Appendix 1: Supplementary material

Supplementary Table S1 – Risk factors for severe COVID-19 as defined in the ALBERTA HOPE COVID-19 trial. Participants in the trial had to have ≥1 of these risk factors.

Medications and Biologic Therapies
Prednisone ≥7.5 mg daily x 3 weeks (or equivalent)
Methotrexate (Greater than or equal to 7.5 -15 mg weekly suggested)
Azathioprine
Cyclophosphamide within the previous 6 months
Mitoxantrone
Cell depleting therapy within the previous 24 months: cladribine
Anti-TNF: infliximab, adalimumab, golimumab, etanercept, certolizumab
Anti-IL17: secukinumab, ixekizumab, brodalumab
mTOR inhibitors: sirolimus, everolimus
Mycophenolate mofetil: mycophenolic acid
Anti-IL12/23: Ustekinumab, risankizumab, guselkumab
Anti-CD28: abatacept
JAK2 inhibitors: tofacitinib, baricitinib, upadacitinib
Anti-CD20: rituximab, ocrelizumab within the previous 12 months
S1P inhibitors: fingolimod
Anti-alpha4beta7: vedolozimab
Anti-IL4: dupilumab
Anti-IgE FcR: omalizumab
Medical Conditions and Other Risk Factors
Age 40 or over
BMI >40 (calculated by self-report height and weight)
Hypertension (on medical treatment)
Current cigarette smoker
Bone Marrow Transplant within previous 12 months
Solid Organ Transplant
AIDS/HIV CD4 <200 within last 6 months or CD4>200 but not on treatment
Moderate Lymphopenia (within previous 6 months: Adults <500)
Chronic Kidney Disease (eGFR < 60 including people on dialysis)
Diabetes (on a hypoglycemic or insulin)
Coronary Artery Disease (non-revascularized and as per physician diagnosis in medical chart)
Heart Failure/Reduced LVEF (as per physician diagnosis in medical chart)
Chronic Lung Disease (COPD, Asthma, interstitial lung disease, as per physician diagnosis)
Any Current Cancer diagnosis (as per physician diagnosis)
Acquired or Congenital Immune Deficiency (as per physician diagnosis in medical chart)
Cirrhosis (normal INR and bilirubin and no history of ascites, encephalopathy, or variceal bleeding as per history and medical chart)
Homelessness

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Supplementary Table S2. Neurological Manifestations Checklist completed by the study assessors as part of a detailed interview with the patient.

Please ask the patient (or the carer/informant): **While you (the patient) were experiencing symptoms of COVID-19 or since then, have you experienced any of the following symptoms, <u>not present in the months before COVID-19?</u>**	At any time since onset of Illness (Y/N)	Estimated day of onset in relation to first COVID symptom ("day 1")*	Still Present? 1. Yes, this problem remains the same 2. Yes, but there's been some improvement 3. No, this is back to normal
Confusion or memory problems			
Difficulty with language (exceptional difficulty finding the right words, understanding other people, reading/writing)			
Hallucinations (seeing, hearing, or otherwise experiencing things others cannot): *may not have insight*			
Agitation or aggression			
Depression			
Anxiety			
Difficulty falling or staying asleep			
Sleeping excessively			
Difficulty speaking – articulating words (outside of being intubated or shortly after extubation)			
Difficulty swallowing (outside of being intubated or shortly after extubation)			
Loss of consciousness (outside of being intubated for difficulty breathing)			
If yes, specify if transient (few minutes maximum) or prolonged			
If yes, specify if occurred once or recurrent			
Seizures or fits			
If yes, specify if received seizure medication			
New diagnosis of Stroke			
Weakness of your face, arms, or legs			

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If yes, specify affected body part(s)			
Difficulty with coordination or feeling clumsy			
Slowness of movements (e.g. walking, getting out of bed)			
Abnormal movements (tremors, jerks)			
Loss of smell			
Loss of taste			
Vision loss – being unable to see part of the world			
If yes, specify if it is unilateral/hemifield			
Double vision			
Headaches			
Dizziness			
Numbness (loss of sensation)			
If yes, specify affected body part(s)			
Burning or pins-and-needles sensations			
If yes, specify affected body part(s)			
Muscle aches/pains			
Other comments/details:			

* If this was their first symptom, then list day of onset as day 1.

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Supplementary Table S3. List of province-wide health records used in the study

Name	Description
Alberta Netcare, Connect Care	Encompasses all hospitalizations, diagnostic test results and outpatient pharmacy prescriptions, captured through provincial heathcare number (PHN) linkage. The NeuroCOVID study had secondary use access to the data extracted from Netcare as part of the main HOPE trial. Beyond the trial period, further health records followup for 1-year was accomplished through Connect Care, which the province transitioned to as a one-stop health record, and contains the same information, as well as emergency/urgent-care and clinic consultation notes and hospital discharge summaries.
Discharge Abstract Database	Used to capture hospitalizations for participants following their positive SARS-CoV-2 test, using PHN linkage.
National Ambulatory Care Reporting System (Alberta)	Captures ambulatory care visits for participants through PHN linkage.

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Supplementary Table S4. Operationalized definitions for the presence, persistence, and absence of improvement in neurological/neuropsychiatric symptoms in the Alberta Neuro-COVID study.

Symptom-related outcome	Operationalized definition (with example)
Presence of symptom(s)	The patient reported ≥1 symptom that emerged with or after their COVID-19 infection at some point prior to the time of assessment. E.g. if at their 3-month visit, the patient reported new issues with confusion that emerged two days after onset of their COVID-19 illness, then they would be considered to have had "presence" of symptoms at some point of their illness course.
Persistence of symptom(s)	The patient reported ≥1 symptom that emerged post-COVID-19 and was still present at the time of assessment. E.g. if the patient reported new issues with confusion that was still present at the time of their 3-month visit, they would be considered to have "persistent symptoms" at that visit.
No improvement of symptom(s)	When a patient reported a symptom, they were asked whether they were still experiencing that symptom, and to choose between these three options when comparing the symptom to their pre-COVID-19 state: (1) "Yes, this problem remains the same"; (2) "Yes, but there's been SOME improvement"; or (3) "No, this is back to normal". The patient was classified as having "no improvement" at 1-year if they reported ≥1 symptom at both visits, for which they indicated that the problem remained the same at 1-year. E.g. if the patient reported new confusion at 3-months, which was still present at 1-year, with them indicating "Yes, this problem remains the same" at the 1-year visit, they were classified as having no improvement at 1-year for our analysis.

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Supplementary Table S5. Comments on neurological symptoms or presentations of interest as abstracted from study visit notes. The frequencies of all symptoms are reported in Figure 2.

Symptom or Presentation	Comment
Stroke	None of the patients were diagnosed with stroke
Encephalitis	None were diagnosed with encephalitis or meningitis
Seizure or epilepsy	Only one patient reported a seizure-like episode, but this patient had a long-standing history of schizophrenia and their spell was not deemed to require treatment with anti-epileptic drugs on review by their primary physician.
Loss of Consciousness	Any episodes of loss of consciousness reported were transient (few minutes maximum); however, they recurred at least once.
Vision Loss	Vision loss complaints were described as monocular or bilateral partial blurring rather than any frank loss of vision.
Weakness and sensory loss	Complaints of weakness and sensory symptoms were generally diffuse or bilateral. For example, among five patients reporting leg weakness, all reported bilateral leg weakness, and of nine patients reporting arm/hand weakness, five reported bilateral weakness. Of five patients reporting hand numbness or paresthesia, four reported bilateral symptoms.

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Supplementary Table S6. Summary of neurologically relevant investigations received by the patients as part of their regular care during the follow-up period.

Neurological investigation	Comment
Neuroimaging – CT	• 10 patients (5.1%) underwent CT head imaging (2 CT with CT angiography, 8 non-contrast CT): 7 for headaches (one with neck pain), one for delirium, one for psychosis, and one for a frontal sinus mass • Two of these were performed within a week of illness, and the rest between 3-month and 1-year follow-ups and were associated with emergency department visits.
Neuroimaging – MRI	• Three of the patients above subsequently had MRI brain, whereas three had repeat non-contrast CT(all for headaches). • Six other patients also had MRI brain scans – four to follow benign tumours, one for small vessel disease.
Lumbar Puncture	None of the patients underwent lumbar puncture over 1-year follow-up
Electrophysiological tests	None of the patients underwent electroencephalography, nerve conduction study, or electromyography over 1-year follow-up

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Supplementary Table S7. Comparison of neurological/neuropsychiatric symptoms reported by patients in the cohort, stratified by whether or not they received hydroxychloroquine.

Neurological and/or neuropsychiatric symptoms	**Hydroxychloroquine** (n=90), N (%)	**No hydroxychloroquine** (n=89), N (%)	**P-value**	**aOR (95%CI)**
Any symptoms	67 (74.4)	72 (80.9)	0.37	0.81 (0.35-1.83)
Persistence of ≥1 symptom at 1-year	16 (17.8)	24 (27.0)	0.16	0.86 (0.26-2.84)
No improvement in ≥1 symptom at 1-year	10 (11.1)	17 (19.1)	0.15	0.63 (0.18-2.28)

P-values shown are from Fisher's exact test for comparison of proportions. Odds ratios presented are from logistic regressions adjusted for age, sex, race, body mass index (BMI), asthma, and prior history of any neurological/psychiatric conditions.

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Supplementary Table S8. Comparison of key variables between patients with available cognitive or patient/informant-reported outcome data versus those with missing data in the Alberta Neuro-COVID cohort.

Characteristic	**Patients with data** (n=126)	**Patients without data** (n=72)	**P-value**
Age	47 (40-54)	45 (35-55)	0.29
Sex – female	61 (48.4)	26 (36.1)	0.10
Treatment assignment	56 (44.4)	34 (47.2)	0.77
Prior neurological/psychiatric history	21 (16.7)	7 (9.7)	0.14
Presence of any neurological/psychiatric symptoms	89 (70.6)	50 (69.4)	0.87
Presence of strictly-defined symptoms (excluding anosmia, dysgeusia, headache, myalgia)	40 (31.7)	8 (11.1)	0.001*

P-values shown are from Fisher's exact test for comparison of proportions and from the Wilcoxon rank-sum for comparison of continuous data. Significant differences at $p<0.05$ are indicated with an asterisk (*).

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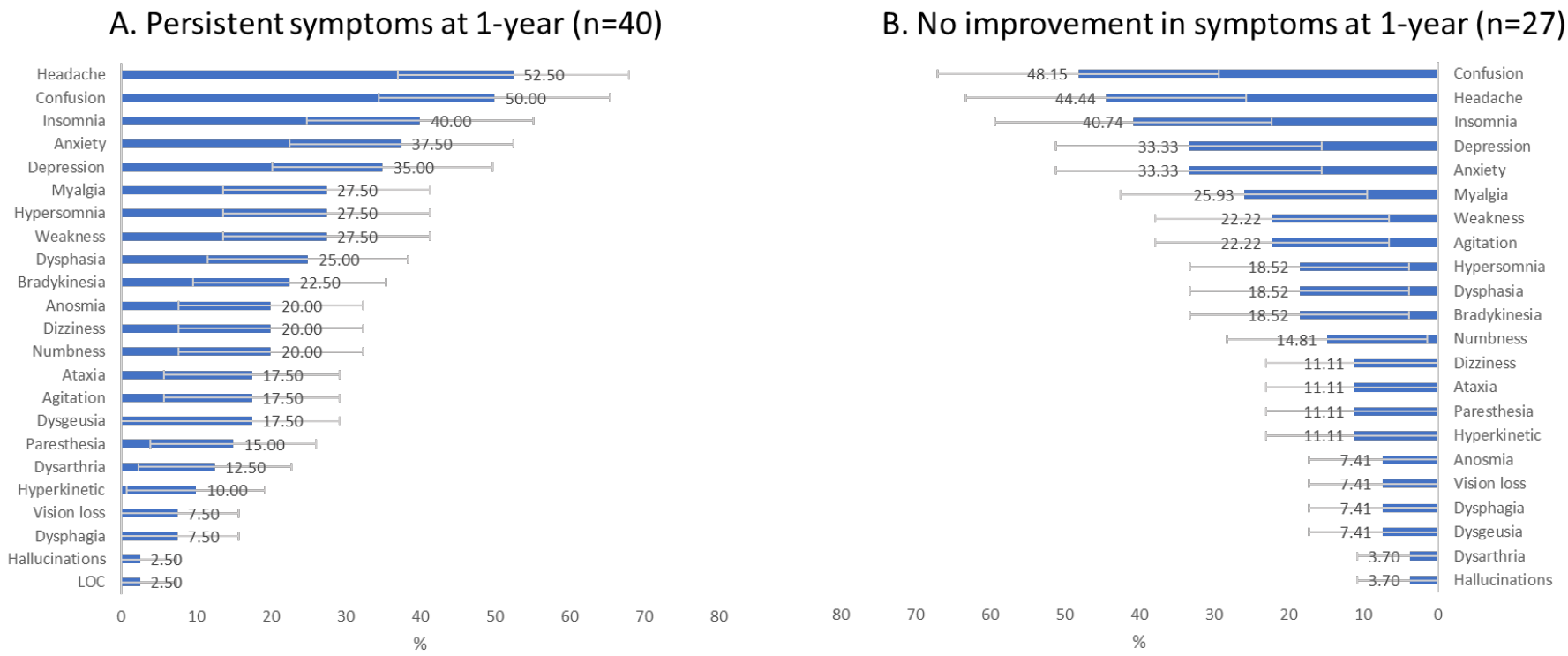
Supplementary Table S9. Unadjusted and adjusted odds ratios from logistic regressions for neuropsychological and functional outcomes at 1-year (n=126).

	T-MoCA score <18		K10 score ≥20		MBI-C score ≥6.5		Independent for IADLs	
Independent variable	**OR (95%CI)**	**aOR (95%CI)**	**OR (95%CI)**	**aOR (95%CI)**	**OR (95%CI)**	**aOR (95%CI)**	**OR (95%CI)**	**aOR (95%CI)**
Any neurological symptoms	2.05 (0.65-6.48)	1.03 (0.17-6.0)	12.5 (1.6-99.4)	12.1 (1.4-97.2)	None without symptoms had MBI+		None without symptoms were dependent	
Strictly-defined symptoms Excluding anosmia/ dysgeusia/myalgia/headache	1.62 (0.62-4.2)	2.15 (0.48-9.6)	21.6 (4.6-102)	17.3 (1.7-78)	11.8 (1.4-98.6)	9.2 (0.6-16.1)	0.15(0.02-1.27)	0.13 (0.01-1.25)
Persistent neurological symptoms	0.72 (0.29-1.8)	0.79 (0.18-3.6)	21.6 (4.6-102)	16.9 (1.7-68)	19.5 (2.3-64)	9.4 (0.6-15.8)	0.12 (0.01-1.02)	0.11 (0.01-0.97)
No improvement in symptoms	0.45 (0.16-1.3)	0.82 (0.18-3.9)	19.6 (5.8-66.3)	29.3 (4.2-85)	14.7 (3.3-65.3)	18.3 (3.4-98.4)	0.06 (0.01-0.57)	0.06 (0.01-0.58)
Female sex	0.38 (0.16-0.95)	0.37 (0.10-1.4)	2.5 (0.85-7.2)	6.5 (1.0-40.3)	2.0 (0.57.3)	1.4 (0.18-10.6)	0.54 (0.10-3.0)	0.55 (0.11-3.2)
Years of education	0.84 (0.71-0.96)	0.95 (0.76-1.2)	0.94 (0.80-1.1)	0.85 (0.65-1.1)	0.89 (0.71-1.1)	0.91 (0.60-1.4)	1.2 (0.88-1.6)	1.5 (0.79-2.8)
Confusion	1.7 (0.53-5.2)	1.8 (0.56-5.9)	13.3 (3.8-46.6)	6.3 (1.4-28.8)	14.2 (2.9-69.6)	15.0 (2.4-92.6)	0.14 (0.02-0.85)	0.09 (0.01-0.74)
Depression	2.8 (0.90-8.6)	4.6 (1.2-16.9)	16.1 (4.5-57.2)	13.9 (3.8-51.5)	6.0 (1.5-24.6)	6.3 (1.4-28.8)	0.05 (0.01-0.49)	0.05 (0.005-0.52)
Insomnia	0.60 (0.17-2.1)	0.74 (0.19-2.8)	3.9 (1.3-11.7)	3.2 (0.96-10.8)	8.7 (2.1-35.4)	9.5 (2.1-43.3)	0.31 (0.06-1.7)	0.28 (0.04-1.9)
Anxiety	1.5 (0.44-4.8)	2.1 (0.57-8.0)	14.1 (3.8-52.9)	12.1 (3.0-48.4)	2.7 (0.7-10.9)	2.6 (0.59-11.7)	0.04 (0.004-0.37)	0.04 (0.004-0.42)
Hypersomnia	0.97 (0.26-3.6)	1.2 (0.31-4.9)	4.3 (1.3-14.5)	3.3 (0.91-11.9)	2.7 (0.7-10.9)	2.5 (0.59-10.7)	0.20 (0.03-1.1)	0.20 (0.03-1.26)
Dizziness	0.79 (0.19-3.4)	1.0 (0.22-4.7)	20.4 (3.9-86)	18.1 (3.3-81)	8.0 (1.6-39.1)	9.6 (1.5-61.9)	0.02 (0.002-0.23)	0.03 (0.002-0.28)
Weakness	0.38 (0.07-1.9)	0.36 (0.07-2.0)	4.3 (1.2-15.6)	4.8 (1.2-20.3)	4.3 (1.0-19.5)	4.9 (0.82-28.8)	0.16 (0.03-0.89)	0.21 (0.03-1.47)
Speech/language issues	1.1 (0.2-5.0)	1.7 (0.32-9.5)	5.5 (1.4-21.3)	4.2 (1.0-18.1)	4.3 (1.0-19.5)	5.0 (1.0-27.9)	0.13 (0.02-0.79)	0.14 (0.02-0.98)
Bradykinesia	3.3 (0.8-14.1)	5.2 (1.0-25.8)	34.6 (4.0-98)	31.1 (3.4-86)	9.2 (1.5-55.3)	10.7 (1.5-74.8)	0.12 (0.02-0.69)	0.10 (0.01-0.76)
Numbness/paresthesia	2.5 (0.6-11.2)	2.9 (0.58-14.9)	28.6 (3.3-48)	49.8 (4.3-82)	9.2 (1.5-55.3)	8.1 (1.3-51.9)	0.23 (0.04-1.51)	0.30 (0.04-2.11)

Covariates on multivariable regressions included age, sex, years of education, and prior history of neurological/neuropsychiatric conditions.



Supplementary Figure S1. The distribution of neurological and neuropsychiatric symptoms among patients reporting (A) persistent symptoms and (B) no improvement in these symptoms at 1-year follow-up after mild COVID-19, shown as the percentage of patients with each symptom. Whiskers represent 95% confidence intervals. LOC – loss of consciousness.

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