

Table 1 | Summary of studies that have explored the persisting symptoms post-covid-19 infection, or during long covid

Study reference	Number of subjects in study	Hospitalized / non-hospitalized	Study design	Time to assessment (average)	Symptoms (% of patients)
Carfi A, et al, 2020 ¹⁵	143	Hospitalized	Case series	60.3 days after onset	Fatigue (53.1%); dyspnea (43.4%); joint pain (27.3%); chest pain (21.7%)
Mandal S, et al, 2020 ¹⁶	384	Hospitalized	Cross sectional (analytic)	54 days post-hospital discharge	Fatigue (46.6%); cough (28.6%); breathlessness (56.25%); poor sleep quality (57%)
Halpin SJ, et al, 2020 ¹⁷	100	Hospitalized (32 ICU treated, 68 ward treated)	Cross sectional (analytic)	48 days after onset	Fatigue (64%); breathlessness (48%); neuropsychological (30%); speech and swallow (8%)
Dennis A, et al, 2020 ¹³	201	Hospitalized: n=37; non-hospitalized: n=164	Cross sectional (analytic)	140 days after onset	Fatigue (98%); muscle ache (87.6%); shortness of breath (87.1%); headache (82.6%); joint pain (78.1%); fever (75.1%); chest pain (73.6%); sore throat (71.1%); diarrhea (59.2%)
Tenforde MW, et al, 2020 ¹⁸	274	Non-hospitalized	Cross sectional (survey)	14-21 days after onset	Fatigue (38%); cough (46%); headache (18%); body ache (20%); loss of taste (28%); loss of smell (27%); diarrhea (14%); congestion (32%); dyspnea (31%); nausea (13%); sore throat (18%); chest pain (20%); abdominal pain (18%); confusion (20%)
Goertz YMJ, et al, 2020 ¹⁹	2113	Hospitalized: n=112; non-hospitalized: n=2001	Cross sectional (survey)	79 days after onset	Fatigue (87%); dyspnea (71%); chest tightness (44%); cough (29%)
Townsend L, et al, 2020 ²⁰	128	Hospitalized: n=71; non-hospitalized: n=57	Cross sectional (analytic)	72 days after initial symptoms	Fatigue (52.3%)
Boscolo-Rizzo P, et al, 2020 ²¹	187	Non-hospitalized	Cross sectional (survey)	28 days after onset	Loss of taste or smell (10.6%)
Paderno A, et al, 2020 ²²	151	Non-hospitalized	Cohort study	30 days after onset	Olfactory dysfunction (17%); gustatory dysfunction (11%)
Puntmann VO, et al, 2020 ²³	100	Hospitalized: n=33; non-hospitalized: n=67	Cohort study	71 days after onset	Cardiac involvement (78%); inflammation (60%); shortness of breath (36%); troponin levels (71%); ongoing myocardial
Helms J, et al, 2020 ²⁴	58	Hospitalized	Case series	At discharge from hospital	Agitation (69%); corticospinal tract syndrome (67%); delirium development (65%); dysexecutive syndrome (36%)
Vaes AW, et al, 2020 ²⁵	1837	Non-hospitalized	Cross sectional (survey)	79 days after onset	Requirement of personal care (52.4%)
Arnold DT, et al, 2020 ²⁶	110	Hospitalized	Cross sectional (analytic)	8-12 weeks after onset	Breathlessness (39%); fatigue (39%); insomnia (24%)
Cruz RF, et al, 2020 ²⁷	119	Hospitalized	Cohort study	4-6 weeks post-discharge	Fatigue (67.8%); breathlessness (32.2%); persistent cough (42.6%); insomnia (56.5%); pain (49.5%)
Daher A, et al, 2020 ²⁸	33	Hospitalized	Cohort study	6 weeks post-discharge	Fever (3%); cough (33%); dyspnea (45%); tiredness (45%); sore throat (9%); headache (15%); loss of smell (12%); loss of taste (9%); diarrhea (9%); angina pectoris (18%)
Huang L, et al, 2020 ²⁹	26	Hospitalized	Cross sectional (analytic)	Not reported	Abnormal cardiac findings (58%); myocardial edema (54%)
Huang Y, et al, 2020 ³⁰	57	Hospitalized	Cross sectional (analytic)	At least 30 days since acute infection	Slight cough (10.5%); shortness of breath (7%); occasional wheezing (5.3%)
Raman B, et al, 2020 ¹¹	58	Hospitalized	Cohort study	2-3 months after onset	Lung parenchymal abnormalities (32/53 60.4%); breathlessness (36/53 64%); fatigue (30/55 55%); Liver injury (11%); renal impairment (3%)
Savarraj JPI, et al, 2020 ³¹	48	Hospitalized	Cohort study	90 days after onset	Any neurological symptom (71%); cognitive deficit (BNST) (12%); fatigue (42%); post-traumatic stress (PC-PTSD-5) (29%); depression symptoms (PHQ-9) (11%); anxiety (GAD-7) (9%); Pain (PEG) (64%)
Sonnweber T, et al, 2020 ³²	109	Hospitalized: n=87; non-hospitalized: n=22	Cohort study	60 days after onset	Iron deficiency (30%); anemia (9.2%); hyperferritinemia (38%)
Valiente-De S, et al, 2020 ³³	82	Non-hospitalized	Observational study	12 weeks after onset	Dyspnea (55.6%); asthenia (44.9%); cough (25.9%); chest pain (25.9%); palpitations (22.2%); anxiety (6.4%); insomnia (1.9%); headache (9.3%); anosmia (9.3%); loss of memory (1.9%); difficulty concentrating (1.9%); dysgeusia (5.6%); fever (3.7%)
Sudre CH, et al, 2020 ³⁴	4182	13.9% required hospital treatment, 86.1% required no hospital treatment	Cohort study	28 days after onset	Fatigue (97.7%); headache (91.2%)
Vaira LA, et al, 2020 ³⁵	138	Hospitalized: n=32; non-hospitalized: n=106	Cohort study	60 days after onset	Smell or taste dysfunction (7.2%)
Tomasoni D, et al, 2020 ³⁶	105	Hospitalized	Cross sectional (analytic)	90 days after onset	Smell or taste dysfunction (5.7%); dyspnea (6.7%); fatigue (31.4%); gastrointestinal symptoms (1%); cognitive deficits (17.1%); burning pain (10.5%)
Mazza MG, et al, 2020 ³⁷	402	Hospitalized: n=300; non-hospitalized: n=102	Cross sectional (analytic)	30 days post-discharge	PTSD (28%); depression (31%); anxiety (4.2%); obsessive-compulsive symptoms (20%); insomnia (40%)
Klein H, et al, 2020 ³⁸	112	Hospitalized: n=6; non-hospitalized: n=106	Cross sectional (survey)	6 months after onset	Fatigue (20.5%); smell change (13.4%); breathing difficulty (8.9%); taste change (7.1%); memory disorders (5.4%); muscle aches (7.14%); headaches (3.57%); hair loss (2.68%)

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Table 1 | Continued

Study reference	Number of subjects in study	Hospitalized / non-hospitalized	Study design	Time to assessment (average)	Symptoms (% of patients)
Fjaeldstad AW, et al, 2020 ³⁹	204	Non-hospitalized	Cross sectional (survey)	24 days after onset	Olfactory loss (28/100 28%); gustatory loss (21/104 20%)
Eiros R, et al, 2020 ⁴⁰	139	Hospitalized: n=23; non-hospitalized: n=116	Cross sectional (analytic)	10.4 weeks after onset	No symptoms (34%); fatigue (27%); anosmia (9%); ageusia (5%); headache (5%); sore throat (5%); abdominal pain (4%); memory loss (3%); joint pain (2%); piloerection (1%); shortness of breath (26%); chest pain (19%); pericarditis-like chest pain (13%); palpitations (14%); dizziness (6%); at least one cardiac symptom (42%)
Xiong Q, et al 2020 ⁴¹	538	Hospitalized	Cohort study	97 days post-discharge	General symptoms (49.6%); physical decline/fatigue (28.3%); sweating (23.6%); myalgia (4.5%); arthralgia (7.6%); chills (4.6%); limb edema (2.6%); dizziness (2.6%); respiratory symptoms (39%); post-activity polypnea (21.4%); non-motor polypnea (4.7%); chest distress (14.1%); chest pain (12.3%); sputum (3%); throat pain (3.2%); Cardiovascular related symptoms (13%); increase in resting heart rate (11.2%); discontinuous flushing (4.8%); newly diagnosed hypertension (1.3%); psychosocial symptoms (22.7%); somniphobia (17.7%); depression (4.3%); anxiety (6.5%); dysphoria (1.7%); feelings of inferiority (0.6%); alopecia (28.6%)
Weerahandi H, et al, 2020 ⁴²	152	Hospitalized	Cohort study	37 days post-discharge	Shortness of breath (74%)
Kamal M, et al, 2020 ⁴³	287	Hospitalized: n=14; non-hospitalized: n=273	Cross sectional (survey)	Unclear	Fatigue (72.8%); anxiety (38%); joint pain (31.4%); continuous headache (28.9%); chest pain (28.9%); dementia (28.6%); depression (28.6%); dyspnea (28.2%); blurred vision (17.1%); tinnitus (16.7%); intermittent fever (11.1%); obsessive-compulsive disorder (4.9%); pulmonary fibrosis (4.9%); diabetes mellitus (4.2%); migraine (2.8%); stroke (2.8%); renal failure (1.4%); myocarditis (1.4%); arrhythmia (0.3%)
Poyraz BC, et al. 2020 ⁴⁴	284	Hospitalized: n=112; non-hospitalized: n=169	Cross sectional (survey)	50 days following diagnosis	Fatigue (40%); muscle aches (22%); alteration of taste (18%); headache (17%); alteration of smell (17%); difficulty in concentration (15%); daytime sleepiness (10%); light-headedness (7%); numbness and tingling sensations on the skin (6%); dyspnea (4%); chest pain (3%); cough (2%);
Landi F, et al, 2020 ⁴⁵	131	Hospitalized	Cohort study	55.8 days after onset	Cough (16.7%); fatigue (51.1%); diarrhea (3.8%); headache (10.6%); smell disorder (13.7%); dysgeusia (11.4%); red eyes (16%); joint pain (25.1%); shortness of breath (44.2%); loss of appetite (9.9%); sore throat (6.8%); rhinitis (14.5%)
Carvalho-Schneider C, et al, 2020 ⁴⁶	150	Hospitalized: n=53; non-hospitalized: n=97	Cohort study	30 days after onset	Fever (3.6%); shortness of breath (10.7%); chest pain (18%); flu-like symptoms (36%); digestive disorders (17.3%); weight loss (15.9%); anosmia/ageusia (27.8%); heart palpitations (6.5%); arthralgia (9.8%); cutaneous signs (15.4%)
Otte MS, et al, 2020 ⁴⁷	91	Non-hospitalized	Cross sectional (survey)	56.55 days after onset	Olfactory impairment (45.1%)
Zhao YM, et al, 2020 ⁴⁸	55	Hospitalized	Cohort study	3 months after onset	Gastrointestinal symptoms (30.9%); headache (18.2%); fatigue (16.4%); exertional dyspnea (14.6%); cough and sputum (1.8%)
Frontera JA, et al, 2021 ⁴⁹	382	Hospitalized	Cohort study	6 months post-discharge	Fatigue (36%); anxiety (46%); cognitive impairment (50%); sleep problems (38%); depression (25%); limited activities of daily living (56%)

at 12 months following recovery from the acute illness.⁶¹ In long covid, fatigue is one of the most reported manifestations, with the ONS estimating the five week prevalence of fatigue to be 11.9% among people who have had covid-19.⁵³ Fatigue is a common persisting symptom regardless of severity of the acute stage of covid-19. One cross-sectional study found that 92.9% and 93.5% of hospitalized and non-hospitalized covid-19 patients, respectively, reported ongoing fatigue at 79 days following onset of illness.¹⁹ Many other cross-sectional and cohort studies report that chronic fatigue is the most frequently reported symptom following recovery from acute covid-19,^{15 17 20 27 43} with one showing no association between covid-19 severity and long term

fatigue.²⁰ These findings show that fatigue is a major manifestation of long covid.

Possible mechanisms

Chronic fatigue following viral infection may be the result of miscommunication in the inflammatory response pathways⁶²; however, a cross-sectional analytical study found no association between pro-inflammatory markers and long term fatigue in covid-19 patients with persisting fatigue.²⁰ It is likely that a range of central, peripheral, and psychological factors play a role in the development of post-covid-19 fatigue. A narrative review explains that congestion of the glymphatic system and the subsequent toxic build-up within the central nervous