life-threatening events defined by an acute worsening of the disease, mostly due to viral infections. As coronaviruses are commonly detected in the airways of asthmatic patients, concerns have arisen about more frequent and/or more severe respiratory symptoms among asthmatic patients during the 2019 coronavirus disease (COVID-19) pandemic [2]. Surprisingly, the first observations from China reported a low prevalence of asthma among hospitalised patients [3, 4], which was further corroborated by multinational data [5–7]. In a French study conducted in the Greater Paris area, asthmatic patients were not over-represented among patients with COVID-19 who required hospitalisation, and worse outcomes were observed mainly in patients with major comorbidities [5]. Another study in New York City concluded that asthma diagnosis was not associated with worse outcomes among hospitalised patients 65 years or younger with severe COVID-19, after controlling for age, obesity or other high-risk comorbidities [8]. While many studies focused on patients with a severe form of the disease, the prognosis of asthmatic patients with mild COVID-19 receiving initial ambulatory care still needs to be clarified [2]. At the beginning of the outbreak in France, a telesurveillance solution called Covidom that was dedicated to COVID-19 outpatients was initially deployed in the Greater Paris area. Covidom is the first and largest telesurveillance solution described for the home monitoring of COVID-19 cases [9, 10]. It allows close, but minimally invasive, outpatient surveillance using daily short questionnaires and algorithm-based alerts which trigger an adequate medical response. The objectives of this study were: 1) to investigate the characteristics and outcomes of asthmatic patients receiving initial ambulatory care and home monitoring for COVID-19 with Covidom; and 2) to compare the characteristics and outcomes between asthmatic and non-asthmatic patients.

Material and methods

Patients and study design

In this study we have included outpatients from the Greater Paris area, with suspected or confirmed COVID-19, that were given the opportunity to use the Covidom solution for home monitoring of mild COVID-19 as initial outpatient management. As previously reported [9, 10], registration of patients in Covidom could be performed by any physician in case of suspected or confirmed COVID-19 after obtaining informed consent, in the context of initial outpatient management or after COVID-19-related hospitalisation. Registration was completed by the patient through a dedicated link received *via* mobile message or e-mail. Depending on their baseline risk evaluation, as defined by their treating physician, patients received one or two daily self-administrated monitoring questionnaires for 30 days after symptoms onset in order to assess respiratory rate, heart rate, temperature and dyspnoea as described elsewhere [9]. The answers could trigger alerts, which were handled in the Covidom regional control centre, that led to various medical responses, including emergency medical services (EMS) intervention if required. Patients agreed to the potential use of their anonymised data for research purposes. This study was approved by the scientific and ethical committee of the Greater Paris University Hospitals (Assistance Publique-Hôpitaux de Paris) (IRB00011591). Eligible patients for this study were all those registered in Covidom after 9 March 2020, and with symptom onset before 2 April 2021. Non-inclusion criteria were defined as follows: age <18 years; non-confirmed registration; registration in Covidom at hospital discharge and non-completion of initial medical questionnaire.

Characteristics at diagnosis and outcomes

Age and sex were collected by the including physician. The following data were collected after inclusion by using a self-reported questionnaire: weight and height, declared chronic conditions or comorbidities using discrete questions (asthma, diabetes, hypertension, heart failure, COPD, coronary artery disease, cancer under treatment, chronic renal disease) and initial symptoms. The following outcomes were investigated until 30 days after the onset of symptoms: alerts triggered (detailed as total events; alerts leading to EMS call; number of alerts per patient; and rate per daily questionnaire), hospitalisation and death. Our primary outcome was clinical worsening, defined as hospitalisation or death within 30 days after symptom onset. We used different approaches to assess this outcome as precisely as possible: 1) patient answers to the follow-up questionnaires (15 and 30 days after symptom onset); 2) regional centre reports after alerts management and the end of follow-up reasons in case of premature ending (patients or their relatives were called by the regional control centre if they did not answer the daily questionnaires to check on their status); 3) data on patients hospitalised from the Greater Paris University Hospitals (AP-HP) data warehouse (Entrepôt de données de santé (EDS) de l'AP-HP), which includes 39 university hospitals in the Greater Paris area covering a large part of this area's population (12 million inhabitants). Both hospitalisation and death within 30 days after symptom onset were analysed separately as secondary outcomes. The characteristics and outcomes of patients hospitalised in one of the AP-HP hospitals with accessible medical records on the AP-HP data warehouse system were also investigated.

Statistical methods

Quantitative data were expressed as mean±$_{SD}$ or median (interquartile range (IQR)), with the IQR presented as first quartile to third quartile. Qualitative data were expressed as frequencies and percentages. Where there were missing data, the number of patients with available information was provided for each variable. We compared patient characteristics, number of alerts and outcomes between asthmatic and non-asthmatic patients using t-tests or Mann–Whitney U-tests (if not normally distributed) for continuous variables and Chi-squared tests for discrete variables. Univariate followed by multivariate logistic regression models were used to identify whether asthma was independently associated with clinical worsening. Odds ratios were adjusted on age, sex, current tobacco use and comorbidities: body mass index (BMI), hypertension, diabetes, heart failure, COPD, coronary artery disease, cancer under treatment and chronic renal disease. These variables were considered as relevant to evaluate factors associated with clinical worsening, based on current literature. Alpha risk was set at 5% for all analyses.

Results

Overall population

A flow chart providing details on patient selection is presented in figure 1. The number of patients registered in Covidom was 80 773. 19 264 patients (23.8%) were not included because they did not confirm their enrolment and 17 257 (21.4%) because their medical history was not provided. 33 815 patients met the inclusion criteria, of which 4276 (12.6%) reported being asthmatic. As compared with non-asthmatic patients, patients with asthma were younger (mean age 42.2 *versus* 43.8 years, p<0.001) and more likely to be female (70.0 *versus* 62.1%, p<0.001). The following comorbidities were more prevalent among asthmatic patients: obesity (23.1 *versus* 17.6%, p<0.001), COPD (5.1 *versus* 1.3%, p<0.001) and heart failure (2.4 *versus* 1.9%, p=0.024). A lower proportion of asthmatic patients were treated for cancer (0.8 *versus* 1.2%, p=0.024). Patients with asthma were more prone to experience respiratory symptoms, especially cough (68.2 *versus* 61.3%, p<0.001) and shortness of breath (67.8 *versus* 44.7%, p<0.001). Chest pain and tightness were also more prevalent among asthmatic patients (table 1).

Outcomes

The rate of clinical worsening did not differ between asthmatic and non-asthmatic patients (4.7 *versus* 4.3%, p=0.235). The rate of hospitalisation was similar (4.7 *versus* 4.2%, p=0.203). No death was reported at 30 days among asthmatic patients (*versus* 25 deaths or 0.1% among non-asthmatic patients, p=0.109) (table 2). Asthmatic patients were more prone to trigger at least one Covidom alert (90 *versus* 85%, p<0.001), and the proportion of alerts leading to emergency service call was higher among asthmatic patients (1.5 *versus* 0.8%, p<0.001). In multivariate analysis, asthma was independently associated with clinical worsening (OR 1.23, 95% CI 1.04–1.44, p=0.013) (table 3). Among patients with available and

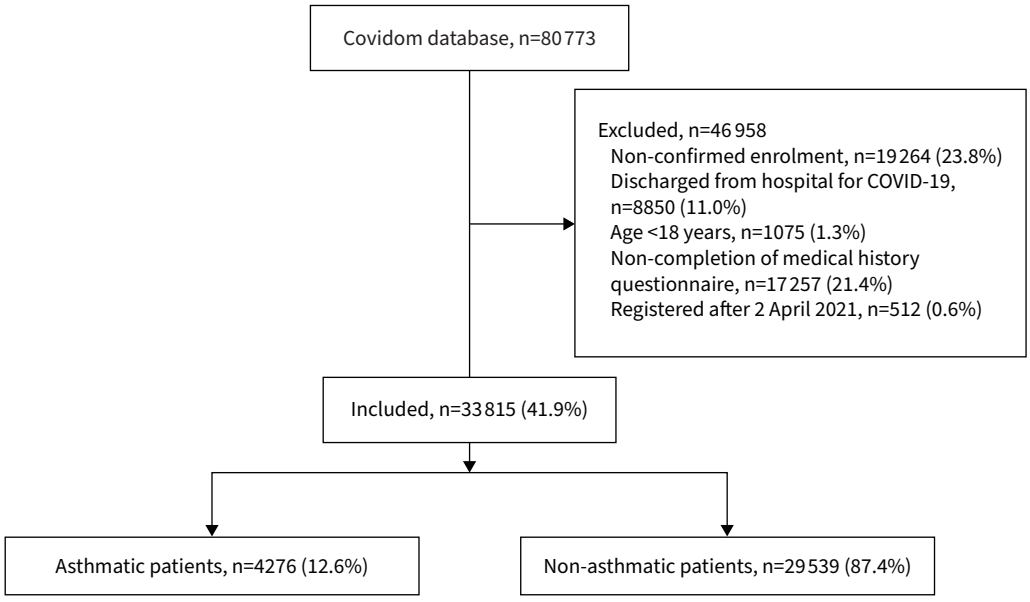

FIGURE 1 Selection of patients from the Covidom database.

TABLE 1 Clinical characteristics of patients with or without asthma (n=33 815)

Patient characteristics	Asthmatic patients	Non-asthmatic patients	p-value
Subjects n	4276	29 539	
Age years, mean±SD	42.2±13.7	43.8±14.2	<0.001
Age 46 to ⩽65 years	1394 (32.6)	10 729 (36.3)	
BMI kg m^{-2}, median (IQR), n=33 347	25.3 (22.3–29.4)	24.8 (22.0–28.3)	<0.001
Female sex, n=33 774	2989 (70.0)	18 312 (62.1)	<0.001
Comorbid conditions			
Overweight (BMI 25–30 kg m^{-2}), n=33 347	1210 (28.6)	8704 (29.9)	<0.001
Obesity (BMI >30 kg m^{-2}), n=33 347	979 (23.1)	5124 (17.6)	
Hypertension	541 (12.7)	3591 (12.2)	0.369
Diabetes	193 (4.5)	1494 (5.1)	0.136
Heart failure	102 (2.4)	551 (1.9)	0.024
COPD	217 (5.1)	378 (1.3)	<0.001
Coronary artery disease	72 (1.7)	393 (1.3)	0.074
Cancer under treatment	34 (0.8)	355 (1.2)	0.024
Chronic renal disease	61 (1.4)	325 (1.1)	0.072
Respiratory symptoms			
Cough	2916 (68.2)	18 120 (61.3)	<0.001
Shortness of breath	2898 (67.8)	13 205 (44.7)	<0.001
Chest pain	1371 (32.1)	7043 (23.8)	<0.001
Chest tightness	1491 (34.9)	7215 (24.4)	<0.001
General symptoms			
Fatigue	3758 (87.9)	25 368 (85.9)	<0.001
Fever	2062 (48.2)	14 405 (48.8)	0.517
Shivers	2439 (57.0)	15 808 (53.5)	<0.001
Myalgia	2505 (58.6)	15 932 (53.9)	<0.001
Gastrointestinal symptoms			
Anorexia	1695 (39.6)	11 387 (38.5)	0.176
Nausea/vomiting	1210 (28.3)	6838 (23.1)	<0.001
Diarrhoea	1655 (38.7)	10 175 (34.4)	<0.001
Neurological symptoms			
Anosmia	1300 (30.4)	9924 (33.6)	<0.001
Ageusia	1326 (31.0)	9700 (32.8)	0.018
Cutaneous symptoms			
Rash	507 (11.9)	2614 (8.8)	<0.001
Chilblains	88 (2.1)	530 (1.8)	0.253
Conjunctivitis	392 (9.2)	2021 (6.8)	<0.001

Qualitative data are expressed as frequency (% of total). In case of variable with missing data, the number of patients with available information is specified. BMI: body mass index; IQR: interquartile range presented as first quartile (Q1)–third quartile (Q3); SD: standard deviation.

TABLE 2 Outcomes of patients with or without asthma (n=33 815)

Outcomes	Asthmatic patients	Non-asthmatic patients	p-value
Worsening (hospitalisation or death)	200 (4.7)	1261 (4.3)	0.235
Hospitalisation	200 (4.7)	1253 (4.2)	0.203
Death	0 (0.0)	25 (0.1)	0.109
At least one Covidom alert	3849 (90.0)	25 095 (85.0)	<0.001
Alert leading to emergency service call	65 (1.5)	249 (0.8)	<0.001
Number of alerts per patient, median (IQR), n=28 944	5.0 (2.0–11.0)	4.0 (2.0–9.0)	<0.001
Rate of alerts per follow-up, median (IQR), n=28 944	0.4 (0.1–0.8)	0.3 (0.1–0.7)	<0.001

Qualitative data are expressed as frequency (% of total). In case of variable with missing data, the number of patients with available information is specified. IQR: interquartile range presented as first quartile (Q1)–third quartile (Q3).

TABLE 3 Association between asthma and clinical worsening

Multivariate analysis	OR (95% CI)	p-value
Unadjusted	1.10 (0.94–1.28)	0.235
Adjusted on age, sex, current tobacco use and comorbidities	1.23 (1.04–1.44)	0.013

Comorbidities are body mass index (BMI), hypertension, diabetes, heart failure, COPD, coronary artery disease, cancer under treatment and chronic renal disease. Age and BMI as three categories (18–45 years, 46–65 years, >65 years and <25 kg m^{-2}, 25–30 kg m^{-2}, >30 kg m^{-2}).

positive reverse transcriptase PCR (RT-PCR) (n=12 212; 36.1%), asthma was also independently associated with clinical worsening (OR 1.29, 95% CI 1.06–1.56, p=0.012).

Characteristics and outcomes of asthmatic patients requiring hospitalisation during follow-up

Medical records were accessible for 61 (31%) of the 200 hospitalised asthmatic patients. In this subset of patients, the mean±SD age was 49.5±16.2 years with a predominance of females (62.3%). Obesity was the most prevalent comorbidity (33.3%), followed by hypertension (21.3%), diabetes (6.6%) and heart failure (6.6%). SARS-CoV-2 pneumonia was documented in 30 cases (49%) and was mostly associated with mild-to-moderate radiological extension (83%). Three patients (8%) were admitted to a critical care unit. None of them died. Of note, one patient was diagnosed with an asthma exacerbation. She was a 46-year-old female with positive RT-PCR and no comorbidity, previously treated for mild asthma with salbutamol as needed. She was admitted to hospital for dyspnoea, cough and wheezing 4 days after the onset of symptoms. No pneumonia was found on the chest CT scan, and she was successfully treated with nebulisation of bronchodilators. No systemic corticosteroids were administrated, and she was quickly discharged from hospital at day 2. One patient was treated with a biologic for severe asthma (omalizumab). She was a 50-year-old female without comorbidity admitted to hospital due to worsening of diarrhoea and vomiting without any respiratory distress. She was discharged from hospital at day 2.

Discussion

In a large French cohort of patients from the Greater Paris area receiving initial ambulatory care and home monitoring with a telesurveillance solution for COVID-19, asthma was independently associated with clinical worsening, but no asthmatic died within the 30-day follow-up.

Asthmatic patients accounted for 12.8% of this cohort total population, whereas the prevalence of asthma in France has been recently reported at 6.4% [11]. Although it might reflect a higher risk of SARS-CoV-2 infection among asthmatic patients, several factors must be taken into consideration when interpreting this finding. Firstly, we found an over-representation of women in the entire cohort (which is consistent with better healthcare programmes adherence in women, as previously described [12]); since asthma is more frequently diagnosed in adult women [13], this unbalanced sex ratio may contribute to overestimate its prevalence. Likewise, we can assume that asthmatic patients were more likely to accept registration on a home-monitoring telesurveillance solution than patients without respiratory comorbidity [14]. Consistent with our results, the study from Chhiba *et al*. [15] found that 14% of 1526 COVID-19 outpatients were asthmatic; the mortality rate was low in these patients and did not differ significantly from the non-asthmatic patients.

In the present study, asthma was independently associated with clinical worsening, which was not found in a previous study describing factors associated with clinical worsening among COVID-19 outpatients managed with the Covidom telesurveillance solution [10]. In the present work we included more patients and reached statistical significance, which could be clinically relevant, but could also have enhanced some bias. Indeed, in the context of real-life settings we cannot exclude overdiagnosis of asthma, as already reported in industrialised countries [14] and among obese patients [16]. As defined in the Global Initiative for Asthma (GINA) report [17], the diagnosis of asthma should be based on both history of variable respiratory symptoms and evidence of airflow limitation. In this large cohort, we were not able to verify that those criteria were obtained for each individual, and self-reported comorbidities might have resulted in misdiagnoses (*i.e.*, misclassification of asthma by respondants). We can also hypothesise that asthmatic patients are more likely to report symptoms, which may precipitate hospitalisation. Given the real-life setting of our study, COVID-19 was clinically diagnosed by a physician, regardless of the positivity of RT-PCR. Despite the fact that COVID-19 was a major cause of viral symptoms in the Greater Paris area during the study period (March 2020–April 2021), diagnostic errors cannot be excluded. Notably, similar

results were obtained in the subset of patients with available and positive RT-PCR. Other conditions associated with COVID-19-related clinical worsening can masquerade as asthma (such as cardiac insufficiency or COPD) [17], which would impact our main outcome. In the study of Choi *et al*. [7], asthma was not an independent risk factor for the clinical outcomes of COVID-19 after adjustment. Other authors emphasised the prognostic impact of asthma control during the previous year in COVID-19 patients, reporting an increase in COVID-19-related mortality in asthmatic patients who experienced an exacerbation within 1 year [18, 19]. As highlighted elsewhere, chronic use of systemic corticosteroids is an independent risk factor for worse COVID-19 severity and all-cause mortality in asthmatic patients infected with SARS-CoV-2 [20]. Of note, we did not observe any deaths in our study of 4276 asthmatic patients with COVID-19.

Alerts were more often triggered by asthmatic patients; however only a few led to EMS call. We found that asthmatic patients were more prone to experiencing respiratory symptoms such as cough and shortness of breath. Symptoms of asthma exacerbation may overlap with those of COVID-19, and the distinction between those two clinical presentations might be difficult. Thus, the proportion of alerts related to asthma worsening remains uncertain. We can speculate it was low and some respiratory discomfort might be due to anxiety and dysfunctional breathing disorders, which are notably more frequent in asthmatic women [21] and prevalent among post-COVID-19 patients [22–26]. In a subset of 61 patients with accessible medical records, we found that SARS-CoV-2 pneumonia was the main cause for hospitalisation. Only three patients (5%) required admission in an intensive care unit, and the only patient diagnosed with an asthma exacerbation had a quick recovery. Moreover, we did not find an over-representation of severe asthmatic patients treated with biologics. The presence of other comorbidities such as obesity is probably a crucial element that determines the prognosis of asthmatic patients infected with SARS-COV-2 [5, 27, 28]. Findings also suggest that the risk of SARS-CoV-2 infection and disease severity depends on asthma phenotype and may be reduced by Th2-high inflammation [29]. Several hypotheses have been proposed to explain the limited impact of asthma on COVID-19-related outcomes: lower bronchial expression of ACE2 viral receptor in asthmatic patients, protective role of bronchial mucus, advantageous immune profile and better compliance with medical recommendations during the COVID-19 pandemic (social distancing, hand washing, use of mask, *etc.*) [30]. There is also moderate evidence for a protective role of inhaled corticosteroids [31], which was not analysed in our study because this information was not systematically collected. In addition, we can hypothesise that careful telesurveillance with the Covidom solution had beneficial effects on asthma control, as previously described with other home-monitoring devices [32]. The Covidom solution does not allow self-monitoring of lung function using mobile spirometry at home, as previously described by others [33]. This might be a relevant option, as long as enhanced coaching and education by video and telemedicine can be provided [34].

In conclusion, asthma appeared independently associated with clinical worsening in outpatients receiving ambulatory care for COVID-19 using the Covidom telesurveillance solution for home monitoring, but no death was reported among asthmatic patients. These results may reflect an increased risk of COVID-19-related clinical worsening among asthmatic patients, but we cannot exclude underlying epidemiological biases inherent to this particular population in our convenience sample (*i.e.*, patients who were more likely to get medical attention and over-interpret symptoms). Further research is needed to investigate the potential benefits of home monitoring among asthmatic patients during the COVID-19 pandemic.

Acknowledgements: We thank A. Falzon, G. Fayolle, F. Laporte, Amélie Tortel and all the Nouveal-e Santé team for their help with the web application and regional centre surveillance interface development. We also thank L. Debastard, A. Grenier, J. Hody, T. Penn and the Paris region Union régionale des professionnels de santé for their help in the development and spreading of the Covidom solution. We thank A. Banzet, J. Marchand-Arvier, N. Schmidt and P Villie from the AP-HP headquarters for their invaluable help. The Covidom solution would not have been possible without the including physicians, supervising physicians and remote monitoring responders; the complete list is available in the supplementary material.

Provenance: Submitted article, peer reviewed.

Author contributions: A. Beurnier (guarantor) was involved in the study conception, data analysis, interpretation of results and drafting the manuscript. Y. Yordanov, A. Dechartres and L. Jaulmes were involved in the study conception, data extraction, data analysis, interpretation of results and drafting the manuscript. A. Dinh, E. Debuc, F-X. Lescure and P. Jourdain were involved in the Covidom solution development, interpretation of results and

critically revising the manuscript. M. Humbert was involved in the study conception, data analysis, interpretation of results and critically revising the manuscript.

Conflict of interest: A. Beurnier reports personal fees from AstraZeneca and personal fees from Sanofi, outside the submitted work. Y. Yordanov has nothing to disclose. A. Dechartres has nothing to disclose. A. Dinh has nothing to disclose. E. Debuc has nothing to disclose. F-X. Lescure has nothing to disclose. P. Jourdain has nothing to disclose. L. Jaulmes have nothing to disclose. M. Humbert reports personal fees and nonfinancial support from GlaxoSmithKline, and personal fees from AstraZeneca, Novartis, Sanofi and Chiesi, outside the submitted work.

Support statement: This work was supported by the Programme Hospitalier de Recherche Clinique 2020 of the French Ministry of Health, by a research fund by AP-HP–Fondation de France. The Covidom platform received a funding from EIT Health specific COVID-19 fund. Funding information for this article has been deposited with the Crossref Funder Registry.

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