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Research

Patient-reported outcomes of neurologic and neuropsychiatric symptoms in mild COVID-19: a prospective cohort study

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Abstract

Background: Various neurologic manifestations have been reported in patients with COVID-19, mostly in retrospective studies of patients admitted to hospital, but there are few data on patients with mild COVID-19. We examined the frequency and persistence of neurologic/neuropsychiatric symptoms in patients with mild COVID-19 in a 1-year prospective cohort study, as well as assessment of use of health care services and patient-reported outcomes.

Methods: Participants in the Alberta HOPE COVID-19 trial (hydroxychloroquine v. placebo for 5 d), managed as outpatients, were prospectively assessed 3 months and 1 year after their positive test result. They completed detailed neurologic/neuropsychiatric symptom questionnaires, the telephone version of the Montreal Cognitive Assessment (T-MoCA), the Kessler Psychological Distress Scale (K10) and the EuroQol EQ-5D-3L (measure of quality of life). Close informants completed the Mild Behavioural Impairment Checklist (MBI-C) and the Informant Questionnaire on Cognitive Decline in the Elderly. We also tracked use of health care services and neurologic investigations.

Results: The cohort consisted of 198 participants (87 female [43.9%] median age 45 yr, interquartile range 37–54 yr). Of the 179 participants with symptom assessments, 139 (77.6%) reported at least 1 neurologic symptom, the most common being anosmia/dysgeusia (99 [55.3%]), myalgia (76 [42.5%]) and headache (75 [41.9%]). Forty patients (22.3%) reported persistent symptoms at 1 year, including confusion (20 [50.0%]), headache (21 [52.5%]), insomnia (16 [40.0%]) and depression (14 [35.0%]); 27/179 (15.1%) reported no improvement. Body mass index (BMI), a history of asthma and lack of full-time employment were associated with the presence and persistence of neurologic/neuropsychiatric symptoms; female sex was independently associated with both (presence: odds ratio [OR] adjusted for age, race, BMI, history of asthma and neuropsychiatric history 5.04, 95% confidence interval [CI] 1.58 to 16.10). Compared to participants without persistent symptoms, those with persistent symptoms had more hospital admissions and family physician visits, and worse MBI-C scores and less frequent independence for instrumental activities at 1 year (83.8% v. 97.8%, $p = 0.005$). Patients with any or persistent neurologic symptoms had worse psychologic distress (K10 score ≥ 20: adjusted OR 12.1, 95% CI 1.4 to 97.2) and quality of life (median EQ-5D-3L visual analogue scale rating 75 v. 90, $p < 0.001$); 42/84 (50.0%) had a T-MoCA score less than 18 at 3 months, as did 36 (42.9%) at 1 year. Participants who reported memory loss were more likely than those who did not report such symptoms to have informant-reported cognitive-behavioural decline (1-yr MBI-C score ≥ 6.5: adjusted OR 15.0, 95% CI 2.42 to 92.60).

Interpretation: Neurologic/neuropsychiatric symptoms were commonly reported in survivors of mild COVID-19, and they persisted in 1 in 5 patients 1 year later. Symptoms were associated with worse participant- and informant-reported outcomes. **Trial registration:** ClinicalTrials.gov, no. NCT04329611

There is growing appreciation that various neurologic and neuropsychiatric symptoms may be seen in patients with COVID-19.[1] Meta-analyses have shown a range of neurologic symptoms, including headache, myalgia and confusion, and rarer critical manifestations such as stroke and seizures, in one-third of patients admitted to hospital.[2,3] However, a major limitation to the generalizability of such frequency estimates is that published studies have generally included only patients admitted to hospital or those who were critically ill.[2,4] Most patients with COVID-19 do not require hospital admission. The prevalence and spectrum of symptoms among community-dwelling patients with milder COVID-19 may be quite different.

Competing interests: See the end of the article.

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Studies of neurologic/neuropsychiatric symptoms have relied on diagnostic codes in electronic medical records — which may be incomplete or inaccurate — or on the availability of neuroimaging or other neurologic investigations, which may have resulted in underestimation of the frequency of such presentations, even among patients admitted to hospital.[2] Furthermore, the natural history of these symptoms, including their onset relative to that of typical COVID-19 symptoms, and the long-term neuropsychiatric sequelae have been poorly studied.[5] The concept of long COVID-19 has garnered much attention, with some patients reporting persistent neurologic/neuropsychiatric manifestations including headaches, anosmia/dysgeusia, sleep disorders and cognitive impairment.[6] Recent studies have provided retrospective cohort data on symptoms 6 months after the onset of COVID-19,[7,8] but the frequencies and associated phenotypes remain unclear.[6] The extent to which such manifestations may affect the daily functioning, psychologic well-being or quality of life of patients with COVID-19 is unknown. The paucity of evidence limits our ability to counsel patients about potential neuropsychiatric sequelae of mild COVID-19. We examined the frequency and persistence of neurologic/neuropsychiatric symptoms as well as the use of health care services and patient-reported outcomes in patients with mild COVID-19 in a 1-year prospective cohort study.

Methods

Setting and participants

The Alberta Neuro-COVID study was a prospective cohort study recruiting participants from a randomized double-blind placebo-controlled trial, HOPE COVID-19 (ClinicalTrials.gov: NCT04329611), assessing the efficacy and safety of orally administered hydroxychloroquine for preventing severe COVID-19.[9,10] Community-dwelling adults in Alberta, Canada with SARS-CoV-2 infection (confirmed by reverse transcription polymerase chain reaction [RT-PCR] viral ribonucleic acid test) with 1 or more risk factors for severe disease (Appendix 1, Supplementary Table S1, available at www.cmajopen.ca/content/11/4/E696/suppl/DC1) were randomly assigned to receive either orally administered hydroxychloroquine or matching placebo for 5 days. The primary outcomes of hospital admission, mechanical ventilation and death within 30 days did not differ between arms, with only 4 patients being admitted to hospital.[10]

Staff at Alberta Health Services, singularly responsible for testing and reporting SARS-CoV-2 infections to all residents, obtained permission to share contact information with researchers after RT-PCR results were disclosed to infected adults (≥ 18 yr) in Alberta who had received a positive test result within the previous 4 days, whose symptom onset was within the previous 12 days and who were not admitted to hospital. Research coordinators telephoned those who consented to be contacted, discussed the HOPE COVID-19 trial and conducted screening, supported by access to participants' provincial electronic health record and as-needed discussion with study physicians. Screening/enrolment began on Apr. 15, 2020. Recruitment for the trial was halted on May 22, 2020, when a since-retracted publication raised concerns about the safety of hydroxychloroquine for COVID-19, marking the end of recruitment for the cohort study as well.[11] The first 3-month Neuro-COVID study visit was completed on July 15, 2020, and the final 1-year visit on July 7, 2021.

Design and data collection

For the present cohort study, consenting participants with mild COVID-19 — defined as symptomatic, RT-PCR-confirmed infection not requiring hospital admission — were prospectively assessed 3 months and 1 year after their positive test result with the use of a detailed checklist of neurologic symptoms (Appendix 1, Supplementary Table S2), with information gathered on whether each symptom was present at any time since illness onset, estimated symptom onset and whether symptoms were ongoing. Participants completed the telephone version of the Montreal Cognitive Assessment (T-MoCA), a validated test to detect cognitive impairment (optimal cut-off score 18–19).[12,13] To mitigate learning effects, we used telephone components of version 7.1 at 3 months and version 7.2 at 1 year.[14] Participants also completed 2 questionnaires online or by telephone: the Kessler Psychological Distress Scale (K10), used to assess emotional disturbance/anxiety after social upheaval,[15,16] with high scores (typical cut-off score 20) strongly correlated with mood/anxiety disorders;[17] and the EuroQol EQ-5D-3L, a validated quality-of-life measure.[18]

Participants identified a close "informant" to complete the Mild Behavioural Impairment Checklist (MBI-C) and the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), comparing how participants were at 3 months and 1 year after versus before contracting COVID-19. The MBI-C[19,20] identifies new neuropsychiatric symptoms, including amotivation, emotional dysregulation, impulsivity, social inappropriateness and abnormal perception/thought (cut-off score 6.5).[21] The IQCODE detects cognitive decline, including after an acute illness[22] (recommended cut-off score 3.3).[23]

We used province-wide records (Appendix 1, Supplementary Table S3) linked by means of provincial health care numbers to track participants' use of health care services, including hospital admissions, emergency/urgent care and clinic visits, and investigations including blood and cerebrospinal fluid, neuroimaging and electrophysiologic tests. Participants provided informed consent.

Data were managed with REDCap tools hosted at the University of Calgary Clinical Research Unit.

Statistical analysis

As our objectives focused on estimating symptom frequency, we estimated the sample size requirement based on achievable precision. A minimum target of 140 patients would allow us to achieve confidence interval (CI) widths of 10% and 15% for frequencies of 10% and 30%, representing low and high frequency values in the literature.[24–26] We decided a priori to continue enrolling as many consenting patients as possible from among those being screened for the trial.

We reported the frequency of neurologic/neuropsychiatric symptoms at any time since illness onset, persisting at follow-up and with no improvement since onset (operationalized definitions in Appendix 1, Supplementary Table S4) using 3 levels of strictness in defining what constituted such symptoms: endorsement of any checklist symptoms; excluding anosmia and dysgeusia, which may be rhinal/oropharyngeal in origin;[27] and additionally excluding myalgia and headache, which may commonly accompany viral infections.[2] We performed similar analyses using the thresholds for cognitive impairment (T-MoCA, IQCODE), distress (K10) and behavioural impairment (MBI-C).

As secondary analyses, we evaluated the association of neurologic/neuropsychiatric symptoms with use of health care services, independence for instrumental activities of daily living and EQ-5D-3L ratings. We compared proportions using the Fisher exact test for univariable analyses and logistic regressions for multivariable analyses (when ≥ 10 positive outcomes were present). We adjusted models examining the presence or persistence of symptoms for age, sex, race, body mass index (BMI) and asthma, based on published associations with worse COVID-19 outcomes,[28] as well as prior history of neurologic or psychiatric conditions. We converted EQ-5D-3L ratings to Canadian utilities.[29] We compared scale scores and utilities using the Wilcoxon rank-sum test for univariable analyses and quantile regressions for multivariable analyses, adjusted for age, sex, prior neuropsychiatric history and years of formal education.[30] Exploratory analyses included examining associations of the 10 most common strictly defined neurologic symptoms with neuropsychologic test results. We performed the analysis using Stata/MP 16.1 (StataCorp).

Ethics approval

The Conjoint Health Research Ethics Board of the University of Calgary approved the study (REB20-0790).

Results

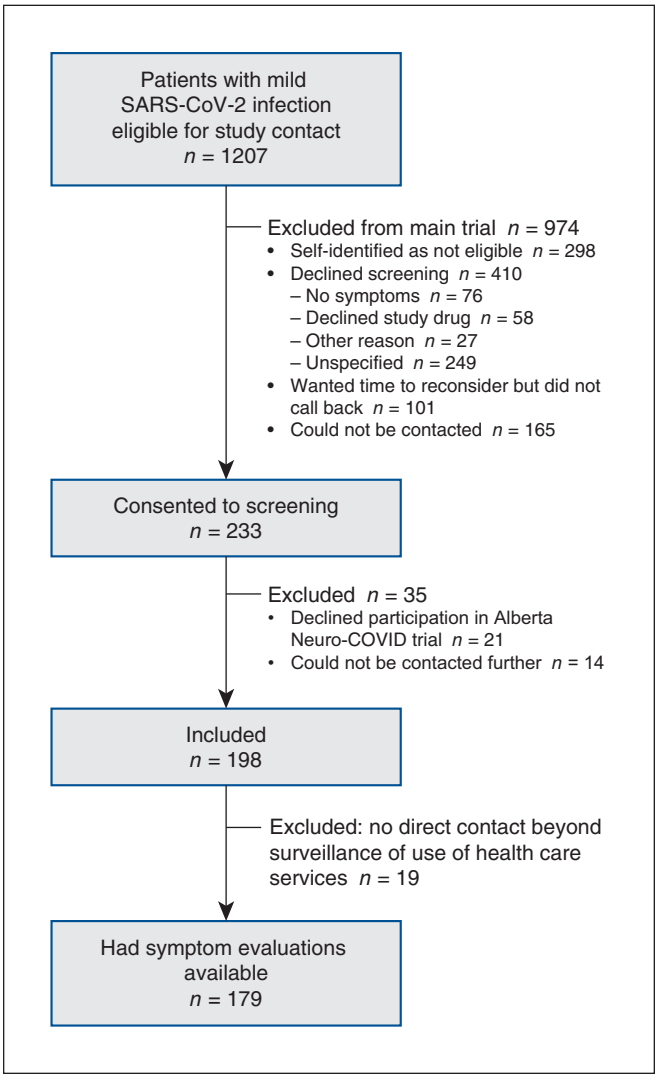

Figure 1: Flow diagram showing patient selection for the Alberta Neuro-COVID study.

Of the 233 patients who were screened for the Neuro-COVID trial, 198 (85.0%) consented to participate in the cohort study (Figure 1), of whom 90 (45.4%) were randomly assigned to the oral hydroxychloroquine arm and 29 (14.6%) to the placebo arm. One-year data from health records were available for all patients, symptom reports for 179 (90.4%), and cognitive testing and patient- and informant-reported outcomes for 126 (63.6%). Of the 198 participants, 87 (43.9%) were female, and 131 (66.2%) were visible minorities (Table 1). Twenty-eight patients (14.1%) had pre-existing neurologic or psychiatric disorders.

Of the 179 patients who underwent neurologic/neuropsychiatric symptom assessment, 139 (77.6%) reported at least 1 symptom (with the most inclusive definition) at any point during follow-up (including 18 with prior neurologic/psychiatric comorbidities); this number declined to 105 (58.7%) when anosmia/dysgeusia was excluded, and to 48 (26.8%) when myalgia and headache were also excluded. The most common symptoms were anosmia/dysgeusia (99 [55.3%]), myalgia (76 [42.5%]), headache (75 [41.9%]), confusion (45 [25.1%]), depression (43 [24.0%]) and insomnia (43 [24.0%]). The median number of symptoms reported increased from 2 (interquartile range [IQR] 1–3) with the most inclusive definition to 3.5 (IQR 1–6) with the strictest definition. With the most inclusive definition, symptoms generally began within the first week (median onset of first symptom at 6 d, IQR 4–8 d; median onset of last symptom at 7 d, IQR 5–10 d) (Figure 2). With the strictest definition, the first symptom generally appeared on the first day of illness (median 1 d, IQR 1–3 d), but the last symptom was often delayed (median 47.5 d, IQR 2–180 d). No concerning neurologic diagnoses were made, and investigations were rare and unremarkable (Appendix 1, Supplementary Tables S5 and S6).

In most cases, symptoms lessened over 1 year (Figure 2). At least 1 new neurologic symptom (compared to before the illness) persisted at 1 year in 40/179 patients (22.3%); when we excluded anosmia/dysgeusia, this declined to 38 patients

Table 1 (part 1 of 2): Baseline characteristics of the participants in the cohort study

Characteristic	No. (%) of participants* *n* = 198
Age, median (IQR), yr	45 (37–54)
Female sex	87 (43.9)
Race/ethnicity	
White	67 (33.8)
Black	20 (10.1)
Asian	85 (42.9)
Hispanic	25 (12.6)
Indigenous	< 5 (< 2.5)
Prior neurologic or psychiatric diagnosis	28 (14.1)
Spinal stenosis and back pain	3 (1.5)
Vertigo	3 (1.5)
Benign brain tumour (pituitary adenoma, schwannoma)	3 (1.5)
Depression and anxiety	1 (0.5)
Epilepsy	2 (1.0)
Parkinson disease	1 (0.5)
Cognitive impairment	1 (0.5)
Dementia	1 (0.5)
Carpal tunnel syndrome	1 (0.5)
Other past medical history (*n* = 148)	
Hypertension	41 (27.7)
Diabetes	29 (19.6)
Asthma	20 (13.5)
Heart failure	3 (2.0)
Chronic lung disease (COPD or interstitial disease)	2 (1.4)
Cancer	2 (1.4)
Chronic kidney disease†	1 (0.7)
Coronary artery disease	1 (0.7)
Cirrhosis	1 (0.7)
Body mass index, median (IQR)	26.7 (23.9–30.6)
Smoking history (*n* = 148)	
Current	21 (14.2)
Past (quit > 1 yr earlier)	42 (28.4)
Never	85 (57.4)
Weekly alcohol use, median standard drinks (IQR)	1 (1–3)
Living situation (*n* = 175)	
Independently secured accommodation	173 (98.9)
With relative or friend	2 (1.1)
Independent for instrumental activities of daily living (*n* = 126)	124 (98.4)
Independent for basic activities of daily living (*n* = 126)	124 (98.4)
Full-time employment before COVID-19 (*n* = 126)	100 (79.4)
Years of full-time education, median (IQR) (*n* = 126)	15 (12–16)
Initial COVID-19 symptoms (nonneurologic) (*n* = 148)	
Cough	112 (75.7)
Malaise	100 (67.6)
Coryza	83 (56.1)
Fever	74 (50.0)
Sore throat	69 (46.6)
Diarrhea	55 (37.2)
Nausea	47 (31.8)
Chest tightness	45 (30.4)
Shortness of breath (dyspnea)	40 (27.0)

Note: COPD = chronic obstructive pulmonary disease, IQR = interquartile range.
*Except where noted otherwise.
†Estimated glomerular filtration rate < 60.

(21.2%), and when we also excluded myalgia and headache, to 37 patients (20.7%). The 40 patients reported a median of 4 (IQR 2.0–7.5) persistent symptoms. Regardless of symptom definition, 27 patients (15.1% of the 179 patients who completed symptom reports and 67.5% of those with persistent symptoms) reported no symptom improvement over follow-up. Among those with persistent symptoms, the most common symptoms at 1 year were headache (21 [52.5%]), confusion (20 [50.0%]) and insomnia (16 [40.0%]) (Appendix 1, Supplementary Figure S1).

On univariable analyses, a higher proportion of female patients than male patients reported neurologic/neuropsychiatric symptoms (73/83 [88.0%] v. 66/96 [68.8%], $p = 0.002$) and persistent symptoms or symptoms without improvement (22 [26.5%] v. 5 [5.2%], $p < 0.001$). A higher proportion of patients without full-time employment before contracting COVID-19, with a history of neuropsychiatric conditions or asthma, and with a higher BMI reported persistent symptoms or no improvement at 1 year. Eight (40.0%) of the 20 patients with a history of asthma reported persistent symptoms, compared to 15 (11.7%) of the 128 without ($p = 0.004$). For BMI, the odds ratio (OR) per 1-point increase was 1.08 (95% CI 1.03 to 1.14).

On multivariable logistic regressions adjusted for age, sex, race, BMI, history of asthma and neuropsychiatric history, female sex remained associated with the presence and persistence of symptoms (adjusted OR 5.04, 95% CI 1.58 to 16.10) and with the absence of improvement at 1 year (adjusted OR 5.42, 95% CI 1.25 to 23.40). Results were similar stricter symptom definitions. No treatment effect was observed for hydroxychloroquine for these symptoms (Appendix 1, Supplementary Table S7).

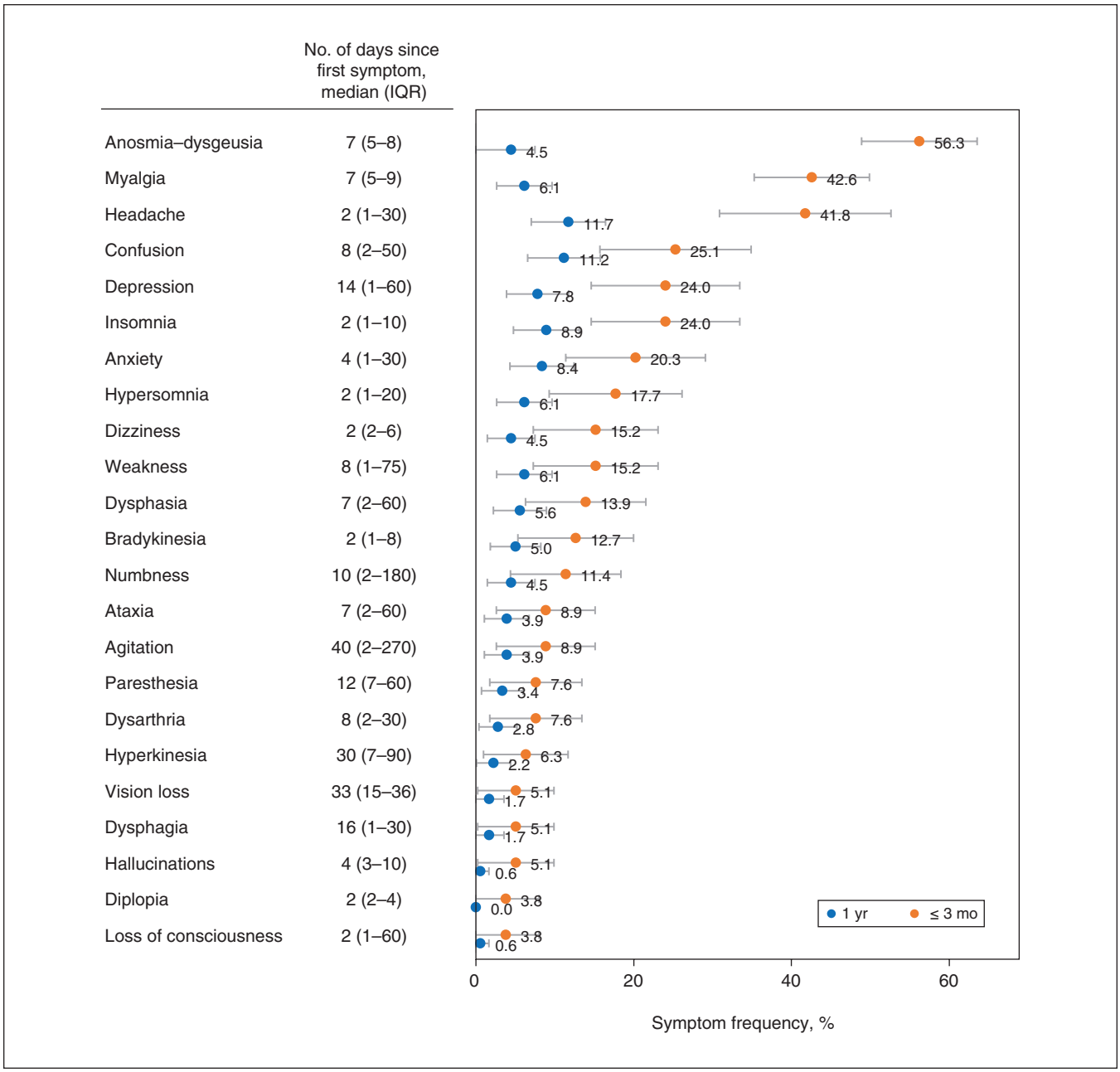

Figure 2: Frequency of new neurologic and neuropsychiatric symptoms reported since the onset of mild COVID-19 at 3-month and 1-year follow-up assessments, and median number of days since the first symptom of COVID-19. The denominator is all patients in the cohort with completed symptom assessments. Whiskers represent 95% confidence intervals. Note: IQR = interquartile range.

Comparisons of key characteristics for patients with cognitive, or patient- or informant-reported outcome data and those with missing data are shown in Appendix 1, Supplementary Table S8; data were available for most patients (40 [83.3%]) with strictly defined neurologic/neuropsychiatric symptoms. Scores on the T-MoCA did not differ between patients with symptoms and those without (Table 2). Half of patients (42/84 [50.0%]) had a T-MoCA score less than 18 at 3 months, as did 36 (42.9%) at 1 year. Females were less likely than males to have a T-MoCA score less than 18 (1 yr: OR 0.38, 95% CI 0.16 to 0.95), as were more educated patients compared to less educated patients (OR per additional year 0.84, 95% CI 0.71 to 0.96). Patients with neurologic/neuropsychiatric symptoms had worse 1-year K10 scores than those without such symptoms (K10 score ≥ 20: OR adjusted for age, sex, education, history 12.1, 95% CI 1.4 to 97.2); results were similar with stricter symptom definitions and among those with persistent symptoms (Appendix 1, Supplementary Table S9). Patients without symptom improvement were more likely than those with symptom improvement to have mild behavioural impairment (e.g., MBI-C score ≥ 6.5 at 1 yr; adjusted OR 18.2, 95% CI 3.38 to 98.60).

Table 2: Median neuropsychiatric test scores, self-reported quality-of-life scores and use of health care services 3 months and 1 year after the onset of mild COVID-19 for patients with and without neurologic/neuropsychiatric symptoms at 3 months*†

	3 mo; median (IQR)			1 yr; median (IQR)		
Test	Any neurologic/ neuropsychiatric symptoms at 3 mo *n* = 40	No neurologic/ neuropsychiatric symptoms at 3 mo *n* = 86	*p* value	Any neurologic/ neuropsychiatric symptoms at 3 mo *n* = 40	No neurologic/ neuropsychiatric symptoms at 3 mo *n* = 86	*p* value
T-MoCA‡	18.0 (16.0–19.0)	17.0 (14.0–19.5)	0.06	18.0 (16.0–20.0)	18.0 (15.0–19.5)	0.3
K10§	20.5 (14.5–23.5)	11.0 (10.0–13.0)	< 0.001	20.5 (12.5–24.0)	11.0 (10.0–13.0)	< 0.001
MBI-C§	3 (0–13)	0 (0–1)	0.02	5 (0–13)	0 (0–1)	0.03
IQCODE§	3.0 (3.0–3.1)	3.0 (3.0–3.0)	0.2	3.0 (3.0–3.1)	3.0 (3.0–3.0)	0.6
EuroQol EQ-5D-3L						
Visual analogue scale‡	70.0 (50.0–78.0)	87.5 (80.0–99.5)	< 0.001	75.0 (60.0–80.0)	90.0 (75.0–98.5)	< 0.001
Mobility§	1.0 (1.0–1.5)	1.0 (1.0–1.0)	0.1	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.3
Self-care§	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.2
Usual activities§	1.0 (1.0–2.0)	1.0 (1.0–1.0)	0.004	1.0 (1.0–1.5)	1.0 (1.0–1.0)	0.02
Pain§	2.0 (1.0–2.0)	1.0 (1.0–2.0)	0.06	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.3
Anxiety§	1.5 (1.0–2.0)	1.0 (1.0–1.0)	< 0.001	2.0 (1.0–2.0)	1.0 (1.0–1.0)	< 0.001
Overall utility§	0.83 (0.77–0.85)	1.00 (0.83–1.00)	< 0.001	0.84 (0.80–1.00)	1.00 (0.83–1.00)	0.006
Hospital or emergency visits	0.5 (0.0–1.0)	0.0	0.04	0.5 (0.0–1.0)	0.0	0.02
Primary care visits	3.5 (1.0–6.0)	1.0 (0.5–2.0)	0.01	3.5 (1.0–5.0)	1.0 (1.0–2.0)	0.02

Note: IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly, IQR = interquartile range, K10 = Kessler Psychological Distress Scale, MBI-C = Mild Behavioural Impairment Checklist, T-MoCA = telephone version of the Montreal Cognitive Assessment.
*Using our strictest definition of symptoms (i.e., excluding anosmia, dysgeusia, myalgia and headache).
†Of the 48 patients who reported neurologic/neuropsychiatric symptoms at 3 months, 40 had data available for the outcomes presented in this table.
‡Lower scores are worse.
§Higher scores are worse.

Patients who reported confusion or memory loss were more likely than those who did not report such symptoms to have informant-reported cognitive decline (IQCODE score > 3.3: 15.0% v. 2.4%, p = 0.02), an MBI-C score of 6.5 or higher (1 yr: adjusted OR 15.0, 95% CI 2.42 to 92.60) and a K10 score of 20 or higher (1 yr: adjusted OR 6.47, 95% CI 1.04 to 40.20). Similar results were seen for patients who reported depression, speech/language difficulties, numbness/paresthesia or dizziness. The adjusted OR for a 1-year T-MoCA score less than 18 for patients who reported depression versus those who did not was 4.56 (95% CI 1.23 to 16.90); for an MBI-C score of 6.5 or higher, it was 6.32 (95% CI 1.39 to 28.80).

Whereas 124/126 patients (98.4%) had been independent for instrumental activities of daily living before contracting COVID-19, 21/27 patients (77.8%) without improvement in neurologic/neuropsychiatric symptoms remained independent at 1 year, compared to 54/55 (98.2%) of the remaining patients (OR adjusted for age, sex and neuropsychiatric history 0.06, 95% CI 0.01 to 0.58). Similarly, a smaller proportion of patients with persistent symptoms than of those without persistent symptoms were independent for instrumental activities of daily living at 1 year (with strictest definition: 32/38 [84.2%] v. 43/44 [97.7%], adjusted OR 0.11, 95% CI 0.01 to 0.97). In addition, patients with persistent symptoms had more hospital admissions and family physician visits than those without persistent symptoms (3.0 additional visits, 95% CI 1.0 to 5.0) (Table 2). Patients with any or persistent symptoms had worse quality-of-life ratings and utility scores at 3 months and at 1 year than those without neurologic/neuropsychiatric symptoms (Table 2, Figure 3). For example, utilities at 1 year for patients with strictly defined symptoms were 0.16 points lower than those for patients without (adjusted difference –0.16, 95% CI –0.25 to –0.06). Compared to patients without neurologic/neuropsychiatric symptoms, patients with such symptoms had worse EQ-5D-3L ratings for usual activities and anxiety/depression at both 3 months and 1 year, and for pain/discomfort at 3 months. Patients with any or persistent symptoms or symptoms without improvement had worse EQ-5D-3L visual analogue scale ratings than patients without neurologic/neuropsychiatric symptoms (Figure 3).

Interpretation

In this prospective cohort of patients with proven mild COVID-19, neurologic/neuropsychiatric symptoms were common, with more than 75% of patients reporting symptoms at some point. Our data help clarify the natural history

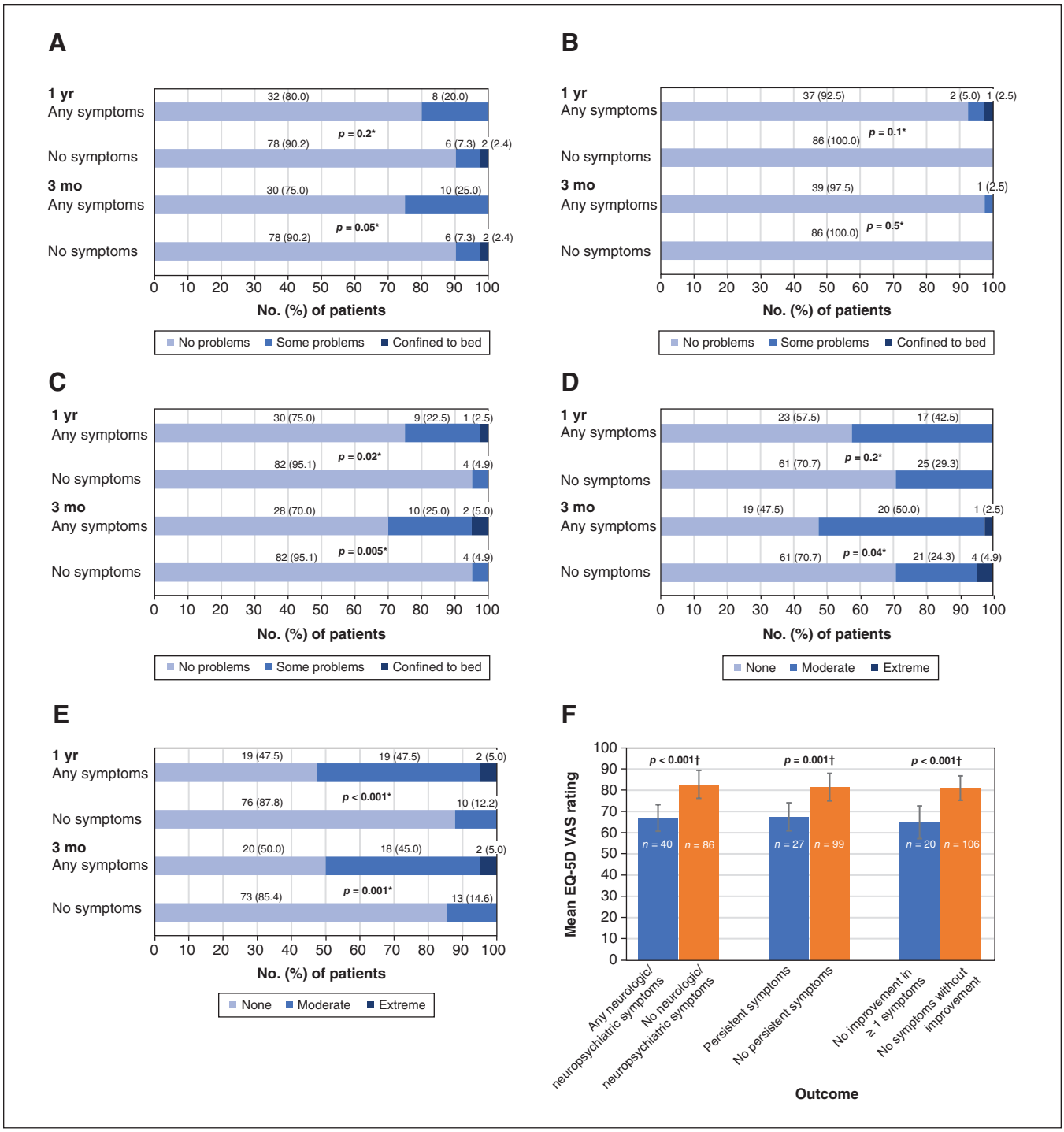

Figure 3: Patients' self-rated health state on the 3-level version of the EuroQol EQ-5D (EQ-5D-3L) for patients with versus without any strictly defined neurologic or neuropsychiatric symptoms (as determined at the 3-mo assessment) at follow-up assessments 3 months and 1 year after the onset of COVID-19: (A) mobility, (B) self-care, (C) usual activities, (D) pain/discomfort and (E) anxiety/depression. (F) Patients' mean self-rated health on the EQ-5D VAS (visual analogue scale), which ranges from 0 ("Best imaginable health state") to 100 ("Worst imaginable health state) for patients with versus without any or persistent symptoms or symptoms lacking improvement at 1 year. Whiskers represent 95% confidence intervals. *Fisher exact test, †Wilcoxon rank-sum test.

of mild COVID-19, with most patients (67%) experiencing symptom onset within the first week of illness, 85% having symptom improvement, and 78% having no symptoms remaining at 1 year. Risk factors for reporting symptoms included female sex, neuropsychiatric history, history of asthma and high BMI. Our results also shed light on neuropsychiatric symptom clusters in long COVID. Among the 22% of patients with persistent neuropsychiatric symptoms at

1 year (who were encouraged by the researchers to seek medical attention for their symptoms through their family physician), the most common symptoms were headache, confusion, insomnia, anxiety and depression.

Our findings also highlight the long-term neuropsychiatric, health economic (quality of life, use of health care services) and patient-reported outcomes after mild COVID-19, and their modification by neurologic/neuropsychiatric symptoms. Patients with persistent neurologic/neuropsychiatric symptoms in our cohort had worse quality-of-life ratings, and more hospital admissions and family physician visits than those without such symptoms. The frequency of neurologic/neuropsychiatric symptoms in our sample was higher than prior estimates from 59 studies of patients with COVID-19 admitted to hospital, 32%–36%.[2,3] As such studies generally rely on administrative coding or health records, they likely underestimate symptom burden. When we excluded anosmia/dysgeusia, myalgia and headache — often seen with viral infections (but included in prior meta-analyses) — symptom frequency remained high, at 26.8%. Our observed frequency of anosmia/dysgeusia, 56.1%, is in keeping with that reported in a meta-analysis of 26 studies, 56%.[2] Symptom distribution in our participants was similar to that reported in a meta-analysis of patients who were mostly admitted to hospital.[3]

The course of symptom improvement in our cohort was better than the trajectories observed in a prospective cohort of 242 patients with COVID-19 admitted to hospital, in which improvements in neuropsychiatric outcomes occurred in around half of patients by 6–12 months.[5] Our observed frequency of persistent symptoms, 22.3%, is comparable to that observed for neuropsychiatric complaints, 15%, in a meta-analysis of long-term symptoms that included survivors of prior coronavirus outbreaks such as SARS and Middle East Respiratory Syndrome.[31]

Half of our participants had an abnormal T-MoCA score; this is in keeping with the frequency of 50% observed in a cohort of patients admitted to hospital in New York City followed for 6–12 months.[5] Our findings also agree with a US study of 57 patients who received rehabilitation after hospital admission for COVID-19, in which more than one-half had cognitive deficits,[32] and with a UK study of 518 patients with self-reported COVID-19 (without in-study confirmation), who scored lower on the Great British Intelligence Test than thousands of control participants.[33] In contrast, in a study of 1438 COVID-19 survivors in Wuhan that also used phone-based testing, Liu and colleagues[34] reported impaired cognition in only 12.5% of participants at 1 year. Whereas prior cohorts identified distress among survivors of severe COVID-19,[35] we found that the presence or persistence of neurologic symptoms after mild COVID-19 was associated with a higher frequency of distress and behavioural impairment, greater use of health care services and worse quality of life.

An important knowledge gap is the paucity of positive control population data with which to compare our findings. Patients with other infections such as influenza or bacterial illnesses treated as outpatients may experience nonspecific long-term symptoms similar to those reported by patients with mild COVID-19. Symptoms such as headache, confusion, insomnia, anxiety and depression are classified as neurologic/neuropsychiatric but may be associated with multiple other conditions. The delayed onset of some symptoms (e.g., agitation) beyond 30 days may be unrelated to COVID-19. We emphasize the need for thoughtful interpretation of our reported associations and for more comparative study of postinfection symptoms. Initial data have been provided by 2 cohort studies from China and South Korea, which showed that 1.1%–9.2% of control patients with respiratory infections other than COVID-19 reported various neuropsychiatric symptoms, compared to 4.9%–28.3% of patients with COVID-19.[36,37] Future studies should include a comparison group of age- and sex-matched people with no COVID-19 infection at the index time point. Future work should also examine whether these symptoms/sequelae can be mitigated by vaccination or COVID-19 treatments.

Limitations

As we relied on participants' responses, we cannot comment on underlying mechanisms of symptoms, including their organic nature. However, our finding that these symptoms corresponded to relevant outcomes helps validate their importance. Although our participants did not undergo in-person examinations or testing beyond standard care, our use of Web- and telephone-based assessments permitted follow-up without risking disease transmission and minimized loss to follow-up. The sampling of patients from a small population who consented to being screened for a trial may have resulted in selection bias; however, our sample was diverse in age (range 20–80 yr), sex, race and comorbidities. Although the recruitment rate of our cohort exceeded that of the main trial, the completion rate means that our sample may not be sufficiently representative to permit estimation of symptom prevalence. The direction of bias is uncertain, as those who did not complete symptom screening may have been sicker, or they may not have been affected enough to be engaged. Some symptoms reported may have been modified by use of treatment or placebo in some participants. The small number of events for some symptoms means that the logistic regression models with 4 covariates may have been somewhat overfitted and may have increased the width of our CIs. We did not additionally adjust for number or presence of nonneurologic/psychiatric comorbidities, which may have increased the rate of nonspecific symptoms. In the subset of participants with prior neurologic/psychiatric disorders, it is difficult to know whether newly reported symptoms (in 18/28) were related to COVID-19 or to these comorbidities. Finally, because our participants were recruited before variants of interest emerged and before availability of COVID-19 vaccines, the generalizability of our findings to current variants and vaccination statuses is unclear. In addition, we do not know how many participants were reinfected, as PCR testing was not repeated routinely.

Conclusion

Neurologic and neuropsychiatric symptoms were commonly reported in survivors of mild COVID-19 and persisted in 1 in 5 patients 1 year after illness onset. These symptoms were associated with worse patient- and informant-reported outcomes and greater use of health care services. We hope that our findings will motivate concerted efforts to help mitigate and address sequelae of COVID-19, including preventive tools such as vaccination, COVID-19-specific treatments and outpatient supports.

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Competing interests: Aravind Ganesh reports membership on the editorial boards of *Neurology*, *Stroke* and *Neurology Clinical Practice*; consulting fees and honoraria from Atheneum, MD Analytics, Figure 1, MyMedicalPanel, Creative Research Designs, CTC Communications Corp, Alexion and Biogen; research support from Alberta Innovates, Campus Alberta Neuroscience, the Canadian Cardiovascular Society, the University of Calgary (Hotchkiss Brain Institute), the Sunnybrook Research Institute INOVAIT program and the Canadian Institutes of Health Research (CIHR), outside the submitted work; and stock/stock options from SnapDx and Let's Get Proof. He has a patent application (US 17/317,771) for a system for prehospital patient monitoring/assessment and delivery of remote ischemic conditioning or other cuff-based therapies. Ryan Rosentreter reports the same patent application (US 17/317,771). Luanne Metz reports grant funding from the MS Society of Canada, outside the submitted work. Eric Smith reports grant funding from the CIHR, Brain Canada and the Weston Brain Institute, outside the submitted work; consulting fees from Bayer, Biogen and Javelin Technologies; royalties from UpToDate; and payment from the American Heart Association for work as associate editor of *Stroke*. Michael Hill is a director of the Canadian Neurological Sciences Federation and the Canadian Stroke Consortium. He reports consulting fees from BrainsGate; industry grant support to the University of Calgary from NoNO, Biogen, Medtronic and Boehringer-Ingelheim Canada; and public grant support to the University of Calgary from Alberta Innovates, CIHR, the Heart & Stroke Foundation of Canada, and the National Institute of Neurological Disorders and Stroke. He reports a patent to US Patent office (US 62/086,077) issued and licensed. He owns stock in PureWeb. No other competing interests were declared.

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Contributors: Aravind Ganesh conceived and designed the study, with contributions from Luanne Metz, Eric Smith and Michael Hill. Aravind Ganesh oversaw data collection, with contributions from Ryan Rosentreter, Yushi Chen, Rahul Mehta, Graham McLeod, Miranda Wan, Jonathan Krett, Yasamin Mahjoub, Angela Lee, Ilan Schwartz, Lawrence Richer, Luanne Metz, Eric Smith and Michael Hill. Aravind Ganesh analyzed and interpreted the data, and drafted the manuscript. Ryan Rosentreter, Yushi Chen, Rahul Mehta, Graham McLeod, Miranda Wan, Jonathan Krett, Yasamin Mahjoub, Angela Lee, Ilan Schwartz, Lawrence Richer, Luanne Metz, Eric Smith and Michael Hill revised the manuscript critically for important intellectual content. All of the authors approved the final version to be published and agreed to act as guarantors of the work.

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