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Risk factors of long term symptoms and outcomes among patients discharged after covid-19: prospective, multicentre observational study

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ABSTRACT

OBJECTIVE To investigate risk factors and subphenotypes associated with long term symptoms and outcomes after hospital admission for covid-19.

DESIGN Prospective, multicentre observational study.

SETTING 93 hospitals in France.

PARTICIPANTS Data from 2187 adults admitted to hospital with covid-19 in France between 1 February 2020 and 30 June 2021.

MAIN OUTCOME MEASURES Primary endpoint was the total number of persistent symptoms at six months after hospital admission that were not present before admission. Outcomes examined at six months were persistent symptoms, Hospital Anxiety and Depression Scale, six minute walk test distances, 36-Item Short Form Health Survey scores, and ability to resume previous professional activities and self-care. Secondary endpoints included vital status at six months, and results of standardised quality-of-life scores. Additionally, an unsupervised consensus clustering algorithm was used to identify subphenotypes based on the severity of hospital course received by patients.

RESULTS 1109 (50.7%) of 2187 participants had at least one persistent symptom. Factors associated with an increased number of persistent symptoms were in-hospital supplemental oxygen (odds ratio 1.12, 95% confidence interval 1 to 1.24), no intensive care unit admission (1.15, 1.01 to 1.32), female sex (1.33, 1.22 to 1.45), gastrointestinal haemorrhage (1.51, 1.02 to 2.23), a thromboembolic event (1.66, 1.17 to 2.34), and congestive heart failure (1.76, 1.27 to 2.43). Three subphenotypes were identified: including patients with the least severe hospital course (based on ventilatory support requirements). Although Hospital Anxiety and Depression Scale scores were within normal values for all groups, patients of intermediate severity and more comorbidities had a higher median Hospital Anxiety and Depression Scale score than did the other subphenotypes. Patients in the subphenotype with most severe hospital course had worse short form-36 scores and were less able to resume their professional activity or care for themselves as before compared with other subphenotypes.

CONCLUSIONS Persistent symptoms after hospital admission were frequent, regardless of acute covid-19 severity. However, patients in more severe subphenotypes had a significantly worse functional status and were less likely to resume their professional activity or able to take care of themselves as before.

TRIAL REGISTRATION NCT04262921.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

⇒ Long term symptoms have been well documented after admission to hospital for covid-19

WHAT THIS STUDY ADDS

⇒ Persistent symptoms were frequent, regardless of acute covid-19 severity

⇒ Risk factors associated with persistent symptoms were identified, as were clusters associated with decreased patients' quality of life or their ability to resume professional activities or take care of themselves

HOW MIGHT THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Future research should aim to identify the specific contribution of SARS-CoV-2 infection over previous comorbidities and critical illness on symptoms of depression and functional impairment

Introduction

More than 178 million cases of covid-19 have been reported worldwide. Persistent fatigue, respiratory symptoms, such as dyspnoea or cough, cognitive decline, or depression are frequently reported after admission to hospital with covid-19 .[1–3] The presence of persistent symptoms has been referred to as "post-covid syndrome" or "long covid," exposing the healthcare system and many patients to a wave of chronic symptoms and disease.[4–6] Understanding risk factors and identifying individuals who are most likely to experience post-covid syndrome is key to the prevention of or treatment of long term consequences of covid-19.[7 8] Identification of patients at risk is critical for improved targeting of patients recovering from covid-19, for both follow-up and treatment.

In this study, we aimed to identify potential risk factors associated with long term symptoms and sequelae in patients admitted to hospital with covid-19 and in those who were discharged. We applied an unsupervised, multivariate clustering algorithm to identify covid-19 subphenotypes and explored their association with long term symptoms

and outcomes. For the visual abstract of this paper, see figure 1.

Methods

Study design

Patients in hospital with a laboratory confirmed SARS-CoV-2 infection were enrolled in a prospective observational study in France (French Covid-19 cohort, clinical trial number NCT04262921). Our study focused on patients discharged from hospital who underwent a follow-up visit at six months after admission.

The protocol was approved by the institutional review board CPP-Ile-de-France VI (ID RCB: 2020-A00256-33). Individual informed consent from patients was obtained before inclusion. All patients included in our final study cohort had a six month follow-up visit after hospital admission, including in-person visits with a physician at six months after admission. We excluded patients lost to follow-up or who died before the six month follow-up from the analysis.

Data collection

We collected the data from the French modified version of the open access case report form of the Clinical Characterisation Protocol for Severe Emerging Infections of International Severe Acute Respiratory and Emerging Infection Consortium.

We identified adults (≥18 years old) using daily listings of positive results of real time, reverse transcriptase polymerase chain reaction assay for SARS-CoV-2 from nasal, pharyngeal, or lower respiratory tract aspirate samples. We examined supportive care received (ie, oxygen supplementation, non-invasive mechanical ventilation, and invasive mechanical ventilation) and the occurrence of complications during hospital stay (ie, viral pneumonitis, bacterial pneumonia, acute respiratory distress syndrome, pneumothorax, pleural effusion, cryptogenic organising pneumonia, bronchiolitis, meningitis or encephalitis, seizure, stroke or cerebrovascular accident, congestive heart failure, endocarditis, myocarditis, pericarditis, cardiac arrhythmia, and cardiac ischaemia).

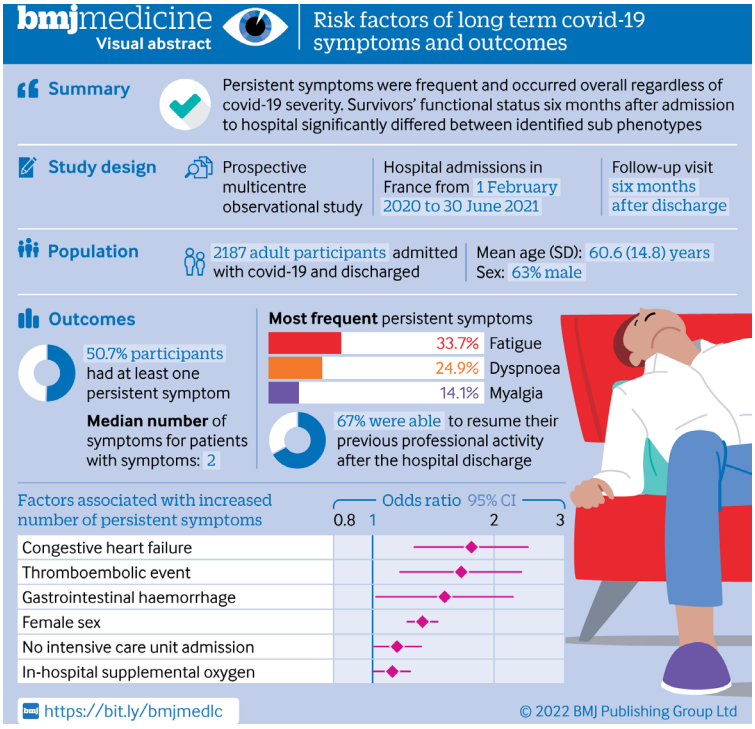

Figure 1 | Visual abstract. SD=standard deviation.

Outcomes

The primary endpoint was the total number of persistent symptoms that were not present before admission to hospital at six months after admission. A checklist of symptoms was used to evaluate if a patient was experiencing new symptoms at follow-up, and the most common symptoms in the study cohort were included in the analysis. These symptoms included cough, shortness of breath, ear, nose, and throat symptoms, myalgia, arthralgia, fatigue, headache, anosmia, and ageusia. Secondary endpoints were vital status at six months after admission to hospital and results of standardised quality-of-life scores including the Hospital Anxiety and Depression Scale, 36-Item Short Form Health Survey, and Six-Minute Walk Test.

Statistical analysis

We described continuous variables using mean (standard deviation) or median (interquartile range) as appropriate. Categorical variables were described using count (percentage). Comparisons were done using ANOVA, Kruskal-Wallis, or χ^2 tests as appropriate. Factors associated with the number of persisting symptoms at six months after hospital admission were identified using a multivariate Poisson regression model.

Using an unsupervised consensus clustering approach (R package ConsensusClusterPlus version 1.54.0), we used the following variables to define subphenotypes: demographic information (age, sex), comorbidities (hypertension, diabetes, asthma, cancer, immunodeficiency, cardiac disease, prescription of renin-angiotensin-aldosterone system inhibitors), complications (viral pneumonitis, bacterial pneumonia, acute respiratory distress syndrome, pneumothorax, pleural effusion, cryptogenic organising pneumonia, bronchiolitis, meningitis, seizure, cerebrovascular accident, cardiac arrhythmia, myocarditis or pericarditis, endocarditis, cardiac ischaemia, cardiac arrest, bacteraemia, coagulation disorder, a thromboembolic event, anaemia, acute kidney injury or failure, gastrointestinal haemorrhage, pancreatitis, liver dysfunction, hyperglycaemic, and hypoglycaemia), and supportive treatments (intensive care unit admission, oxygen therapy, and invasive and non-invasive mechanical ventilation).

Table 1 | Characteristics of patients in study population, and comorbidities, complications, and interventions in each subphenotype. Subphenotypes are based on the severity of hospital course received by study participants; subphenotype A received the least severe, subphenotype C received the most severe.

Characteristic	Subphenotype A (n=1284)	Subphenotype B (n=593)	Subphenotype C (n=310)	Overall (n=2187)
Age				
Mean (standard deviation)	56.7 (15.3)	69.1 (11.4)	60.3 (11.8)	60.6 (14.8)
Median (interquartile range)	57.0 (47.0-68.0)	70.0 (62.0-77.0)	61.0 (53.0-69.0)	62.0 (51.0-71.0)
Missing (No (%))	2 (0.2)	0	0	2 (0.1)
Sex (No (%))				
Female	528 (41.1)	211 (35.6)	79 (25.5)	818 (37.4)
Male	755 (58.8)	382 (64.4)	231 (74.5)	1368 (62.6)
Missing	1 (0.1)	0	0	1 (0.0)
Ethnic origin (No (%))				
Other	162 (12.6)	59 (9.9)	49 (15.8)	288 (13.2)
Black	88 (6.9)	59 (9.9)	27 (8.7)	174 (8.0)
White	593 (46.2)	313 (52.8)	126 (40.6)	1032 (47.2)
Missing	441 (34.3)	144 (24.3)	108 (34.8)	693 (31.7)
No of comorbidities				
Mean (standard deviation)	0.398 (0.630)	2.57 (0.860)	1.08 (1.12)	1.08 (1.22)
Median (interquartile range)	0 (0-1.00)	2.00 (2.00-3.00)	1.00 (0-2.00)	1.00 (0-2.00)
Hypertension (No (%))				
No	1209 (94.2)	0 (0)	177 (57.1)	1386 (63.4)
Yes	75 (5.8)	593 (100)	133 (42.9)	801 (36.6)
Diabetes (No (%))				
No	1158 (90.2)	356 (60.0)	242 (78.1)	1756 (80.3)
Yes	126 (9.8)	237 (40.0)	68 (21.9)	431 (19.7)
Asthma (No (%))				
No	1170 (91.1)	561 (94.6)	286 (92.3)	2017 (92.2)
Yes	114 (8.9)	32 (5.4)	24 (7.7)	170 (7.8)
RAAS inhibitors (No (%))				
No	1284 (100)	212 (35.8)	259 (83.5)	1755 (80.2)
Yes	0 (0)	381 (64.2)	51 (16.5)	432 (19.8)
Cancer (No (%))				
No	1216 (94.7)	532 (89.7)	289 (93.2)	2037 (93.1)
Yes	68 (5.3)	61 (10.3)	21 (6.8)	150 (6.9)
Admission to intensive care (No (%))				
No	1170 (91.1)	479 (80.8)	17 (5.5)	1666 (76.2)
Yes	114 (8.9)	114 (19.2)	293 (94.5)	521 (23.8)
Oxygen therapy (No (%))				
No	594 (46.3)	119 (20.1)	1 (0.3)	714 (32.6)
Yes	690 (53.7)	474 (79.9)	309 (99.7)	1473 (67.4)
Non-invasive mechanical ventilation (No (%))				
No	1199 (93.4)	491 (82.8)	126 (40.6)	1816 (83.0)
Yes	85 (6.6)	102 (17.2)	184 (59.4)	371 (17.0)
Invasive mechanical ventilation (No (%))				
No	1209 (94.2)	531 (89.5)	189 (61.0)	1929 (88.2)
Yes	75 (5.8)	62 (10.5)	121 (39.0)	258 (11.8)
Bacterial pneumonia (No (%))				
No	1200 (93.5)	533 (89.9)	197 (63.5)	1930 (88.2)
Yes	84 (6.5)	60 (10.1)	113 (36.5)	257 (11.8)
ARDS (No (%))				
No	1207 (94.0)	510 (86.0)	24 (7.7)	1741 (79.6)
Yes	77 (6.0)	83 (14.0)	286 (92.3)	446 (20.4)
Arrhythmia (No (%))				
No	1250 (97.4)	536 (90.4)	258 (83.2)	2044 (93.5)
Yes	34 (2.6)	57 (9.6)	52 (16.8)	143 (6.5)
Liver dysfunction (No (%))				

Continued

Table 1 Continued

Characteristic	Subphenotype A (n=1284)	Subphenotype B (n=593)	Subphenotype C (n=310)	Overall (n=2187)
No	1193 (92.9)	547 (92.2)	257 (82.9)	1997 (91.3)
Yes	91 (7.1)	46 (7.8)	53 (17.1)	190 (8.7)
Acute kidney injury or failure (No (%))				
No	1248 (97.2)	519 (87.5)	228 (73.5)	1995 (91.2)
Yes	36 (2.8)	74 (12.5)	82 (26.5)	192 (8.8)
Thromboembolic event (No (%))				
No	1274 (99.2)	589 (99.3)	301 (97.1)	2164 (98.9)
Yes	10 (0.8)	4 (0.7)	9 (2.9)	23 (1.1)
Congestive heart failure (No (%))				
No	1275 (99.3)	584 (98.5)	306 (98.7)	2165 (99.0)
Yes	9 (0.7)	9 (1.5)	4 (1.3)	22 (1.0)
Bacteraemia (No (%))				
No	1263 (98.4)	567 (95.6)	247 (79.7)	2077 (95.0)
Yes	21 (1.6)	26 (4.4)	63 (20.3)	110 (5.0)

Data are number (%) unless stated otherwise. ARDS=acute respiratory distress syndrome; RAASi=renin angiotensin aldosterone system inhibitors.

We determined the optimal number of clusters (also referred to as subphenotypes) based on the area under the cumulative distribution function (online supplemental efigure 2) in conjunction with the purity of the consensus matrix plots (online supplemental efigure 3). Once the algorithm assigned patients to clusters, information about outcomes was added to the data to facilitate a comparison between outcomes when stratified by clusters; these outcomes were not included in the variables used during the clustering process. Further details on the clustering analysis are provided in the supplement.

Subphenotype characteristics were illustrated using chord diagrams. The distribution of long term symptoms in the overall population and in each cluster is illustrated using Venn diagrams. All statistical analyses were done using R version 4.0.2.

Patient and public involvement

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

Results

Patient population

We enrolled 4125 adults admitted to hospital for covid-19 between 1 February 2020 and 30 June 2021 across 93 hospitals in France. Of the study population, 495 patients died during their hospital stay, and 3610 patients who were discharged chose to continue participation at discharge (20 declined to participate after discharge); 1423 died or were lost to follow-up within six months, leaving 2187 patients in the final cohort (table 1, figure 2, online supplemental etable 1,2 and efigure 1).

Factors associated with persistent symptoms

Of 2187 participants, 1109 (50.7%) had at least one symptom six months after admission. Among patients who had at least one persistent symptom, the median number of symptoms per patient was 2.00 (interquartile range 1.00-3.00). The most frequent persistent symptoms were fatigue (33.7%); dyspnoea; (24.9%) myalgia (14.1%); arthralgia (13.7%); ear, nose, or throat symptoms (10.5%); and headache (9.2%; table 2). In multivariate analysis, the factors associated with an increased number of persistent symptoms were treatment with in-hospital supplemental oxygen (odds ratio 1.12, 95% confidence interval 1.01 to 1.24), no intensive care unit admission (1.15, 1.01 to 1.32), female sex (1.33, 1.22 to 1.45), gastrointestinal haemorrhage (1.51, 1.02 to 2.23), thromboembolic event (1.66, 1.17 to 2.34), and congestive heart failure (1.76, 1.27 to 2.43; figure 3).

Subphenotypes at hospital admission

We identified three clinical subphenotypes. Details on the clustering analysis are provided in the online supplemental efigure 1 and 2. The characteristics of patients included in each subphenotype are summarised in figure 2, table 1, and online supplemental etable 1.

Subphenotype A included 1284 patients with the least severe course of treatment in hospital, with a mean age of 56.7 years (standard deviation 15.3), who were mostly men (58.8%), and with few comorbidities (median 0 (interquartile range 0-1)). About half of these patients received oxygen supplementation (53.7%), and most did not receive mechanical ventilation (6.6% and 5.8% non-invasive and invasive mechanical ventilation, respectively. Few patients had complications during the hospital stay, including bacterial pneumonia

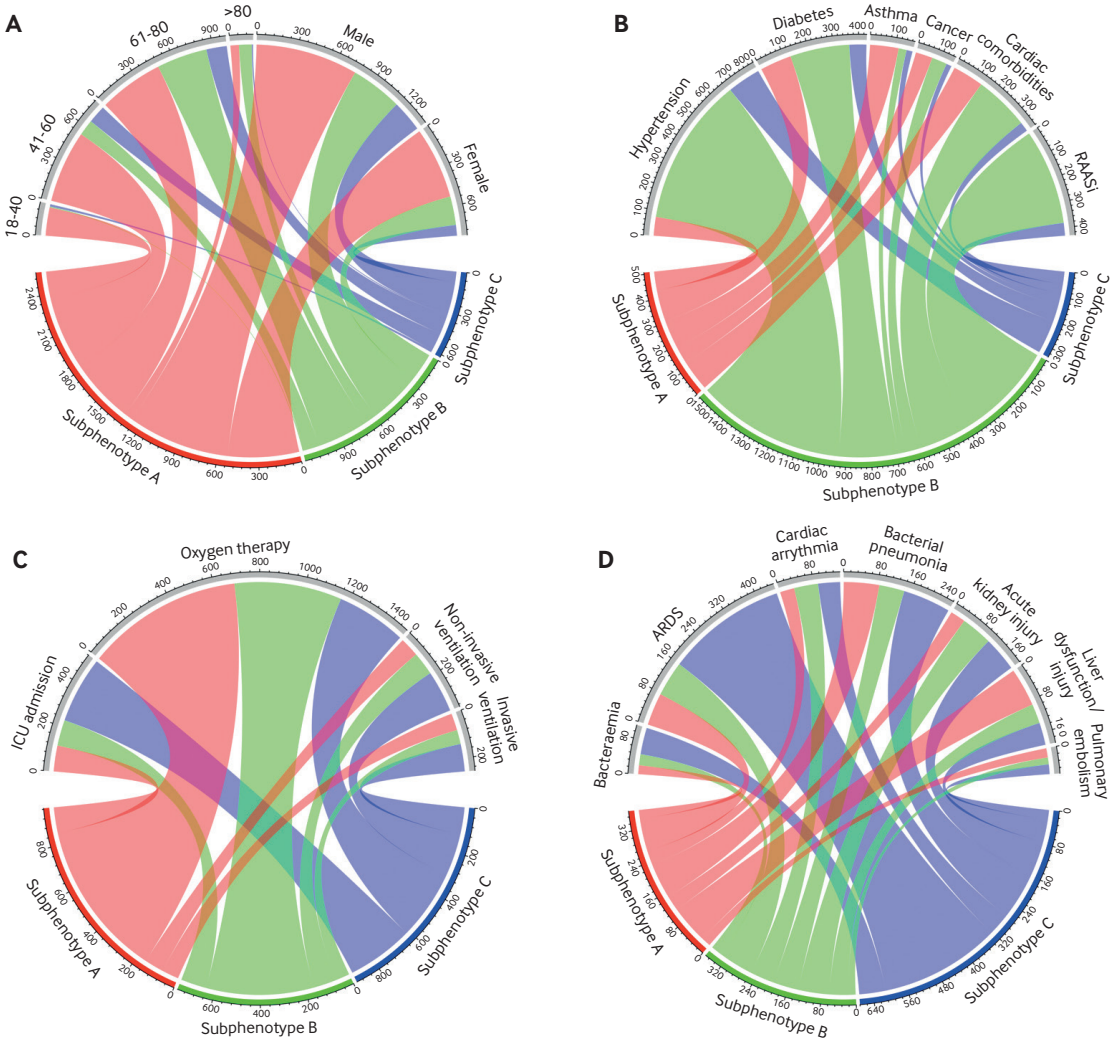

Figure 2 | Chord diagrams showing patient characteristics (panel A), comorbidities (panel B), interventions (panel C) and complications (panel D) in each subphenotype. Subphenotypes are based on the severity of hospital course received by study participants; subphenotype A had the least severe hospital course, subphenotype C had the most severe hospital course. ARDS=acute respiratory distress syndrome; ICU=intensive care unit.

(6.5%), acute kidney injury (2.8%), liver dysfunction or injury (7.1%), cardiac arrhythmia (2.6%), and thromboembolic events (0.8%; table 1).

Subphenotype B included 593 patients with a hospital course of intermediate severity. It included mostly older men (64.4%, mean age 69.1 years (standard deviation 11.4)) with more comorbidities (median two per patient (interquartile range 2-3)). All patients in subphenotype B had a history of hypertension and 40.0% had diabetes. 64.2% were on renin-angiotensin-aldosterone system inhibitors. 79.9% received supplemental oxygen: 17.2% received non-invasive mechanical ventilation, and 10.5% received invasive mechanical ventilation. Most frequent complications during the hospital stay were acute respiratory distress syndrome (14.0%), bacterial pneumonia (10.1%), acute kidney injury (12.5%), cardiac arrhythmia (9.6%), liver dysfunction or injury (7.8%), and bacteraemia (4.4%; table 1).

Subphenotype C included 310 patients with the most severe hospital course. This group of mostly men (74.5%) had a mean age 60.3 years (standard deviation 11.8) with few comorbidities (median one per patient (interquartile range 0-2)); 42.9% had hypertension, and 21.9% had diabetes. Most patients were treated in the intensive care unit (94.5%), nearly all received oxygen supplementation (99.7%), and most received mechanical ventilation (59.4% non-invasive and 39.0% invasive). Most patients had complications, including acute respiratory distress syndrome (92.3%), bacterial pneumonia (36.5%), acute kidney injury (26.5%), bacteraemia (20.3%), liver dysfunction or injury (17.1%), cardiac arrhythmia (16.8%), and thromboembolic events (2.9%; table 1).

Subphenotypes and persistent covid-19 related symptoms

Figure 4 and online supplemental efigure 3 illustrate the distribution of late symptoms (present at six months after admission) in each subphenotype. The median number of symptoms did not differ significantly

Table 2 | Incidence of symptoms in study population six months after hospital admission in the each subphenotype. Subphenotypes are based on the severity of hospital course received by study participants; subphenotype A received the least severe, subphenotype C received the most severe.

Symptom information	Subphenotype A (n=1284)	Subphenotype B (n=593)	Subphenotype C (n=310)	Overall (n=2187)
No of symptoms				
Mean (standard deviation)	0.991 (1.31)	1.05 (1.35)	0.971 (1.17)	1.01 (1.30)
Median (Q1–Q3)	0 (0-2.00)	1.00 (0-2.00)	1.00 (0-2.00)	1.00 (0-2.00)
At least one symptom (No (%))				
No	654 (50.9)	282 (47.6)	142 (45.8)	1078 (49.3)
Yes	630 (49.1)	311 (52.4)	168 (54.2)	1109 (50.7)
Dyspnoea (No (%))				
No	965 (75.2)	452 (76.2)	226 (72.9)	1643 (75.1)
Yes	319 (24.8)	141 (23.8)	84 (27.1)	544 (24.9)
Myalgia (No (%))				
No	1117 (87.0)	502 (84.7)	260 (83.9)	1879 (85.9)
Yes	167 (13.0)	91 (15.3)	50 (16.1)	308 (14.1)
Cough (No (%))				
No	1158 (90.2)	526 (88.7)	283 (91.3)	1967 (89.9)
Yes	126 (9.8)	67 (11.3)	27 (8.7)	220 (10.1)
Ear, nose, or throat symptoms (No (%))				
No	1148 (89.4)	522 (88.0)	288 (92.9)	1958 (89.5)
Yes	136 (10.6)	71 (12.0)	22 (7.1)	229 (10.5)
Fatigue (No (%))				
No	872 (67.9)	380 (64.1)	199 (64.2)	1451 (66.3)
Yes	412 (32.1)	213 (35.9)	111 (35.8)	736 (33.7)
Anosmia (No (%))				
No	1223 (95.2)	573 (96.6)	302 (97.4)	2098 (95.9)
Yes	61 (4.8)	20 (3.4)	8 (2.6)	89 (4.1)
Headache (No (%))				
No	1156 (90.0)	541 (91.2)	289 (93.2)	1986 (90.8)
Yes	128 (10.0)	52 (8.8)	21 (6.8)	201 (9.2)
Arthralgia (No (%))				
No	1117 (87.0)	500 (84.3)	270 (87.1)	1887 (86.3)
Yes	167 (13.0)	93 (15.7)	40 (12.9)	300 (13.7)
Ageusia (No (%))				
No	1233 (96.0)	573 (96.6)	301 (97.1)	2107 (96.3)
Yes	51 (4.0)	20 (3.4)	9 (2.9)	80 (3.7)

Data are number (%) unless stated otherwise.

different between subphenotypes: 0 (interquartile range 0-2) in subphenotype A, 1 (0-2) in subphenotype B, and 1 (0-2) in subphenotype C (online supplemental etable 1–3; P=0.55), and among patients who had at least one persistent symptom 2.00 (1.00-3.00) in subphenotype A, 2.00 (1.00-3.00) in subphenotype B, and 1.50 (1.00-2.00) in subphenotype C (P=0.07). Distribution of persistent symptoms did not differ between subphenotypes (figure 4 and online supplemental efigure 3).

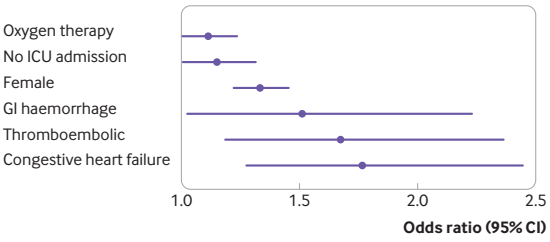

Figure 3 | Forest plot of Poisson results showing odds ratios and 95% confidence intervals for factors associated with an increase in number of covid-19 related symptoms at six months after hospital admission. ICU=intensive care unit; GI=gastrointestinal

Subphenotypes, functional status, and quality of life at six months

Among the 767 (35%) of 2187 patients who had a professional occupation before admission to hospital, 517 (67.4%) reported being able to resume their previous professional activity after hospital admission, with significant differences across the subphenotypes. In subphenotypes B and C, fewer patients were able to resume their previous professional activity compared with subphenotype A (388 (72.1%) of 538 in subphenotype A, 70 (59.8%) of 117 in subphenotype B,

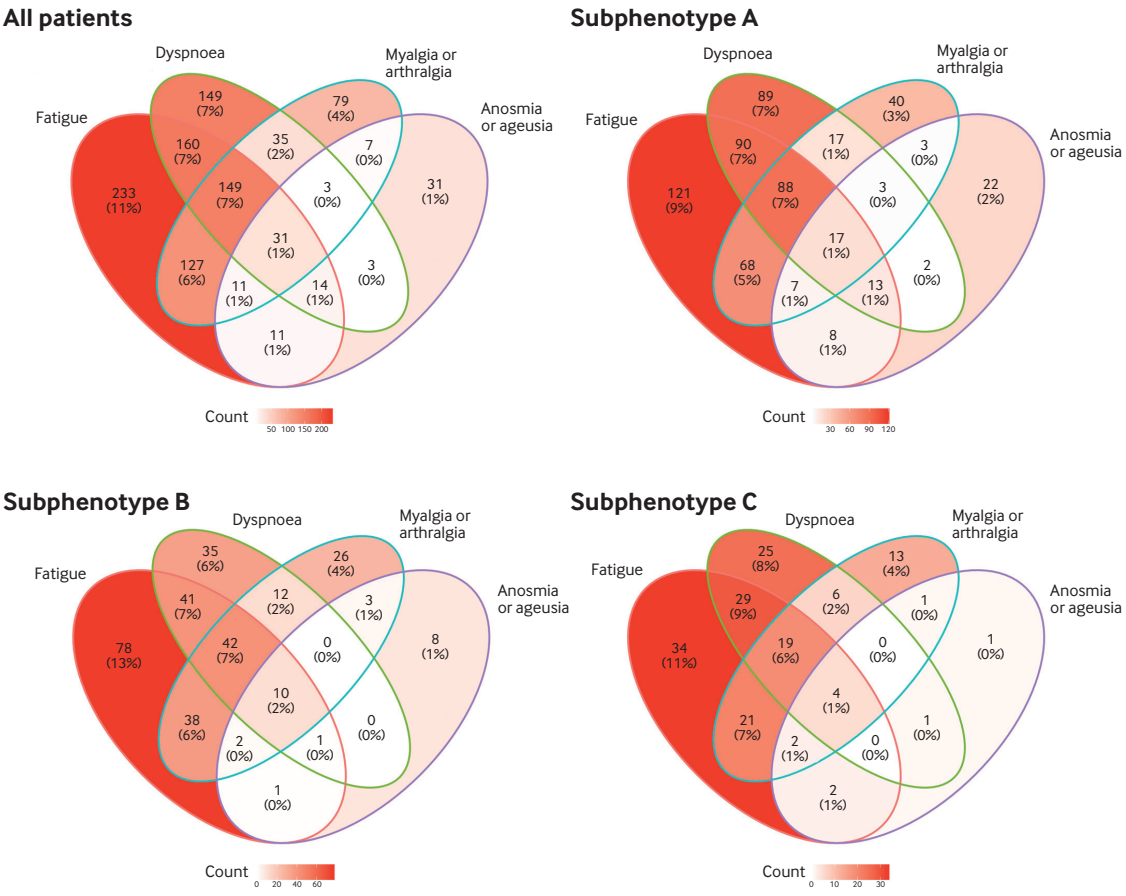

Figure 4 | Venn diagrams showing incidence of symptoms in the study population six months after hospital admission, by subphenotype. Subphenotypes are based on the severity of hospital treatment received by study participants; subphenotype A had the least severe hospital course, subphenotype C had the most severe hospital course. The denominators reflect the study population (all n=2187) and all patients in each subphenotype (subphenotype A, n=1284; subphenotype B, n=593; subphenotype C, n=310).

59 (52.7%) of 112 in subphenotype C; P<0.001) and more patients had worse ability to self-care than before hospital admission (28.4% in subphenotype C *v* 10.5% in subphenotype A and 19.2% in subphenotype B; P<0.001; figure 5).

A total of 724 (33.1%) of 2187 patients had their anxiety and depression levels evaluated with the Hospital Anxiety and Depression Scale (HADS) score on or near the date of hospital admission (online supplemental efigure 5 online supplemental etable 3). Median HADS depression scores and anxiety scores were similar between groups: 5.0 (interquartile range 2.0-9.0) and 6.0 (3.0-9.0) for subphenotype A, 6.0 (3.0-10.0) and 6.0 (3.0-9.0) for B, and 5.0 (2.0-8.5) and 5.0 (3.0-9.0) for C, respectively (P=0.014 and P=0.19). During the study, 742 (33.9%) of 2187 patients were evaluated for quality of life using the 36-Item Short Form Survey (SF-36) (online supplemental efigure 6, online supplemental etable 3). SF-36 values between subphenotypes differed significantly for the following defined categories from the survey: role limitations owing to emotional problems (as a SF-36 category; median 33.3, (interquartile range 0-100), 0 (0-75.0), 0 (0-100) in subphenotype A, B, and C, respectively; P=0.02), emotional well-being (64.0 (52.0-80.0), 60.0 (48.0-76.0), 70.0 (52.0-80.0); P=0.03), and general health (60.0 (45.0-70.0), 50.0 (35.0-65.0), 60.0 (45.0-65.0); P<0.001; table 2, online supplemental etable 3).

A total of 287 patients (13.1%) performed a six minute walk test after hospital admission (online supplemental etable 4). Median distance walked was 526 m (interquartile range 462-595) in subphenotype A, 462 m (383-533) in subphenotype B, and 502 m (420-575) in subphenotype C (P<0.001), with a minimum arterial oxygen saturation of 94.0 (92.0-96.0) in A, 94.0 (91.0-95.0) in B, and 94.0 (91.0-95.0) in C (P=0.93).

Discussion

Principal findings

Persistent long term symptoms have been increasingly described after covid-19, leading many experts and researchers to hypothesise that another pandemic of long term disabilities and chronic

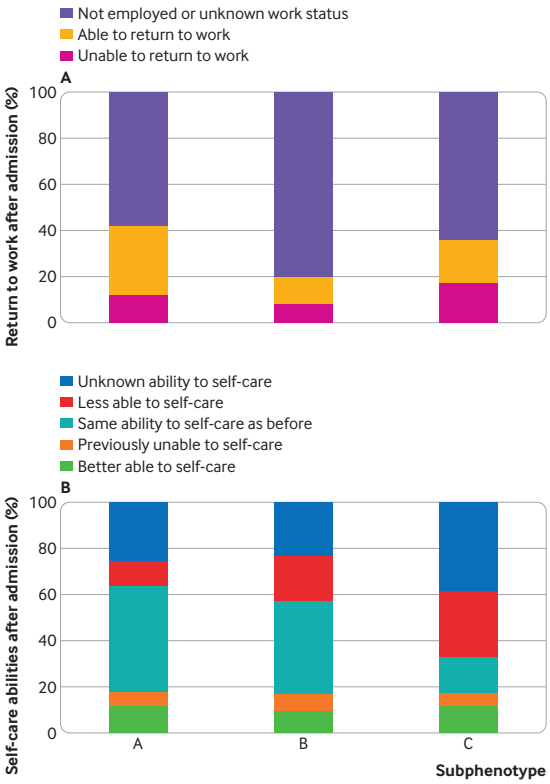

Figure 5 | (A) Ability to return to work and (B) self-care abilities compared to baseline six months after hospital admission in study population, across three subphenotypes in study. Subphenotypes are based on the severity of hospital course received by study participants; subphenotype A had the least severe hospital course, subphenotype C had the most severe hospital course.

illness might follow.[4] In this prospective observational study, fatigue (34%); dyspnoea (25%); myalgia (14%); or arthralgia (14%); ear, nose, and throat symptoms (11%); and headache (9%) were the most common persistent symptoms six months after admission to hospital due to SARS-CoV-2 infection. We identified several factors associated with an increased number of persistent symptoms, including supplemental oxygen, no intensive care unit admission, female sex, gastrointestinal haemorrhage, thromboembolic event, and congestive heart failure. We further identified three subphenotypes (based on severity of hospital course) of patients with covid-19 who were discharged from hospital with very distinct characteristics. These subphenotypes were associated with a significant difference in survivors' subjective and objective functional status at six months. Many patients could not resume their professional activities or take care of themselves as they did before.

Comparison with other studies

Our results add to the growing literature on the sequelae of covid-19; however, most previous research has not examined the risk factors for such symptoms or were carried out in smaller, single centre cohorts.[6 9–12] Among 177 patients enrolled at the University of Washington, Logue et al noted that five (31%) of 16 patients in hospital with covid-19 reported at least one persistent symptom during the nine month follow-up.[9] In the ISARIC cohort (327 patients in hospital who survived and were followed up at least three months after admission), women younger than 50 years were more likely to have greater disability, to report worse fatigue, and to feel more breathless.[13] Huang et al reported on 1230 (50%) of 2469 discharged patients with covid-19 in China with a six month follow-up; 636 (63%) reported fatigue or muscle weakness, 335 (26%) sleep difficulties, and 274 (23%) had anxiety or depression.[14] In a single centre, prospective cohort study conducted in Italy of 377 outpatients who recovered from covid-19, severity was not associated with persistent symptoms whereas female sex, age, and active smoking were also associated with a higher risk of persistent symptoms.[15] In the PHOSP-COVID study, 239 (29%) of 830 participants admitted to hospital with covid-19 in the UK felt fully recovered at six months, 158 (20%) of 806 had a new disability, and 124 (19%) of 641 had a health related change in occupation.[16] In the UK coronavirus infection survey, 232 000 (19%) of 1.2 million people who recovered from covid-19 and reported symptoms also reported that their ability to undertake their day-to-day activities had been "limited a lot." Fatigue (54%), shortness of breath (36%), and loss of smell (35%) were the most common symptoms.[17]

The incidence of symptoms in this population appears to be much higher than in the general population, as shown in a large, observational study in France. Among 116 903 patients surveyed during the lockdown in France in April and May 2020 who did not test positive for SARS-CoV-2, the cumulative incidence of covid-19-like symptoms (defined as a cough, a fever, a dyspnoea, a sudden onset of anosmia, or ageusia or dysgeusia) was 6.2% (95% confidence interval 5.7% to 6.6%).[18]

In our cohort, no major differences in distribution of symptoms or symptom prevalence between subphenotypes was noted, a finding previously reported by others.[9] Our results are consistent with other reports that the severity of the disease was not a strong predictor of persistent symptoms.[1 10 19 20] Despite clear differences in the severity of hospital courses between subphenotypes, dyspnoea, fatigue, and other symptoms at six months after hospital admission did not differ statistically between subphenotypes. Of note, in a multicentre study, a positive serological result for SARS-CoV-2 was positively associated only with persistent anosmia and not with other symptoms.[21]

Patients across the different subphenotypes showed different quality of life outcomes and scores of anxiety and depression. Of note, all median HADS

scores were within normal range (that is, <8 of 21 are defined as normal, 8-10 of 21 are defined as borderline abnormal). Patients in subphenotype C appeared to be associated with more psychological symptoms on the SF-36 score. Patients in subphenotype C were also less likely to resume their previous professional activity after hospital discharge and were less able to care for themselves probably because of underlying impairment in their mental or physical status. Young patients' inability to resume their professional activities and to self-care will obviously have a considerable impact on their lives and be associated with huge costs. Such findings should encourage rehabilitation programmes and follow-up for patients with characteristics identified to be in the subphenotypes at risk or with risk factors for an increased number of symptoms.

The non-specific contribution of critical illness to these symptoms, quality-of-life outcomes, and impaired functional status is unknown. We do know that critical illness is associated with high psychological distress and long term worsened functional status, and covid-19 does not appear to be different. Determining the impact of covid-induced critical illness on long term functional and psychological changes is difficult.[22 23] Notably, the cluster of patients with intermediate severity (with only a small number requiring admission to intensive care) but more comorbidities also had a high burden of long term, poor functional outcomes. This finding suggests an association between covid-19 severity, comorbidities, and outcome. The data highlight the high and frequent psychological and functional burden of covid-19 associated illness and contribute to legitimate the need for recognition, prevention, and treatment of these long term outcomes.[24] The clustering analysis allowed us to identify fairly homogenous populations or groups of patients that could serve as targets for future trials. In other words, an intervention might yield different benefits to subphenotype B (mostly comorbidities) and subphenotype C (mostly severe covid-19 with few comorbidities).

Strengths and limitations of the study

Our study has limits. Our results do not apply to all individuals with covid-19, but only to people admitted to the hospital and who were subsequently discharged. This study was conducted in France so results might not be comparable to other healthcare systems and countries. The dominant SARS-CoV-2 variant in France at the time of the study was the alpha variant. These results do not apply to other variants. Likewise, the study took place before most of the population was vaccinated (<20% of the French population was fully vaccinated in early June 2021). Nonetheless, frequent persistent symptoms in our cohort appear consistent with previous reports. Only a list of symptoms were collected and patients could have developed other symptoms. Patients who died within six months of admission to hospital were not included, and the persistence of symptoms before death was therefore not explored.

Given the unsupervised clustering approach used for this analysis, causal conclusions cannot be drawn because this approach only allows the examining of associations between groups of variables (identifying rather homogenous groups of patients) and comparisons between outcomes when stratified by these groupings. Although all the patients included in this cohort were followed up to determine if they had persistent symptoms, only about 40% had a more comprehensive assessment (that is, HADS and SF-36). The presence of these more comprehensive assessments was potentially driven by the presence of more persistent or severe symptoms in some patients. Also, a substantial number of patients who were discharged then died or were lost to follow-up (nearly 50%). However, the characteristics of the patients included in this study do not differ from the entire cohort (online supplemental etable 5). Finally, the symptoms collected were restricted, qualitative, and not quantitative. For instance, the degree of shortness of breath might be underestimated in patients with the most severe covid-19 and other potential symptoms could exist but were not collected.

Conclusion

In this cohort of patients discharged from the hospital after covid-19 and followed up for six months after hospital admission, persistent symptoms were frequent. While some risk factors of persistent symptoms were identified, persistent symptoms occurred overall regardless of covid-19 severity. However, survivors' subjective and objective functional status six months after hospital admission significantly differed between the identified subphenotypes.

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Collaborators French COVID cohort investigators and study groups.

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substantially to the study design, data analysis and interpretation, and the writing of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: ML (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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