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Long COVID affects home-isolated young patients

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Letter

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Abstract

Long-term complications following COVID-19 are common in hospitalised patients, but the spectrum of symptoms in milder cases remains unclear. In a Norwegian prospective cohort study of 312 patients, 61% of COVID-19 patients (247 home-isolated and 65 hospitalised) had persistent symptoms at six months, most commonly fatigue (37%), impaired concentration (26%), disturbed smell and/or taste (25%), memory loss (24%) and dyspnoea (21%). In young home-isolated adults, aged 16–30, 52% had symptoms at six months, with fatigue (21%), dyspnoea (13%), impaired concentration (13%) and memory loss (11%) posing particular challenges. Pre-existing chronic lung disease and high convalescent antibody titres predicted persistent symptoms, particularly fatigue. Our finding that young, home-isolated adults with mild COVID-19 are at risk of long-lasting dyspnoea and cognitive symptoms highlights the importance of infection control measures, such as vaccination.

Main Text

The COVID-19 pandemic has infected over 100 million people, killed more than two million, and continues to disrupt life across the globe[1]. While the respiratory tract is the site of SARS-CoV-2 entry and infection, COVID-19 is a systemic disease, affecting the cardiovascular, renal, hematologic, gastrointestinal, and central nervous systems[2]. As evidence emerges on predominantly lasting impairment of lung function related to fibrosis, this journal has called for more data on the long-term effects of COVID-19 on other organs[3]. A plethora of symptoms persist in patients surviving severe COVID-19[4,5], and a long COVID syndrome has been proposed[6,7]. However, the severity and duration of symptoms remain largely unknown. Chronic fatigue occurred after SARS infection in 2003 [8], and it is well-known in the aftermath of a spectrum of infectious diseases, including brucellosis, Q-fever, giardiasis, as well as common viral infections such as influenza, Epstein-Barr virus mononucleosis and dengue fever[9-14]. It is known from before the current pandemic, that management in intensive care is associated with mental and physical decline, and this could partially explain long COVID in patients with severe illness[15]. However, the burden of long COVID in mild-to-moderately ill patients is not well known. We assessed persistent symptoms six months following initial COVID-19 illness in a prospective cohort of hospitalised and home-isolated COVID-19 patients from the first pandemic wave in Bergen, Norway.

In a prospective cohort study, we consecutively recruited 353 SARS-CoV-2 positive cases from March to May 2020, during the first pandemic wave in Bergen, Norway. We collected demographic and clinical data, as well as blood samples. At six months follow-up, the study population available for analysis comprised 372 individuals, of whom 247 were home-isolated patients, 65 patients had been admitted to the two city hospitals, and 60 were seronegative controls recruited from households of home-isolated patients (Figure S1).

The median age of the COVID-19 patients was 46 years (IQR 30-58), and 48% were male. Forty-four percent had comorbidities, the most frequent being chronic lung disease (12%, 34/38 with asthma), hypertension (11%), chronic heart disease (7%), diabetes (4%) and immunosuppressive conditions (4%).

The study population had a median body mass index of 24.6 (IQR[Inter-quartile range] 22.8-27.3). Hospitalised patients were older than home-isolated patients, had higher body mass index (OR [odds ratio], 1.21; CI [95% confidence interval], 1.13-1.31), more comorbidities (OR, 3.79; CI, 2.14-6.94), including chronic lung disease, chronic heart disease, hypertension and diabetes (Table 1). Seronegative controls were younger than COVID-19 patients and had fewer comorbidities.

Sixty-one percent of the total patient population had persistent symptoms six months after initial COVID-19 illness, with the most common complaints being fatigue (37%), difficulty concentrating (26%), disturbed smell/taste (25%), memory problems (24%) and dyspnoea (21%) (Table 2). Seven percent reported cough, while only two percent had persistent fever. Even in home-isolated cases, fifty-five percent experienced persistent symptoms at six months, most commonly fatigue (30%), disturbed taste and/or smell (27%), concentration impairment (19%), memory loss (18%) and dyspnoea (15%) (Table 2, figure panels a1-4). While the youngest age group (0-15 years) rarely suffered persistent symptoms, more than half (52%) of young adults (16-30 years old) who were home-isolated for mild-to-moderate initial illness, had persistent symptoms, the most common being fatigue (21%), dyspnoea (13%) and impaired concentration (13%) and memory (11%). In these young adults, comorbidity was not significantly associated with persistent symptoms (33% vs 31%, p=1) or fatigue (47% vs 27%, p=0.2), although numbers were too small to draw firm conclusions. Whereas the frequency of most symptoms increased with age, disturbed smell and/or taste was more frequent in people < 46 years old (Table 2, figure panel a4).

Convalescent antibodies peak after approximately two months and provide a marker for the magnitude of the immune response. SARS-CoV-2 spike protein IgG and microneutralising antibody titres detected after two months were significantly higher in hospitalised than home-isolated patients (Table 1). In multivariable analysis, both older age (aOR [adjusted OR], 1.009; CI, 1.004-1.014), higher body-mass index (aOR, 1.023; CI, 1.001-1.045) and severity of initial COVID-19 illness (aOR, 1.261; CI, 1.144-1.389) were associated with higher antibody titres at two months follow-up (Table 3, figure panels b1-2, c1-2). Subsequently, high antibody titres were markers of both persistent fatigue (aOR, 1.200; CI, 1.063-1.353) and total number of symptoms (aOR, 1.241; CI, 1.033-1.491, table 3, figure panels b3-4, c3-4). Pre-existing chronic lung disease was also a risk factor for persistent fatigue and total number of symptoms (aOR, 1.294; CI,1.027-1.633), Table 3).

Post-viral fatigue has been reported following the SARS epidemic in 2003[8] and other viral infections[12-14]. To assess fatigue, we used the Chalder score, which is validated for adults[16,17]. Fatigue is defined as a total bimodal score of ≥4 of 11 questions. The presence of fatigue in non-hospitalised COVID-19 reconvalescents was 30%, which was less than in hospitalised cases (63%) but more than in seronegative controls (14%, table 2 and S1). Severe fatigue, defined as bimodal score ≥4 + total ordinal score ≥23, was significantly more frequent in hospitalised than home-isolated COVID-19 reconvalescents (24% vs 7%, OR, 4.02; CI, 1.86-8.64, able S1). In non-hospitalised cases, the most frequent symptoms of physical fatigue (questions 1-7) were tiredness (35%), increased need for rest (30%) and lack of energy (29%), and

the most common symptoms of mental fatigue (questions 8-11) were difficulties finding words (23%), difficulties concentrating (19%) and memory problems (18%, table S1).

Female sex, underlying chronic lung disease and severity of initial COVID-19 were independent risk factors for fatigue at six months in binomial logistic regression (Table S2) and zero-inflated Poisson regression (Table 3). Additionally, high convalescent antibody titre was a risk factor for persistent fatigue and for high fatigue score in multivariable analysis (Table 3, figure panels b4 and c4). Increasing age, cardiac comorbidity and use of antibiotics during initial illness, were risk factors for fatigue in univariable analysis, but were not significantly risk factors in multivariable analysis (Table S2).

This study is novel in assessing Long COVID symptoms, not only in hospitalised patients, but also in young patients and home-isolated cases with milder disease. We found that a large proportion of COVID-19 survivors had persisting symptoms six months after initial illness. While it has previously been reported that patients hospitalised for severe COVID-19 frequently suffer long-term symptoms[18], we found that more than half of home-isolated, mildly-to-moderately ill COVID-19 patients suffered symptoms six months post-infection. It is alarming that non-hospitalised, young people (16-30 years old) suffer potentially severe symptoms such as concentration and memory problems, dyspnoea and fatigue, half a year after infection. Particularly for students, such symptoms may interfere with their learning and study progress.

The high prevalence of persistent fatigue in COVID-19 patients is striking and appears higher than seen after common infections such as Influenza, Epstein Barr virus mononucleosis and dengue[12-14]. Data from Norway has previously reported slightly lower chronic fatigue prevalence (11%) in the general population[19] than in the present control group (14%). Although this apparent difference may be a coincidence due to small numbers, a higher rate of fatigue in our control group could be due to factors such as stress related to quarantine, worries about sick family members, and the effect of current restrictions on life during lockdown. For comparison, in January 2021, the prevalence of fatigue was only six percent in employees screened before COVID-19 vaccination at our hospital (data not shown). Our finding that females had higher prevalence of fatigue is in line with results from a prior study on the frequency of fatigue in the general Norwegian population[19]. The association between severity of illness and persistent symptoms is in line with other data from COVID-19 hospitalised patients[18]. As the respiratory tract is the main target organ for COVID-19, our finding of underlying chronic lung disease (mostly asthma) as a risk factor for persistent fatigue is not surprising. The association of high convalescent antibody titres and fatigue alludes to underlying immunological mechanisms for the fatigue.

The association between severe initial disease and high antibody titres at two months may be due to higher viral load, which could trigger the immune system more profoundly[20]. The finding of higher convalescent antibody titres with increasing age could be explained by more severe disease in older people, as age is a well-known and strong risk factor for severe COVID-19. However, multivariable analysis indicated that age and severity of illness were independently associated with high antibody

titres. This contrasts with reduced antibody responses after influenza observed in the elderly, referred to as immunosenescence.

Our main message is that young, home-isolated adults with mild COVID-19 are at risk of long-lasting dyspnoea and cognitive symptoms. Considering the millions of young people infected during the ongoing pandemic, our findings are a strong impetus for comprehensive infection control and population-wide vaccination.

Methods

Study population

As part of a prospective cohort study with long-term follow-up, we enrolled consecutively patients diagnosed with COVID-19 in the period March – May 2020, during the first wave of the pandemic in Bergen, Norway. The study population included SARS-CoV-2 RT-PCR-positive outpatients diagnosed at Bergen Municipality Emergency Department, and those admitted to the two neighbouring city hospitals, Haukeland University Hospital and Haraldsplass Deaconess Hospital. The study was approved by the Regional Ethics Committee of Western Norway (#118664).

Clinical data

All consenting patients provided demographic information, clinical information on symptoms at baseline and six months follow-up, on risk factors including comorbidities, and use of medication. Data was collected on severity of initial illness, i.e. need for hospitalisation, symptoms on diagnosis, need for non-invasive ventilatory support or respirator-treatment. At six months follow-up, all participants aged 16 years or older were invited to complete a validated fatigue questionnaire containing eleven key questions according to the Chalder fatigue scale[16,17]. Fatigue was defined as a total dichotomised score of ≥4. Severe fatigue was defined as fatigue plus a total Chalder score of ≥23.

Laboratory methods

Diagnosis of COVID-19 was based on RT-PCR on samples from nasopharyngeal swabs and on serological evidence of SARS-CoV-2 antibody positivity[21]. Convalescent serum samples were collected two months post-infection for detection of anti-SARS-CoV-2 antibody titres and stored at -80°C until analysed. Samples were heat-inactivated for one hour at 56°C before analysis by a two-step ELISA for detecting SARS-CoV-2-specific antibodies to the receptor-binding domain (screening) and the spike protein (confirmation). Endpoint titres were calculated as the reciprocal of the serum dilution giving an optical density (OD) value of 3 standard deviations above the mean of historical pre-pandemic serum samples (n=128)[21]. Sera with antibodies against the receptor binding domain were tested in microneutralization (MN) assay using the local isolate hCoV-19/Norway/Bergen-01/2020 (GISAID accession ID EPI_ISL_541970) as previously described[22]. The MN titre is the reciprocal of the serum dilution giving 50% inhibition of virus infectivity.

Statistical analysis

Data was entered using electronic case report forms (eCRF) in REDCap® (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee). All analyses were done in R version 4·0·3 (www.R-project.org), and graphs were produced in R using the ggplot and gridExtra packages. Patients who responded to all questions were included in the analysis, and results presented as percentages with means or medians and 95% confidence intervals. Associations with other variables were assessed by Chi square test and binomial logistic regression.

Multivariable analysis was performed by binary logistic regression for dichotomous outcome variables. For convalescent antibody titre as outcome variable, we log10-transformed the titre values to obtain near normal distribution and performed linear regression (Table 3). The outcome variable “number of symptoms”, encoded as integers from 0 to 13, according to symptoms listed in Table 2, had value zero for 39% (123/312) of the observations. Therefore, we employed zero-inflated Poisson regression using the R package “pscl” for multivariable analysis for this outcome variable (Table 3). The Chalder scale for fatigue assessment encompasses values from 0 to 33, with zero as best possible status (“better than usual” on all 11 parameters), and 33 as worst possible outcome (“much worse than usual” on all parameters), and 11 equalling average score “as usual”. A peak of 38% (112/312) of observations were at 12, and only 7% scored lower (range 8-11). For the purpose of multivariable analysis, values from 0 to 12 were recoded as zero, and remaining values transposed by minus 12, to allow for the use of zero-inflated Poisson regression.

Severity of illness was classified using an eight-category ordinal scale, as previously published[23]. The categories are as follows: 1, not hospitalised and no limitations of activities; 2, not hospitalised, with limitation of activities, home oxygen requirement, or both; 3, hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons); 4, hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (related to COVID-19 or to other medical conditions); 5, hospitalised, requiring any supplemental oxygen; 6, hospitalised, requiring non-invasive ventilation or use of high-flow oxygen devices; 7, hospitalised, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death.

Declarations

Data availability

Data may be made available upon reasonable request to the corresponding authors. All requests will be reviewed by Bergen COVID-19 Research Group.

Code availability

The R code used to generate all results of this manuscript is available upon request.

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Tables

Table 1. Characteristics of study population

	Negative controls	All COVID-19	Hospitalised COVID-19	Home-isolated COVID-19	Hospitalised vs home-isolated
	% (n)	% (n)	% (n)	% (n)	OR(CI)
	N=60	*N = 312*	*N=65*	*N=247*	
Male sex	36.7% (22)	48.4% (151)	53.8% (35)	47.0% (116)	1.32 (0.76-2.29)
Age, median (IQR)	29 (14 – 48)¶	46 (30-58)	55 (45 – 68)	43 (27 – 55)	1.04 (1.03-1.06)*
Age categories					
- **0-15 years**	28.3% (17)	5.1% (16)	0.0% (0)	6.5% (16)	
- **16-30 years**	23.3% (14)	20.8% (65)	6.2% (4)	24.7% (61)	
- **31-45 years**	21.7% (13)	22.1% (69)	16.9% (11)	23.5% (58)	
- **46-60 years**	25.0% (15)	28.8% (90)	35.4% (23)	27.1% (67)	
- **>60 years**	1.7% (1)	23.1% (72)	41.5% (27)	18.2% (45)	
BMI, median (IQR)	23.3 (20.9-25.6)	24.6 (22.8-27.3)	27.0 (24.1-29.9)	24.3 (22.5-26.5)	1.21 (1.13-1.31)*
Any comorbidity	15.0% (9)¶	43.9% (137)	69.2% (45)	37.2% (92)	3.79 (2.14-6.94)*
Asthma, COPD†	1.7% (1)¶	12.2% (38)	21.5% (14)	9.7% (24)	2.55 (1.21-5.22)*
Chronic heart disease	0.0% (0)	7.1% (22)	18.5% (12)	4.0% (10)	5.37 (2.20-13.35)*
Hypertension	0.0% (0)	11.2% (35)	24.6% (16)	7.7% (19)	3.92 (1.87-8.17)*
Diabetes mellitus	3.3% (2)	4.2% (13)	9.2% (6)	2.8% (7)	3.49 (1.09-10.88)*
Immunosuppression	0.0% (0)	3.5% (11)	7.7% (5)	2.4% (6)	3.35 (0.94-11.48)
Current or prior smoker‡	19.3% (11/57)	31.0% (96/310)	39.1% (25/64)	28.9% (71/246)	1.58 (0.88-2.79)
Severity of illness, mean (CI)	1.0 (1.0-1.0)¶	2.6 (2.4-2.7)	4.77 (4.5-5.0)	2.0 (2.0-2.0)	NA
Days in hospital, mean (CI)	0.0 (0.0-0.0)	2.0 (1.2-2.8)	9.6 (6.3-12.9)	0.0 (0.0-0.0)	NA
Spike antibodies§	$	3.9 (3.8-4.0)	4.6 (4.4-4.8)	3.7 (3.6-3.8)	11.30 (6.13-22.48)*
Microneutralising antibodies§	$	2.0 (2.0-2.1)	2.9 (2.7-3.1)	1.8 (1.8-1.9)	17.71 (9.29-37.55)*

OR, odds ratio, CI, 95% CI confidence interval calculated by binomial logistic regression.
NA, not applicable comparison as both days in hospital and severity is dependent on hospitalisation.
* Statistically significant difference with $p<0.05$.
¶ Statistically significantly different from COVID-19 positive patients.
†35 of 38 had asthma.
‡Not known for 5 persons
§ Measured 2 months after initial illness, log10 titres of IgG antibodies, means and 95% confidence interval.
$ Below the assay detection limit

Table 2. Long-term complications by age group in 312 COVID-19 patients at six months follow-up compared to 60 SARS-CoV-2 spike protein antibody-negative controls

Characteristic	Seronegative controls	All COVID-19	Hospitalised patients	Home-isolated all	Home-isolated 0-15 years	Home-isolated 16-30 years	Home-isolated 31-45 years	Home-isolated 46-60 years	Home-isolated Over 60 years	Hospitalised vs home-isolated over 15 years old
	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	OR (CI)
	N=60	*N=312*	*N=65*	*N=247*	*N=16*	*N=61*	*N=58*	*N=67*	*N=45*	*N=296*
Age, median (IQR)	29 (14-48)†	46 (30-58)	55 (45-68)	43 (27-55)	8 (6-12)	24(22-27)	37 (34-41)	53 (49-55)	67 (63-73)	1.04 (1.02-1.06)*
Female gender	63% (38)	52% (161)	46% (30)	53% (131)	56% (9)	54% (33)	52% (30)	52% (35)	53% (24)	0.77 (0.44-1.33)
					1.18 (0.39-3.64)	1.08 (0.54-2.17)	0.98 (0.48-1.98)	1	1.04 (0.49-2.24)	
Status at 6 months										
Any symptoms	17% (10)†	61% (189)	82% (53)	55% (136)	13% (2)	52% (32)	59% (34)	61% (41)	60% (27)	3.19 (1.67-6.57)*
					0.09 (0.01-0.36)*	0.70 (0.34-1.41)	0.90 (0.44-1.84)	1	0.95 (0.44-2.07)	
Fever	2% (1)	2% (6)	3% (2)	2% (4)	0% (0)	0% (0)	5% (3)	1% (1)	0% (0)	1.80 (0.25-9.45)
					0 (NA)	0 (NA)	3.60 (0.45-73.90)	1	0 (NA)	
Cough	0% (0)	7% (23)	12% (8)	6% (15)	0% (0)	0% (0)	9% (5)	4% (3)	16% (7)	2.02 (0.78-4.90)
					0 (NA)	0 (NA)	2.01 (0.47-10.18)	1	3.93 (1.03-19.08)*	
Dyspnoea	0% (0)†	21% (65)	42% (27)	15% (38)	0% (0)	13% (8)	17% (10)	18% (12)	18% (8)	3.61 (1.97-6.61)*
					0 (NA)	0.69 (0.25-1.81)	0.95 (0.37-2.41)	1	0.99 (0.46-2.63)	
Palpitations	2% (1)	7% (23)	12% (8)	6% (15)	0% (0)	3% (2)	7% (4)	9% (6)	7% (3)	2.02 (0.78-4.90)
					0 (NA)	0.34 (0.05-1.56)	0.75 (0.18-2.78)	1	0.73 (0.15-2.92)	
Stomach upset	0% (0)†	8% (25)	15% (10)	6% (15)	6% (1)	5% (3)	7% (4)	6% (4)	7% (3)	2.81 (1.16-6.65)*
					1.05 (0.05-7.76)	0.81 (0.16-3.84)	1.17 (0.26-5.15)	1	1.13 (0.21-5.35)	
Disturbed taste/smell	0% (0)†	25% (79)	18% (12)	27% (67)	13% (2)	28% (17)	34% (20)	28% (19)	20% (9)	0.58 (0.28-1.12)
					0.36 (0.05-1.46)	0.98 (0.45-2.11)	1.33 (0.62-2.85)	1	0.63 (0.25-1.53)	
Fatigue§	14.0% (6/43)†	37% (108/293)	63% (39/62)	30% (69/231)	-	21% (13)	31% (18)	33% (22)	36% (16)	3.98 (2.23-7.25)*
						0.55 (0.24-1.22)	0.92 (0.43-1.96)	1	1.13 (0.51-2.50)	
Concentration problems§	4.7% (2/43)†	26% (77/293)	53% (33/62)	19% (44/231)	-	13% (8)	19% (11)	21% (14)	24% (11)	4.84 (2.67-8.85)*
						0.57 (0.21-1.45)	0.89 (0.36-2.14)	1	1.22 (0.49-3.01)	
Memory problems§	2.3% (1/43)†	24% (69/293)	44% (27/62)	18% (42/231)	-	11% (7)	16% (9)	22% (15)	24% (11)	3.47 (1.90-6.36)*
						0.45 (0.16-1.16)	0.64 (0.25-1.57)	1	1.12 (0.45-2.72)	
Sleep problems	2% (1)	10% (32)	29% (19)	5% (13)	0% (0)	5% (3)	7% (4)	4% (3)	7% (3)	6.93 (3.22-15.33)*
					0 (NA)	1.10 (0.20-6.17)	1.58 (0.33-8.31)	1	1.52 (0.27-8.57)	
Headache	0% (0)†	13% (41)	20% (13)	11% (28)	0% (0)	11% (7)	14% (8)	9% (6)	16% (7)	1.81 (0.86-3.69)
					0 (NA)	1.32 (0.41--4.32)	1.63 (0.53-5.23)	1	1.87 (0.58-6.22)	
Dizziness	2% (1)†	13% (39)	23% (15)	10% (24)	0% (0)	7% (4)	10% (6)	10% (7)	16% (7)	2.59 (1.25-5.25)*
					0 (NA)	0.60 (0.15-2.10)	0.99 (0.30-3.16)	1	1.58 (0.50-4.96)	
Tingling in fingers	3% (2)	6% (19)	15% (10)	4% (9)	0% (0)	0% (0)	2% (1)	4% (3)	11% (5)	4.48 (1.73-11.81)*
					0 (NA)	0 (NA)	0.37 (0.02-3.02)	1	2.67 (0.62-13.57)	
No. of symptoms, mean(CI)‡	0.3 (0.1-0.5)†	1.9 (1.7-2.2)	3.4 (2.7-4.2)	1.6 (1.3-1.8)	0.2 (0.0-0.5)	1.2 (0.7-1.6)	1.8 (1.2-2.3)	1.7 (1.2-2.2)	2.0 (1.3-2.7)	1.32 (1.18-2.48)*

OR, odds ratio. CI 95% confidence interval, IQR interquartile range. Univariable analysis using binomial logistic regression.

* Statistically significant at level p<0.05.

† Significantly lower frequency among COVID-19-negative than positive individuals.

‡ Number of symptoms among the 13 symptoms mentioned above.

§ Only 336 individuals were assessed for these symptoms.

Table 3. COVID-19 cases' risk factors for higher convalescent antibody titres and increasing number of symptoms and increasing fatigue score at six months follow-up. Multivariable analysis.

	Spike protein IgG at 2 months†	Number of symptoms at 6 months‡	Fatigue score at 6 months‡§
	n=312	n=312	n=293
	aOR(CI)	aOR(CI)	aOR(CI)
Female sex	0.910 (0.772-1.071)	1.202 (0.990-1.461)	1.186 (1.032-1.364)*
Older age (years)	1.009 (1.004-1.014)*	1.001 (0.994-1.007)	1.000 (0.995-1.005)
BMI	1.023 (1.001-1.045)*	0.997 (0.975-1.021)	1.003 (0.987-1.019)
Comorbidity			
- **Asthma/COPD**	1.053 (0.820-1.353)	1.294 (1.027-1.633)*	1.244 (1.058-1.464)*
- **Chronic heart disease**	0.973 (0.677-1.398)	1.022 (0.705-1.483)	1.008 (0.759-1.337)
- **Hypertension**	1.256 (0.939-1.703)	1.207 (0.878-1.659)	1.250 (0.971-1.608)
- **Diabetes**	1.184 (0.789-1.775)	1.351 (0.922-1.980)	1.199 (0.929-1.548)
- **Immunosuppression**	1.012 (0.655-1.564)	0.801 (0.504-1.274)	1.139 (0.843-1.539)
Current or prior smoker	0.971 (0.810-1.163)	1.081 (0.889-1.313)	1.144 (0.998-1.312)
Severity of initial illness	1.261 (1.144-1.389)*	1.054 (0.963-1.154)	0.993 (0.931-1.060)
Days in hospital	1.003 (0.987-1.018)	0.995 (0.981-1.010)	0.996 (0.987-1.005)
Spike IgG titre at 2 months	-	1.241 (1.033-1.491)*	1.200 (1.063-1.353)*

aOR(CI): adjusted odds ratios and 95% confidence intervals.

* Statistically significant difference at level $p<0.05$.

† Linear regression with log10 transformed antibody titres as outcome variable.

‡ Zero-inflated Poisson regression with outcome variable coded as number of symptoms in the form of integers from 0 to 13 (the 13 symptoms are listed in table 2).

§ Total Chalder score as outcome variable. The Chalder scale encompasses values from 0 (best possible status) to 33 (worst possible). A peak of 38% (112/312) of observations were at score 12, and only 7% scored lower (range 8-11). For the purpose of multivariable analysis, values from 0 to 12 were recoded as zero, and remaining values transposed by minus 12, to allow for the use of zero-inflated Poisson regression.

Figures

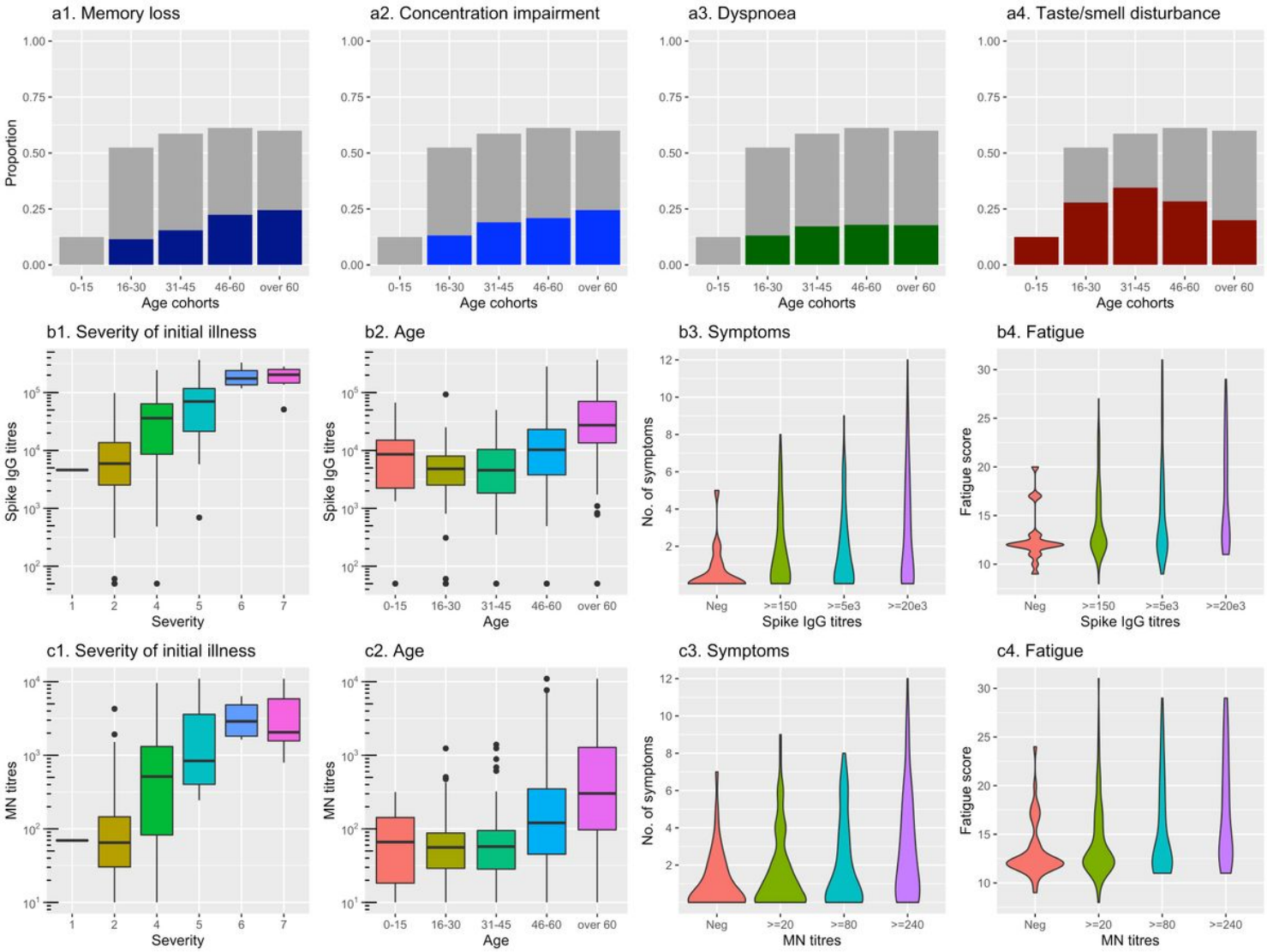

Figure 1

Six-months follow-up of COVID-19 patients in Bergen, Norway. Persisting symptoms by age groups (a1-a4); the grey background column is the proportion of patients with symptoms, while specific symptoms are shown in colours, dark blue = memory problems, light blue = concentration problems, green = dyspnoea, red = problems with taste and/or smell. Relationship severity of initial COVID-19 illness (b1, c1) and of age (b2, c2) with anti-SARS-CoV-2 spike and microneutralising (MN) antibody titres at two months (b1-2, c1-2) with severity defined by eight levels, from asymptomatic to succumbed, as detailed in the online methods section. Relationship of antibody titres at two months with number of persistent symptoms and total fatigue score according to the Chalder scale at six months follow-up (b3-4, c3-4); number of symptoms experienced among 13 symptoms listed in Table 2.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplFigure1flowchart.jpg
- SupplTable1fatiguescore.docx
- SupplTable2riskfactorsfatigue.docx