Initial characteristics and course of disease in patients with suspected COVID-19 managed in general practice: a prospective, multicentre cohort study

Tan-Trung Phan, William Mirat, Sophie Brossier, Emmauelle Boutin, Julie Fabre, Jean-Denis Hoonakker, Sylvie Bastuji-Garin, Vincent Renard, Emilie Ferrat

BMJ Open

Initial characteristics and course of disease in patients with suspected COVID-19 managed in general practice: a prospective, multicentre cohort study

Tan-Trung Phan ,[1,2] William Mirat,[1,3] Sophie Brossier,[1,2] Emmauelle Boutin,[4,5] Julie Fabre,[1,6] Jean-Denis Hoonakker,[1,7] Sylvie Bastuji-Garin,[4,8] Vincent Renard,[1,4] Emilie Ferrat[1,4,9]

To cite: Phan T-T, Mirat W, Brossier S, *et al*. Initial characteristics and course of disease in patients with suspected COVID-19 managed in general practice: a prospective, multicentre cohort study. *BMJ Open* 2023;**13**:e068424. doi:10.1136/bmjopen-2022-068424

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-068424).

Received 17 September 2022
Accepted 24 April 2023

For numbered affiliations see end of article.

Correspondence to
Dr Emilie Ferrat;
emilie.ferrat@u-pec.fr

ABSTRACT

Objectives To describe and compare the initial clinical characteristics of a cohort of patients with suspected COVID-19 managed by general practitioners (GPs); to assess whether 3-month persistent symptoms were more frequent among confirmed cases than among no-COVID cases; and to identify factors predictive of persistent symptoms and adverse outcomes among confirmed cases.

Design and setting A comparative, prospective, multicentre cohort study in primary care in the Paris region of France.

Participants 521 patients aged ≥18 with suspected COVID-19 were enrolled between March and May 2020.

Outcome measures Initial symptoms, COVID-19 status, persistent symptoms 3 months after inclusion and a composite criterion for potentially COVID-19-related events (hospitalisation, death, emergency department visits). The final COVID-19 status ('confirmed', 'no-COVID' and 'uncertain' cases) was determined by the GP after the receipt of the laboratory test results.

Results 516 patients were analysed; 166 (32.2%) were classified into the 'confirmed COVID' group, 180 (34.9%) into the 'no-COVID' group and 170 (32.9%) in the 'uncertain COVID' group. Confirmed cases were more likely to have persistent symptoms than no-COVID cases (p=0.09); initial fever/feeling feverish and anosmia were independently associated with persistent symptoms. At 3 months, we observed 16 (9.8%) COVID-19-related hospital admissions, 3 (1.8%) intensive care unit admissions, 13 (37.1%) referrals to an emergency department and no death. Age >70 and/or at least one comorbidity (OR 6.53; 95% CI 1.13–37.84; p=0.036), abnormalities in a lung examination (15.39; 95% CI 1.61–146.77; p=0.057) and two or more systemic symptoms (38.61; 95% CI 2.30–647.40; p=0.011) were associated with the composite criterion.

Conclusions Although most patients with COVID-19 in primary care had mild disease with a benign course, almost one in six had persistent symptoms at 3 months. These symptoms were more frequent in the 'confirmed COVID' group. Our findings need to be confirmed in a prospective study with longer follow-up.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This work is one of the few French studies to have included solely patients managed in primary care early on in the first wave of the COVID-19 pandemic.
⇒ In contrast to most research on COVID-19, our study featured a control group (a 'confirmed COVID' group, which was compared with 'no-COVID' and 'uncertain COVID' groups).
⇒ The large number of primary care centres involved in the study suggests that our results can be extrapolated to the local and regional levels.
⇒ Early on in the pandemic, COVID-19 reverse transcription PCR tests were not widely available; COVID-19 status was not therefore confirmed in all patients.
⇒ The small size of some subgroups (eg, the subgroup of patients with persistent symptoms) might have led to a lack of statistical power and thus prevented us from drawing formal conclusions in that respect.

BACKGROUND

The first wave of COVID-19 in France prompted a lockdown from mid-March to mid-May 2020. General practitioners (GPs) were in the front line[1]; they referred severe cases to hospital and managed less severe cases.[2] Early on in the epidemic, researchers sought to describe the demographic and clinical characteristics of patients with COVID-19 and their course of disease. However, these studies were fully[3–8] or partly[9] conducted in hospital. The most frequently reported initial signs were fever, cough and dyspnoea.[3] Anosmia and ageusia were also prevalent, and their concomitant presence was quite specific for a SARS-CoV-2 infection.[10–12] At the time when our study data were collected, some researchers had highlighted 'long COVID-19' as an entity with some or all the following symptoms 3–12 months after disease onset[8 13 14]: persistent asthenia, headache,

dyspnoea, sleep difficulties, anxiety or depression, and anosmia.[13 14] The significance of these symptoms is subject to debate, particularly since the literature data were somewhat contradictory; however, some researchers have suggested that these symptoms are correlated with the severity of the initial disease[8] and the number of initial symptoms.[15] Most of these studies of 'long COVID-19' estimated the frequency of persistent symptoms or adverse outcomes in hospital cohorts of patients with a confirmed diagnosis of COVID-19 but lacked a control group.[3 4 7 8] Hence, these studies were not representative of patients in primary care—even though most COVID-19 cases are diagnosed by GPs.[2] Therefore, the objectives of the present study were to (1) describe and compare the initial clinical characteristics of a cohort of patients with suspected COVID-19 managed by GPs and whose COVID-19 status ('confirmed', 'no-COVID' and 'uncertain' cases) was determined by the GP after he/she had received the laboratory test results; (2) determine whether persistent symptoms at 3 months were more frequent among confirmed cases than among no-COVID cases; and (3) identify factors predictive of persistent symptoms and adverse outcomes among confirmed cases.

METHODS

Patient and public involvement

All patients received an information sheet and gave their verbal consent to participation. They were not involved in the study design, conduct or reporting or the plans for dissemination.

Study design

This prospective, multicentre cohort study was conducted in four counties in the Paris region: Val-de-Marne, Seine-et-Marne, Essonne and Seine-Saint-Denis. Forty-four GPs were recruited from multiprofessional primary care practices affiliated with the Faculty of Health at Université Paris-Est Créteil (Créteil, France), because some of the GPs tutored the university's medical students. The GPs' characteristics are summarised in online supplemental table S1.

Population

During the first wave's lockdown period, we prospectively included all consecutive adult patients who consulted one of the participating GPs for a suspected COVID-19 infection. The exclusion criteria were age under 18, no suspicion of COVID-19 and residence in an institution. The first patient was included on 6 March 2020, and the last was included on 12 May 2020. Patients were followed up for 3 months, and study data were extracted on 22 October 2020.

Data sources

The patients' data were extracted from the GPs' electronic medical records. The clinical criteria for a diagnosis of COVID-19 were left to the GP's discretion. Patients were followed up as usual by their GP, and all consultations with healthcare professionals and/or hospital visits were registered. Three months after inclusion, the GP phoned or visited patients to collect data on persistent symptoms or recovery. For confirmed cases, they also looked for COVID-19-related hospital admissions, referrals to an emergency department, admissions to an intensive care unit and deaths. These data were completed with information from hospital discharge reports, if available.

COVID-19 status

The GPs prescribed SARS-CoV-2 serology and/or reverse transcription PCR (RT-PCR) tests and/or a CT scan of the chest, in line with the French national guidelines.[16–20] During the first wave of COVID-19 (mid-March to mid-May 2020), RT-PCR and serology tests were not widely available. An RT-PCR test was recommended for patients with severity criteria and/or with comorbidities, and for healthcare professionals.[16 17] The French national guidelines recommended a CT scan if the patient had trouble breathing, in order to assess the extent of any lung damage and to have a reference examination.[20] Serology tests became available from May 2020 and were prescribed a posteriori to (1) patients with compatible symptoms and who had not had an RT-PCR test and (2) patients with a negative RT-PCR test.[17 18]

The patient's COVID-19 status was ultimately classified by the GP as 'confirmed COVID', 'no-COVID' or 'uncertain COVID' after he/she had received the laboratory test results. Confirmed COVID status was defined as a positive RT-PCR and/or serology test, and/or a chest CT result suggestive of COVID-19. 'No-COVID' status was defined as both a negative RT-PCR test and a negative serology test, a negative RT-PCR test in the absence of a positive serology test or a positive chest CT, or a negative serology test in the absence of a positive RT-PCR test or a positive chest CT. 'Uncertain COVID' status was defined as the presence of suggestive symptoms and the absence of both RT-PCR and serology test and chest CT results.

Outcomes

We considered the two following outcomes: the persistence of symptoms 3 months after study inclusion (as assessed by the GP), and (for confirmed cases only) adverse outcomes defined by a composite criterion that included COVID-19-related hospital admissions, referral to an emergency department, intensive care unit admissions and deaths. The relationship with COVID-19 was determined from hospital records. The GP identified and recorded the patient's persistent symptoms (if any), according to his/her usual clinical practice. We asked the GPs three questions: '*Do you consider that the patient has been cured?*', '*If not, which symptoms persisted?*' and '*Do you attribute those symptoms to the initial disease?*'. Persistent symptoms (if any) were not rated on a scale or using a questionnaire.

Potential factors predictive of 3-month persistent symptoms and adverse outcomes

Among confirmed cases, the following variables (online supplemental appendix 1) collected at the initial consultation were considered as potentially predictive factors for persistent symptoms and adverse outcomes: demographic characteristics (age, sex, being a caregiver), smoking, obesity, comorbidities, initial COVID-19 symptoms, the number of symptoms, systemic symptoms (ie, fever, headache, asthenia and skin symptoms), ear-nose-throat symptoms and data from an initial clinical examination.

Statistical analysis

Qualitative variables were described as the number (percentage), and quantitative variables were described as the median (IQR) or tertile values, as appropriate. Univariate analyses used the χ^2 test, the Fisher's test or the Kruskal-Wallis test, as appropriate. Given the hierarchical nature of the data (level 1: the patient; level 2: the GP), we used multilevel logistic models[21] to estimate univariate and multivariate ORs and their 95% CIs.

The distribution of the patient initial characteristics was compared across the three groups (confirmed, no-COVID and uncertain). When the p value was ≤0.15, we used age-adjusted multilevel logistic models to perform post hoc pairwise comparisons for confirmed cases versus no-COVID cases on one hand, and between confirmed cases and uncertain cases on the other.

Next, we compared the prevalence of persistent symptoms in the confirmed versus no-COVID groups. To assess predictive factors for 3-month persistent symptoms and adverse outcomes among the COVID-confirmed cases, we compared the groups with versus without persistent symptoms and with versus without adverse outcomes in univariate analyses. Factors with p<0.15 in the univariable analysis were considered for inclusion in multivariable multilevel logistic analyses after the assessment of confounders and interactions in bivariate models. As 'older age'and 'at least one comorbidity' were highly correlated, we built the following composite variable: 'age>70 and/or at least one comorbidity'. Lastly, in a sensitivity analysis, patients with both anosmia and ageusia but no test results were moved from the 'uncertain COVID' group to the 'confirmed COVID' group, and similar analyses were performed. All tests were two sided, and the threshold for statistical significance was set to p≤0.05. We used the false discovery rate method for post hoc analyses. All analyses were performed with Stata software (V.14.2, StataCorp, College Station, Texas, USA).

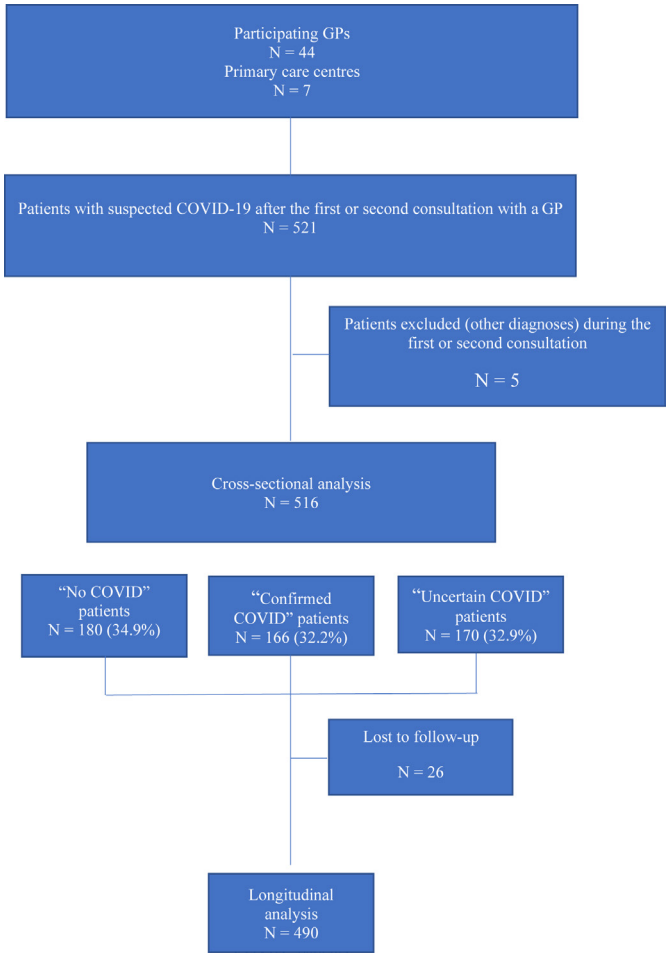

Figure 1 Study flow diagram. GP, general practitioner.

RESULTS

Study population

During the study period, 521 patients were included. Of these, 516 were analysed: 166 (32.2%) were classified as 'confirmed COVID', 180 (34.9%) were classified as 'no-COVID' and 170 (32.9%) were classified as 'uncertain COVID' (figure 1). The characteristics of the groups' test results and disease classifications are summarised in online supplemental table S2.

Characteristics of the population and intergroup comparisons

In the overall population, median (IQR) age was 43 years (33–56), 62.2% were female, 12.5% were caregivers and 40.7% had at least one comorbidity (online supplemental appendix 1). The three groups differed significantly with regard to the following initial characteristics: age, being a caregiver, having been in contact with a positive case, having at least one comorbidity, fever or feeling feverish, having muscle ache, chest pain, dyspnoea, a sore throat, anosmia, ageusia, diarrhoea and the number of systemic symptoms.

Relative to the no-COVID group, confirmed cases were significantly older and were more likely to be caregivers, to have been in contact with a confirmed case of COVID-19 and to have had anosmia or ageusia. A non-significant trend towards an association with a higher number of systemic symptoms was also observed. In contrast, chest pain and sore throat were less frequent in the 'confirmed case' group.

Relative to the uncertain COVID group, confirmed cases were significantly older and were more likely to be caregiver, to have been in contact with a confirmed case of COVID-19, to have had fever or feeling feverish,

Table 1 Comparison of 3-month persistent symptoms between COVID and no-COVID groups (N=346)

	No-COVID n=180	Main analysis				Sensitivity analysis	
		Confirmed COVID n=166	P value*	OR (95% CI)	P value†	OR (95% CI) (n=195 vs 180)	P value†
Any persistent symptom combined (n=177/159//182)	17 (9.6)	25 (15.7)	0.090	1.66 (0.86–3.23)	0.133	1.67 (0.88–3.19)	0.118
Asthenia (n=177/159//182)	8 (4.5)	6 (3.8)	0.733				
Cough (n=177/159//182)	3 (1.7)	4 (2.5)	0.712				
Dyspnoea (n=177/159//182)	8 (4.5)	5 (3.1)	0.514				
Chest pain (n=177/159//182)	3 (1.7)	3 (1.9)	1				
Anosmia (n=177/159//182)	1 (0.6)	7 (4.4)	0.029	8.51 (1.03–70.43)	0.047	8.36 (1.03–67.68)	0.047
Ageusia (n=177/159//182)	3 (1.7)	4 (2.5)	0.712				
Other symptoms (n=177/159//182)	1 (0.6)	7 (4.4)	0.029	7.02 (0.84–58.29)	0.071	7.62 (0.94–61.87)	0.058
Deep vein thrombosis	0 (0)	1 (14.3)					
Alopecia	0 (0)	1 (14.3)					
Myalgia	0 (0)	1 (14.3)					
Palpitations	0 (0)	1 (14.3)					
Pruritus, rash	1 (100)	0 (0)					
Feeling feverish	0 (0)	2 (28.6)					
Memory impairments	0 (0)	1 (14.3)					

Data are quoted as n (%).
*The p values were obtained from a χ^2 test or Fisher's exact test.
†Age-adjusted multilevel logistic regression.

muscle ache, anosmia, ageusia, diarrhoea and more than two systemic symptoms. In contrast, they were less likely to be male.

Three-month persistent symptoms in the 'confirmed COVID' and 'no-COVID' groups

Overall, the percentage of 3-month persistent symptoms was higher in the confirmed COVID group than in the no-COVID group, although the difference was not statistically significant (p=0.090) (table 1). The confirmed COVID group was more likely to have persistent anosmia (OR=8.51; 95% CI 1.03–70.43; p=0047). Similar results were found in the sensitivity analysis (table 1).

Predictive factors for 3-month persistent symptoms and adverse outcomes in confirmed COVID cases

In a univariate analysis, the factors associated with 3-month persistent symptoms were fever or feeling feverish and anosmia (table 2). In a multivariate analysis, fever and anosmia were independently associated with 3-month persistent symptoms. Similar results were found in the sensitivity analysis (OR_{fever}=8.49; 95% CI 1.34–53.83; p=0023 and $OR_{anosmia}$=4.24; 95% CI 0.99–18.23; p=0052).

Among the confirmed cases, we observed 16 (9.8%) COVID-19-related hospital admissions, 3 (1.8%) admissions to an intensive care unit, 13 (37.1%) referrals to an emergency department and no death. In a univariate analysis, patients with 3-month adverse outcomes were older, and more likely to have at least one comorbidity (hypertension, dyslipidaemia, diabetes and cardiovascular disease), fever or feeling feverish and a higher number of systemic symptoms (table 3). A trend was observed for abnormalities in a lung clinical examination. In a multivariate analysis, the composite variable 'age>70 and/or at least one comorbidity', abnormalities in a lung clinical examination and two or more systemic symptoms were independently associated with 3-month adverse outcomes (table 3). Similar results were found in the sensitivity analysis (OR_{fever}=6.72; 95% CI 1.24–36.54; p=0027, $OR_{\geq 2\ systemic\ symptoms}$=44.52; 95% CI 2.67–741.89; p=0008 and $OR_{abnormalities\ in\ a\ lung\ examination}$=17.58; 95% CI 1.80–171.63; p=0.047).

DISCUSSION

Principal findings

We included 516 patients managed by GPs for suspected COVID-19 during the first wave of the disease in France: 32.2% were classified as 'confirmed COVID' cases, 34.9% were classified as 'no-COVID' cases and 32.9% were classified as 'uncertain COVID' cases. The clinical course was mainly benign, although the hospital admission rate (with no death) was 9.8% in the 'confirmed COVID' group. In the latter group, the variable 'age>70 and/or at least one comorbidity', abnormalities in a lung examination and two or more systemic symptoms were independently associated with 3-month hospital admission and referral to an emergency department. Moreover, 'confirmed COVID'

Table 2 Multilevel univariate and multivariate analyses of factors associated with 3-month persistent symptoms among patients with confirmed COVID-19 (N=159)

	3-month persistent symptoms			Univariate analysis		Multivariate analysis (final model)	
	No, n=134 (84.3%)	Yes, n=25 (15.7%)	P value*	OR (95% CI)	P value†	OR (95% CI)	P value†
Age (years)	48 (39–58)	51 (41–59)	0.509				
Male sex	49 (36.6)	6 (24.0)	0.225				
Caregivers (n=120/22)	24 (20.0)	5 (22.7)	0.776				
Smoking (n=38/10)	14 (36.8)	2 (20.0)	0.460				
At least one comorbidity (n=133/25)	60 (45.1)	13 (52.0)	0.526				
Dyslipidaemia (n=133/25)	5 (3.8)	2 (8.0)	0.306				
Obesity (n=47/9)	18 (38.3)	5 (55.6)	0.464				
Hypertension (n=133/25)	23 (17.3)	3 (12.0)	0.769				
Diabetes (n=133/25)	6 (4.5)	1 (4.0)	1				
Cardiovascular disease (n=133/25)	11 (8.3)	3 (12.0)	0.466				
Asthma (n=133/25)	11 (8.3)	4 (16.0)	0.261				
Age >70 and/or presence of at least one comorbidity (n=133/25)	61 (45.9)	13 (52.0)	0.573				
Symptoms at the initial consultation							
Fever or feeling feverish (n=122/22)	59 (48.4)	17 (77.3)	0.012	3.63 (1.26–10.46)	0.017	6.93 (1.62–29.53)	0.009
Asthenia (n=51/7)	42 (82.4)	7 (100)	0.581				
Muscle ache (n=99/19)	68 (68.7)	16 (84.2)	0.171				
Headache (n=88/16)	49 (55.7)	10 (62.5)	0.613				
Rhinorrhoea (n=86/17)	42 (48.8)	11 (64.7)	0.232				
Cough (n=121/23)	93 (76.9)	21 (91.3)	0.163				
Expectorations (n=62/15)	15 (24.2)	3 (20.0)	1				
Chest pain (n=80/17)	15 (18.8)	4 (23.5)	0.737				
Dyspnoea at rest and/or on exertion (n=96/16)	29 (30.2)	5 (31.3)	1				
Sore throat (n=82/16)	36 (43.9)	6 (37.5)	0.636				
Anosmia (n=81/15)	32 (39.5)	10 (66.7)	0.051	3.06 (0.96–9.797)	0.059	4.79 (1.30–17.66)	0.019
Ageusia (n=73/17)	30 (41.1)	11 (64.7)	0.078	2.63 (0.88–7.88)	0.085		
Nausea and/or vomiting (n=77/17)	12 (15.6)	1 (5.9)	0.451				
Diarrhoea (n=86/18)	25 (29.1)	5 (27.8)	0.912				
Abdominal pain (n=31/8)	6 (19.4)	0 (0)	0.313				
Number of symptoms (tertile; n=132/25)			0.108		0.130		
≤4	72 (54.5)	8 (32.0)		1 (ref)			
5	21 (15.9)	6 (24.0)		2.57 (0.80–8.24)			
>5	39 (29.6)	11 (44.0)		2.54 (0.94–6.84)			
Number of systemic symptoms (tertile; n=132/25)			0.355				
≤1	45 (34.1)	7 (28.0)					
2–3	70 (53.0)	12 (48.0)					
>3	17 (12.9)	6 (24.0)					
Number of ENT symptoms (tertile; n=132/25)			0.189				
0	47 (35.6)	6 (24.0)					
1	46 (34.8)	7 (28.0)					
>1	39 (29.6)	12 (48.0)					

Continued

Table 2 Continued

	3-month persistent symptoms			Univariate analysis		Multivariate analysis (final model)	
	No, n=134 (84.3%)	Yes, n=25 (15.7%)	P value*	OR (95% CI)	P value†	OR (95% CI)	P value†
Clinical examination							
Temperature >38°C			0.375				
No	77 (57.5)	11 (44.0)					
Yes	14 (10.4)	4 (16.0)					
Not reported or missing	43 (32.1)	10 (40.0)					
Respiratory rate (per min) (n=27/8)	20 (18–20)	19 (15–20)	0.434				
SaO_2 (%) (n=80/12)	98 (97–99)	98 (97–98.5)	0.624				
Abnormalities in a lung examination			0.261				
No	74 (55.2)	10 (40.0)					
Yes	14 (10.5)	2 (8.0)					
Not reported or missing	46 (34.3)	13 (52.0)					

Data are quoted as n (%) for qualitative variables and median [IQR] for quantitative variables.
*The p values were obtained from a χ^2 test or the Fisher's exact test for qualitative variables, and from the Mann-Whitney test for quantitative variables.
†Multilevel logistic regression; the multivariate model included the following variables: fever or feeling feverish and anosmia.
ENT, ear, nose, throat; SaO_2, arterial oxygen saturation.

patients tended to have more persistent symptoms at 3 months—mainly anosmia and 'other persistent symptoms'. Fever or feeling feverish and anosmia were independently associated with the persistence of symptoms.

Strengths and weaknesses of the study

This is one of the few studies to have included solely patients consulting in general practice; most longitudinal studies of patients with COVID-19 assessed hospital-based or mixed cohorts. Moreover, our assessment of a prospective multicentre cohort recruited at different primary care health centres means that our results can be more readily extrapolated to the local or regional level. Another study strength was our comparison of 'confirmed COVID', 'no-COVID' and 'uncertain COVID' groups; this provided a more accurate comparison of the initial and subsequent signs and symptoms of COVID-19. The 'no-COVID' group was particularly relevant for comparing the prevalence of persistent symptoms because it probably comprised patients with other viral diseases.

However, our study had some limitations. Selection bias might have been present because the RT-PCR test was only initially recommended for patients with severity criteria and/or with comorbidities and for healthcare professionals. This may explain some of the demographic characteristics of confirmed cases. However, this bias was limited by the prescription of serology tests a posteriori to patients with compatible symptoms and who had not had an RT-PCR test and to patients with a negative RT-PCR test. We did not include under-18 patients and institutionalised patients. The study was limited to the greater Paris region and so might not be representative of the French population as a whole. Moreover, the groups' size might have led to a lack of statistical power. Given the small number of patients with persistent symptoms, the corresponding results should be interpreted with caution (especially the ORs with very broad CIs). The methods for determining the presence or absence of persistent symptoms were left to the GP's discretion; the use of particular questionnaires or scales was not imposed on them. This lack of standardisation might have influenced the estimated prevalence of persistent symptoms. However, this unconstrained type of assessment was similar to that used in the GPs' routine clinical medical practice. Lastly, COVID-19-related hospital admissions were recorded; it would have been useful to collect data on the symptom burden associated with all-cause hospital admissions.

Comparison with other studies

The demographic characteristics of our patients with COVID-19 consulting in general practice were similar to those in the literature, particularly with regard to the mean age (43 in our study and in Yordanov *et al*'s study[22]), the proportion of caregivers[23 24] and the most prevalent comorbidities (hypertension and diabetes).[20] Several studies of ambulatory patients have shown that systemic symptoms (including asthenia, fever, cough, myalgia and headaches) were frequent.[4 25–27] Anosmia and ageusia were also frequent and appeared later in the course of disease. Some experts consider that the anosmia-ageusia combination is specific for COVID-19.[12] Digestive tract symptoms were less frequent.[4 6 28–30] Our patients also varied with regard to the signs in the GPs' clinical examination (including abnormalities in a lung examination), as found in systematic reviews.[12 31] In line with our results, most studies of outpatients have found that the course of the disease is benign and that hospital admission is not required.[17 22 23] As found in the present research,

Table 3 Multilevel univariate and multivariate analyses of factors associated with 3-month composite criterion among patients with confirmed COVID-19 (N=165)

	No composite criterion, n=147 (89.1%)	Composite criterion, n=18 (10.9%)	P value*	Univariate analysis		Multivariate analysis (final model)	
				OR (95% CI)	P value†	OR (95% CI)	P value†
Age (years)	47 [37–58]	62.5 [50–78]	<0.001	1.08 (1.03–1.13)	0.003		
Male sex	49 (33.3)	9 (50.0)	0.162				
Caregivers (n=133/15)	29 (21.8)	1 (6.7)	0.307				
Smoking (n=46/6)	14 (30.4)	2 (33.3)	1				
At least one comorbidity (n=145/18)	63 (43.5)	13 (72.2)	0.021	4.04 (1.16–14.00)	0.028		
Dyslipidaemia (n=145/18)	4 (2.8)	3 (16.7)	0.030	8.82 (1.28–60.64)	0.027		
Obesity (n=53/5)	22 (41.5)	1 (20.0)	0.639				
Hypertension (n=145/18)	21 (14.5)	7 (38.9)	0.017	3.71 (1.19–11.53)	0.023		
Diabetes (n=145/18)	4 (2.8)	3 (16.7)	0.030	8.23 (1.32–51.34)	0.024		
Cardiovascular disease (n=145/18)	10 (6.9)	6 (33.3)	0.003	7.51 (1.95–28.93)	0.003		
Asthma (n=145/18)	13 (9.0)	2 (11.1)	0.673				
Age >70 and/or presence of at least one comorbidity (n=145/18)	64 (44.1)	13 (72.2)	0.024	3.92 (1.13–13.60)	0.032	6.53 (1.13–37.84)	0.036
Symptoms at the initial consultation							
Fever or feeling feverish (n=133/17)	66 (49.6)	14 (82.4)	0.011	4.68 (1.24–17.79)	0.023		
Asthenia (n=48/12)	37 (77.1)	12 (100)	0.099	–	–	–	–
Muscle ache (n=111/11)	75 (67.6)	10 (90.9)	0.170				
Headache (n=99/8)	55 (55.6)	4 (50.0)	1				
Rhinorrhoea (n=99/9)	51 (51.5)	4 (44.4)	0.740				
Cough (n=133/15)	108 (81.2)	10 (66.7)	0.188				
Expectorations (n=74/6)	15 (20.3)	3 (50.0)	0.124	4.73 (0.48–47.01)	0.184		
Chest pain (n=92/10)	18 (19.6)	1 (10.0)	0.683				
Dyspnoea at rest and/or on exertion (n=103/13)	30 (29.1)	5 (38.5)	0.528				
Sore throat (n=93/9)	41 (44.1)	3 (33.3)	0.728				
Anosmia (n=90/10)	39 (43.3)	3 (30.0)	0.513				
Ageusia (n=86/8)	39 (45.4)	3 (37.5)	0.728				
Nausea and/or vomiting (n=90/9)	13 (14.4)	1 (11.1)	1				
Diarrhoea (n=100/9)	28 (28.0)	3 (33.3)	0.712				
Abdominal pain (n=39/5)	6 (15.4)	1 (20.0)	1				

Continued

Table 3 Continued

	No composite criterion, n=147 (89.1%)	Composite criterion, n=18 (10.9%)	P value*	Univariate analysis		Multivariate analysis (final model)	
				OR (95% CI)	P value†	OR (95% CI)	P value†
Number of symptoms (tertile; n=145/17)			0.379				
≤4	76 (52.4)	7 (41.2)					
5	26 (17.9)	2 (11.8)					
>5	43 (26.7)	8 (47.0)					
Number of systemic symptoms (median; n=145/17)			0.009		0.022		0.011
≤1	55 (37.9)	1 (5.9)		1 (ref)		1 (ref)	
≥2	90 (62.1)	16 (94.1)		13.82 (1.45–131.88)		38.61 (2.30–647.40)	
Number of ENT symptoms (tertile; n=145/17)			0.378				
0	48 (33.1)	7 (41.2)					
1	47 (32.4)	7 (41.2)					
>1	50 (34.5)	3 (17.6)					
Clinical examination							
Temperature >38°C			0.051		0.082		
No	84 (57.2)	7 (38.9)		1 (ref)			
Yes	13 (8.8)	5 (27.8)		5.16 (1.20–22.30)			
Not reported or missing	50 (34.0)	6 (33.3)		1.27 (0.36–4.49)			
Respiratory rate (per min) (n=32/5)	18.5 [16–20]	21 [20–24]	0.058	1.14 (0.97–1.34)	0.103		
SaO_2 (%) (n=85/10)	98 [97–99]	94.5 [90–98]	0.002	0.28 (0.09–0.91)	0.034		
Abnormalities in a lung examination			0.126		0.179		0.057
No	82 (55.8)	7 (38.9)		1 (ref)		1 (ref)	
Yes	12 (8.2)	4 (22.2)		4.33 (0.92–20.37)		15.39 (1.61–146.77)	
Not reported or missing	53 (36.0)	7 (38.9)		1.55 (0.47–5.17)		2.63 (0.52–13.34)	

Data are quoted as n (%) for qualitative variables and median [IQR] for quantitative variables.
*The p values were obtained from a χ^2 test or Fisher's exact test for qualitative variables, and from the Mann-Whitney test for quantitative variables.
†Multilevel logistic regression; the multivariate model included the following variables: age >70 and/or presence of at least one comorbidity, number of systemic symptoms and abnormalities in a lung examination.
ENT, ear, nose, throat; SaO_2, arterial oxygen saturation.

literature data have shown that a higher frequency of negative outcomes (hospital admission and death) is associated with older age[32 33] and with comorbidities like cardiovascular disease and diabetes.[22 33 34] In contrast to another study, we did not find an association with male sex.[35] However, no other studies have found that more than two systemic symptoms at the initial GP visit and abnormalities in a lung examination are predictive of an adverse outcome. These present findings and the literature data[12 31] highlight the need for a clinical consultation with the GP.

It has been widely reported that patients can experience persistent symptoms more than 4 weeks after an episode of COVID-19.[36] Here, we observed a non-significant trend towards a greater prevalence of persistent symptoms at 3 months in the 'confirmed COVID' group (15.7%) versus the no-COVID group (9.6%). This finding is in line with the results of a UK study in which 13.7% of outpatients had symptoms that persisted for at least 12 weeks.[36] However, the association remained significant in our 'confirmed COVID' group for anosmia and 'other symptoms' (ie, deep vein thrombosis, alopecia, palpitations, feeling feverish and memory impairments), as also reported elsewhere.[37] A recent large cohort study suggested that self-reported infection was positively associated with persistent physical symptoms, whereas a positive serology test result for SARS-CoV-2 was positively associated only with persistent anosmia.[13] Furthermore, it appears that one of the factors determining the presence of persistent symptoms in our patients with COVID-19 was the presence of fever during the initial GP visit. This association with fever has only previously been found in one study of elderly people[38] but not in other studies.[39]

In our study, a comparison at 3 months showed that some persistent symptoms (asthenia, cough, chest pain and dyspnoea) were not significantly more frequent in the 'confirmed COVID' group—suggesting they were not specific for 'long COVID-19'. Asthenia and dyspnoea were the two most common persistent symptoms in hospitalised and non-hospitalised patients.[40] However, we observed asthenia and dyspnoea, respectively, in only around 4% and 3% of our 'confirmed COVID' patients, and with much the same frequency as in no-COVID patients (4.5% and 4.5%, respectively). Outpatient studies with a control group found the presence of persistent symptoms up to 10[41] and 12 months[42] after mild COVID-19, with miscellaneous symptoms: asthenia, headaches, smell and taste disorders, dyspnoea, memory disorders, insomnia and difficulty concentrating.[41 42] The French health authorities also included neurological, cardiothoracic and sensory disorders in the list of persistent symptoms.[43]

The results of these 'long COVID-19' studies are relatively disparate and appear to show that this entity is non-specific because of the multisymptomatic, fluctuating nature of the clinical manifestations.[43]

Implications for clinicians and policymakers

It is important to provide GPs with primary care-specific data that enable them to optimise patient management. GPs have an essential role in combating the pandemic[44] and diagnose most patients with COVID-19.[2] Identifying prognostic factors and examining patients for clinical abnormalities could help detect patients at risk, set up follow-up procedures and anticipate possible worsening.[2 45] These strategies might be needed in France, with a view to enabling primary care to withstand future health emergencies and pandemics, as has been mentioned in Australia, New Zealand, Canada, the Netherlands, the UK and the USA.[46] The trend towards more frequent persistent symptoms in patients with COVID-19 (more specifically anosmia and 'other symptoms') suggests that follow-up by the GP should take account of the disease's impact on quality of life, overall health and life context via a patient-centred approach.[47]

Unanswered questions and future research

Our findings (notably concerning persistent symptoms) need to be confirmed in the longer term and in other patient populations (eg, institutionalised people, children and adolescents). Our study was partly based on electronic medical records and showed that primary care can provide important public health data. This work could be expanded with patient surveys and GP interviews, so as to combine real-time data on patients' symptoms and adverse outcomes with patient responses to public health messaging and information on the GPs' adaptive coping mechanisms.[46]

CONCLUSIONS

Cases of COVID-19 seen in primary care have an essentially benign course. However, age >70 and/or at least one comorbidity, abnormalities in a lung examination and a higher number of systemic symptoms were associated with hospital admission and referral to an emergency department. Our results reinforce the need for a face-to-face medical consultation by the GP to identify patients at risk of severe disease. Almost one in six patients with COVID-19 had persistent symptoms at 3 months—emphasising the need for an overall patient-centred approach. This frequency of persistent symptoms tended to be higher in patients with COVID-19 than in no-COVID cases. Anosmia and a group of rarer symptoms were more prevalent in the 'confirmed COVID' group. Asthenia, chest pain, cough and dyspnoea were also present in the other groups and might not be specific for a possible 'long COVID-19'. Our findings in primary care need to be confirmed in prospective studies with a longer follow-up period.

Author affiliations
[1]Univ Paris Est Creteil, Department of General Practice, F-94010 Creteil, France
[2]Maison de Sante Pluriprofessionnelle Universitaire (MSPU) Fontainebleau, F-77300 Fontainebleau, France

[3]Maison de Sante Pluriprofessionnelle Universitaire (MSPU) Torcy, F-77200 Torcy, France
[4]Univ Paris Est Creteil, INSERM, IMRB, F-94010 Creteil, France
[5]AP-HP, Hopital Henri-Mondor, Clinical Research Unit (URC Mondor), F-94010 Creteil, France
[6]Maison de Sante Pluriprofessionnelle Universitaire (MSPU) Coulommiers, F-77120 Coulommiers, France
[7]Maison de Sante Pluriprofessionnelle Universitaire (MSPU) Nemours, F-77140 Nemours, France
[8]AP-HP, Hopital Henri-Mondor, Public Health Department, F-94010 Creteil, France
[9]Maison de Sante Pluriprofessionnelle Universitaire (MSPU) Saint-Maur-des-Fosses, F-94100 Saint-Maur-des-Fosses, France

Acknowledgements We thank Camille Hug and Faïka Bacar for help with data collection and interpretation. We thank all the study participants and the participating health centres. Lastly, we thank David Fraser, PhD (Biotech Communication, Ploudalmézeau, France) for copy-editing assistance.

Contributors Conceptualisation: EF. Methodology: EF and SB-G. Data analysis: EB. Data interpretation: EF, SB-G and EB. Drafting and revision of the manuscript: T-TP, WM, EF and SB-G. All authors have read and agreed to the published version of the manuscript. EF is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study database was registered with the French National Data Protection Commission (reference: 2211627 v0). The study protocol was approved by an independent ethics committee (Comité de Protection des Personnes Est IV (Strasbourg, France); reference: IDRCB 2020-A01693-36).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are avaiable upon reasonable request.

ORCID iD
Tan-Trung Phan http://orcid.org/0000-0001-9990-7398

REFERENCES

1 Saint-Lary O, Gautier S, Le Breton J, *et al*. How GPs adapted their practices and organisations at the beginning of COVID-19 outbreak: a French national observational survey. *BMJ Open* 2020;10:e042119.
2 Greenhalgh T, Koh GCH, Car J. Covid-19: a remote assessment in primary care. *BMJ* 2020:m1182.
3 Argenziano MG, Bruce SL, Slater CL, *et al*. Characterization and clinical course of 1000 patients with Coronavirus disease 2019 in New York: retrospective case series. *BMJ* 2020;369:m1996.
4 Docherty AB, Harrison EM, Green CA, *et al*. Features of 20 133 UK patients in hospital with COVID-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ* 2020;369:m1985.
5 Tostmann A, Bradley J, Bousema T, *et al*. Strong associations and moderate predictive value of early symptoms for SARS-CoV-2 test positivity among Healthcare workers. *Euro Surveill* 2020;25:2000508.
6 Zhang J-J, Dong X, Cao Y-Y, *et al*. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy* 2020;75:1730–41.
7 Lechien JR, Chiesa-Estomba CM, De Siati DR, *et al*. Olfactory and Gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the Coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020;277:2251–61.
8 Huang C, Huang L, Wang Y, *et al*. 6-Month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021;397:220–32.
9 Lechien JR, Chiesa-Estomba CM, Place S, *et al*. Clinical and Epidemiological characteristics of 1420 European patients with mild-to-moderate Coronavirus disease 2019. *J Intern Med* 2020;288:335–44.
10 Villerabel C, Makinson A, Jaussent A, *et al*. Dépistage de la COVID-19: Valeurs Diagnostiques D'Une Anosmie Rapportée Ou Objectivée par UN test Clinique. *Médecine et Maladies Infectieuses* 2020;50:S78.
11 Zayet S, Klopfenstein T, Royer P, *et al*. Sensibilité, Spécificité et Valeurs Prédictives des Signes Fonctionnels de L'Infection par SARS-Cov-2. *Med Maladies Infect* 2020;50:S77.
12 Struyf T, Deeks JJ, Dinnes J, *et al*. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. *Cochrane Database Syst Rev* 2021;2:CD013665.
13 Matta J, Wiernik E, Robineau O, *et al*. Association of self-reported COVID-19 infection and SARS-CoV-2 Serology test results with persistent physical symptoms among French adults during the COVID-19 pandemic. *JAMA Intern Med* 2022;182:19.
14 Nehme M, Braillard O, Chappuis F, *et al*. Prevalence of symptoms more than seven months after diagnosis of symptomatic COVID-19 in an outpatient setting. *Ann Intern Med* 2021;174:1252–60.
15 Cirulli ET, Schiabor Barrett KM, Riffle S, *et al*. Long-term COVID-19 symptoms in a large Unselected population. *medRxiv* [Preprint] 2020.
16 French High Council of Public Health. Haut Conseil de la Santé Publique. 2020. Available: https://solidarites-sante.gouv.fr/IMG/pdf/hcsp_sars-cov2-priorisationtestsdiagnostiques-2020-03-11-2.pdf
17 French High Autority for Health. Réponses rapides dans le cadre de la COVID-19. Prise en charge de premier recours des patients atteints de Covid-19 [Haute Autorité de Santé]. 2020. Available: https://www.has-sante.fr/upload/docs/application/pdf/2022-02/reco453_rr_covid_19_premier_recours_20220216_mel.pdf
18 French High Autority for Health. Premières indications pour les tests sérologiques du COVID-19 [Haute Autorité de Santé]. 2020. Available: https://www.has-sante.fr/jcms/p_3182370/fr/premieres-indications-pour-les-tests-serologiques-du-covid-19
19 French Society of Radiology. Epidémie de COVID-19: POINT SUR L'IMAGERIE [Société Française de Radiologie]. 2020. Available: https://ebulletin.radiologie.fr/actualites-covid-19/epidemie-covid-19-point-limagerie
20 French High Autority for Health. Réponses rapides dans le cadre de la COVID-19 - Place du scanner thoracique [Haute Autorité de Santé]. 2020. Available: https://www.has-sante.fr/upload/docs/application/pdf/2020-04/reponse_rapide_codid-19_indication_tdm_mel2.pdf
21 Hox JJ, Moerbeek M, van de Schoot R. *Multilevel Analysis, techniques and applications, 3rd ed*. New York: Routledge, 2018.
22 Yordanov Y, Dinh A, Bleibtreu A, *et al*. Clinical characteristics and factors associated with hospital admission or death in 43 103 adult outpatients with Coronavirus disease 2019 managed with the Covidom Telesurveillance solution: a prospective cohort study. *Clin Microbiol Infect* 2021;27:1158–66.
23 Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA* 2020;323:1239–42.
24 Riccardo F, Ajelli M, Andrianou XD, *et al*. Epidemiological characteristics of COVID-19 cases and estimates of the reproductive numbers 1 month into the epidemic, Italy, 28 January to 31 March 2020. *Euro Surveill* 2020;25:2000790.
25 Lapostolle F, Schneider E, Vianu I, *et al*. Clinical features of 1487 COVID-19 patients with outpatient management in the greater Paris: the COVID-call study. *Intern Emerg Med* 2020;15:813–7.
26 Khan M, Khan H, Khan S, *et al*. Epidemiological and clinical characteristics of Coronavirus disease (COVID-19) cases at a screening clinic during the early outbreak period: a single-centre study. *J Med Microbiol* 2020;69:1114–23.
27 Ayaz CM, Dizman GT, Metan G, *et al*. Out-patient management of patients with COVID-19 on home isolation. *Infez Med* 2020;28:351–6.
28 Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel Coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.

29 Guan W-J, Ni Z-Y, Hu Y, *et al*. Clinical characteristics of Coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20.
30 Cholankeril G, Podboy A, Aivaliotis VI, *et al*. High prevalence of concurrent gastrointestinal manifestations in patients with severe acute respiratory syndrome Coronavirus 2: early experience from California. *Gastroenterology* 2020;159:775–7.
31 Izcovich A, Ragusa MA, Tortosa F, *et al*. Correction: prognostic factors for severity and mortality in patients infected with COVID-19: a systematic review. *PLoS One* 2022;17:e0269291.
32 Dres M, Hajage D, Lebbah S, *et al*. Characteristics, management, and prognosis of elderly patients with COVID-19 admitted in the ICU during the first wave: Insights from the COVID-ICU study: prognosis of COVID-19 elderly critically ill patients in the ICU. *Ann Intensive Care* 2021;11:77.
33 Tenreiro P, Ramalho A, Santos P. COVID-19 patients followed in Portuguese primary care: a retrospective cohort study based on the National case series. *Fam Pract* 2022;39:52–8.
34 Semenzato L, Botton J, Drouin J, *et al*. Maladies chroniques, états de santé et risque d'hospitalisation et de décès hospitalier pour COVID-19: analyse comparative de données des deux vagues épidémiques de 2020 en France à partir d'une cohorte de 67 millions de personnes. 2021. Available: https://www.epi-phare.fr/app/uploads/2021/07/epi-phare_risques_hospitalisations_deces_covid19_20210721.pdf
35 Peckham H, de Gruijter NM, Raine C, *et al*. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat Commun* 2020;11:6317.
36 Nalbandian A, Sehgal K, Gupta A, *et al*. Post-acute COVID-19 syndrome. *Nat Med* 2021;27:601–15.
37 French High Council of Public Health. Avis relatif aux symptômes cliniques persistants au décours d'un COVID-19 [Haut Conseil de la Santé Publique]. 2021. Available: https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=1037
38 Sudre CH, Murray B, Varsavsky T, *et al*. Attributes and predictors of long-COVID. *Nat Med* 2021;27:626–31.
39 Augustin M, Schommers P, Stecher M, *et al*. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. *Lancet Reg Health Eur* 2021;6:100122.
40 Rajan S, Khunti K, Alwan N, *et al*. In the wake of the pandemic: preparing for long COVID. 2021. Available: https://apps.who.int/iris/bitstream/handle/10665/339629/Policy-brief-39-1997-8073-eng.pdf
41 Desgranges F, Tadini E, Munting A, *et al*. Post-COVID-19 syndrome in outpatients: a cohort study. *J Gen Intern Med* 2022;37:1943–52.
42 Nehme M, Braillard O, Chappuis F, *et al*. One-year persistent symptoms and functional impairment in SARS-CoV-2 positive and negative individuals. *J Intern Med* 2022;292:103–15.
43 French High Autority for Health. Symptômes prolongés suite à une Covid-19 de l'adulte - Diagnostic et prise en charge [Haute Autorité de Santé]. 2021. Available: https://www.has-sante.fr/jcms/p_3237041/fr/symptomes-prolonges-suite-a-une-covid-19-de-l-adulte-diagnostic-et-prise-en-charge
44 Sarti TD, Lazarini WS, Fontenelle LF, *et al*. What is the role of primary health care in the COVID-19 pandemic. *Epidemiol Serv Saude* 2020;29.
45 Prado N de B, Biscarde D, Pinto Junior EP, *et al*. Primary care-based health surveillance actions in response to the COVID-19 pandemic: contributions to the debate Cien Saude Colet. *Cien Saude Colet* 2021;26:2843–57.
46 Huston P, Campbell J, Russell G, *et al*. COVID-19 and primary care in six countries. *BJGP Open* 2020;4:bjgpopen20X101128.
47 Stewart M. *Patient-Centred Medicine: Transforming the Clinical Method, 3rd ed*. London: CRC Press, 2019: 442.