

Post COVID-19 Sequelae in Adults

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Pendahuluan: Sindrom pasca-COVID merupakan kelainan multisistem yang berkembang setelah penyakit akut. Sejumlah penelitian tentang pandemi virus pernapasan di masa lalu menunjukkan berbagai gejala tersering yang muncul terus-menerus, kelelahan, sesak napas, dan disfungsi kognitif. Metode: Pencarian literatur sistematis dari publikasi dilakukan di database *PubMed* dan *ScienceDirect*. Untuk menemukan istilah penelusuran makalah “*Post Covid-19*”, “*SARS-Cov-2*”, “*Sequae*”, dan “*Adults*”. Pengelolaan data dilakukan pada Desember 2022 hingga April 2023. Hasil: Hasil dari 14 jurnal yang digunakan dalam penelitian ini terdiri dari 9 jurnal dengan studi kohort, 3 jurnal cross sectional, 2 jurnal sistematik review. Kelelahan adalah gejala sisa yang paling umum (71,4%), sesak napas (64,1%), kecemasan/depresi (35,7%), defisit memori dan perhatian (21,4%), mialgia/nyeri sendi (21,4%), Gangguan bau/rasa (21,4%), rambut rontok (14,2%), dan (7,1%) kaki lemah, nyeri saat bernapas, batuk, mudah lelah, sakit kepala, gangguan penglihatan atau penglihatan kabur, hiperhidrosis, insomnia, sakit tenggorokan, rinitis, diare, ageusia, gangguan fungsi paru, temuan CT abnormal termasuk fibrosis paru, menimbulkan risiko gagal jantung yang lebih besar. Kesimpulan: Gejala sisa pada penderita pasca Covid-19 banyak, hal ini akan mempengaruhi organ target dalam tubuh. Kelelahan adalah gejala gejala sisa yang paling banyak dilaporkan.

INTRODUCTION

Patients who recover from SARS-CoV-2 infection experience various systemic and organ-specific health problems, which can last a long time and persist or appear only after recovering from infection.¹ Defines a post-COVID-19 condition as a condition characterized by symptoms that usually appear within three months of the onset of acute SARS-CoV-2 infection, last at least two months, and have no alternative diagnosis.^{1,2} Post-COVID syndrome is a multisystem disorder that develops after an acute illness. Numerous studies of past respiratory virus pandemics have shown persistence of various symptoms after an acute episode, it means that the post-COVID syndrome is not a new entity.³ consequences lasting for longer than three months after infection are currently referred to as “post-COVID-19 syndrome” or “Long Covid”.⁴

Among other things, Fatigue, shortness of breath, and cognitive dysfunction are among the long COVID symptoms that are frequently mentioned.² Additionally, COVID has been around connected to restrictions on daily activities and a lower quality of life.⁴ Persistent pulmonary illness, one of the post-COVID-19 sequelae, has recently attracted attention due to the possible ramifications for morbidity and mortality.⁵ Following COVID19, a number of symptoms or clinical aftereffects have been described. The majority of patients describe bothersome symptoms such Fatigue, dyspnea, cognitive impairment, sleep disruptions, muscle discomfort, attention issues, and headache.⁶ There is no clear evidence suggesting the exact pathogenesis for the development of chronic post-COVID illness. One study shows the role of mast cell activation in developing long-term symptoms.⁷

Several studies have investigated respiratory consequences after acute COVID-19 illness, reported lung survival differently abnormalities or functional impairment in up to 70% of cases patients at different follow-up times.^{8,9} However, current data suggest that the post-Covid-19 syndrome occurs not only in those with severe illness requiring hospitalization or in older adults with comorbidities, but also in young and previously healthy individuals with mildly illness person.^{10,11,12}



Previous research has provided a lot of insight into the symptoms of Covid-19 positive patients and following the recovery of Covid-19 cases, especially in countries serious case. However, systematic review of COVID-19 based on residual symptoms or sequele after the patient is declared cured and symptoms persist in adults with long-term COVID-19 disease is still rare.¹³ In this systematic review, we identify and summarize the original articles published data on the December 2022. Focus on historical data. healthy adult people. Children and elderly exception.

METHODS

Using information from a literature search, A systemic search of published was performed in the databases PubMed and ELSEVIER (ScienceDirect). English literature course are offered. To find papers search terms include "Post COVID-19", "SARS-Cov-2", "Sequele" and "Adult". The online search performed between December 2022 to April 2023. A study that Discusses literature must full access. References found through systematic search will be included to Mendeley, a reference management tool. After the first deletion duplicates, reference files created and uploaded, Covidence online tools, non-profit screening and support services systematic review process. Authority to resolve including children (under 18 years) or elderly people only (60) age and older) are not included. The purpose of this system review is focus on young people aged between 18 and 60, as they constitute the majority of the adult population. Other systematic reviews have looked at COVID-19 sequele in the adult 18 and before 60 years. The study period including follow-up after recovery to normal and/or discharge from hospital. Animal, laboratory or in vitro studies have been excluded. This paper focuses on sequele in previously healthy individuals.

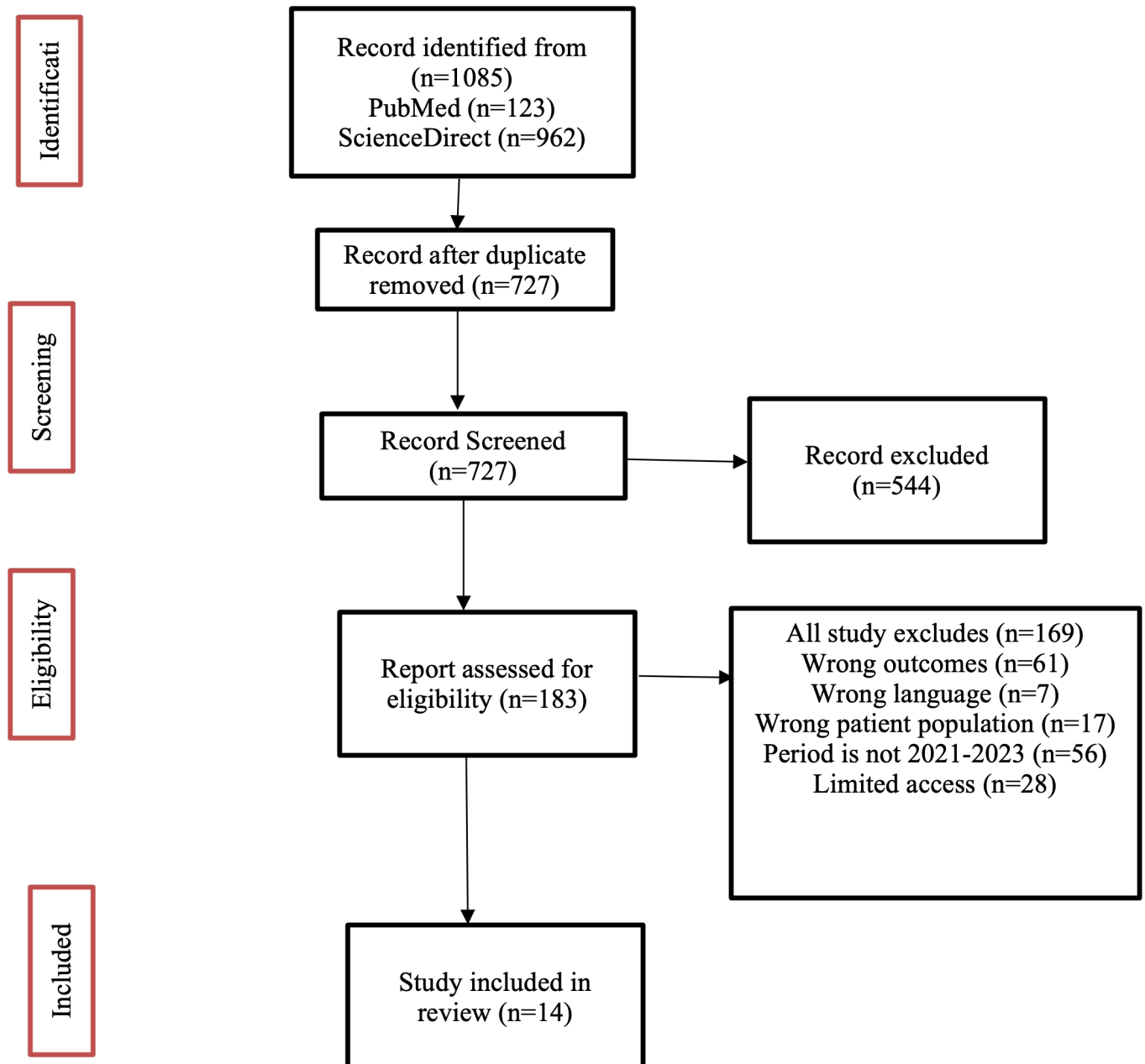


Figure 1. PRISMA flow diagram

RESULT

A total of 1085 references were retrieved during the search and imported into Mendeley where 358 duplicates were removed. Leaving 727 references for title and abstract screening. A total of 727 references were deemed irrelevant during the title and abstract screening 544 record exclude. Of the remaining 14 references, 12 references containing original data were finally included during the full text review.

The results obtained from the 14 journals used in this study consisted of 9 journals with cohort studies, 3 journals with cross sectionals, 2 journals with systematic reviews. The most residual symptom reported in post-Covid-19 patients who have been declared cured is fatigue. 10 of 14 journals stated that fatigue was the most common sequela in Covid-19 patients after recovery,

namely fatigue (36.9% vs. 26.1%, 1.76).¹ Another study reported 233 (55%) participants reported symptoms of fatigue At six to eight months after covid-19 recovery (10). The most common post-covid-19 sequele in the respiratory system was shortness of breath (23.0% vs. 9.5%, 3.46).^{1,3} the 9 out of 14 studies reporting sequele of covid-19 were shortness of breath. 5 of 14 studies reported anxiety or depression, 3 of 14 studies reported memory and attention deficits, 3 of 14 studies reported myalgia/joint pain, 3 of 14 studies reported Smell/taste disorders, 2 of 14 studies reported hair loss and 1 of 14 studies reported weakness in legs, pain when breathing, cough, tiredness, headaches and problems seeing or blurred vision, hyperhidrosis, insomnia, sore throat, rhinitis, diarrhea, ageusia, impaired pulmonary function, abnormal CT findings including pulmonary fibrosis, incurred greater risk of heart failure.

NO.	Author, Year	Title	journal	Participants	Methods	Result
1.	Heidemann (2023)	Long-term health consequences among individuals with SARS-CoV-2 infection compared to individuals without infection: results of the population-based cohort study CoMoLo Follow-up	BMC Public Health	Participants who had given consent for re-contact (n=8372) to investigate	Cohort study	Smell/taste disorders (12.8% vs. 3.4%, OR 4.11), shortness of breath (23.0% vs. 9.5%, 3.46), pain when breathing (4.7% vs. 1.9%, 2.36), fatigue (36.9% vs. 26.1%, 1.76), weakness in legs (12.8% vs. 7.8%, 1.93), myalgia/joint pain (21.9% vs. 15.1%, 1.53) and cough (30.8% vs. 24.8%, 1.34) and 3 out of 6 groups of incident diseases: liver/kidney (2.7% vs. 0.9%, 3.70), lung (3.2% vs. 1.1%, 3.50) and cardiovascular (6.5% vs. 4.0%, 1.68) diseases.
2.	Mannan (2021)	A multi-centre, cross-sectional study on coronavirus disease 2019 in Bangladesh: clinical epidemiology and short-term outcomes in recovered individuals	New Microbes and New Infections	Of the 1021 patients, male population (75%)	A cross-sectional study based on retrospective interviews	Among the recovered individuals, short-term outcomes including pains and aches (31.8%), weakened attention span (24.4%) and anxiety or depression (23.1%) were also significantly prevalent in the symptomatic cases with comorbidities.
3.	Menges (2021)	Burden of post-COVID-19 syndrome and	Plos One	431 adults from the general population	Prospective cohort study	At six to eight months, 111 (26%) reported



		implications for healthcare service planning: A population-based cohort study				not having fully recovered. 233 (55%) participants reported symptoms of fatigue, 96 (25%) had at least grade 1 dyspnea, and 111 (26%) had DASS-21 scores indicating symptoms of depression
4.	Badinlou (2023)	Impairments following COVID-19 infection: manifestations and investigations of related factors	Scientific Reports	A total of 501 individuals were included in the study (with a mean age of 47.6 years)	A cross-sectional study based on the data from self-reported questionnaire	96% of the respondents reported at least one moderate-to-severe impairment due to COVID-19 infection and the most frequent one was fatigue. In that, 79.6% and 86.9% of the study sample reported moderate-to-severe brain fatigue and tiredness or lack of energy, respectively
5.	Martino (2022)	6 and 12 month outcomes in patients following COVID-19-related hospitalization: a prospective monocentric study	Internal and Emergency Medicine	A total of 64 patients were evaluated and participated in this study	Prospective cohort study	After 6 months, 36% of patients reported persistent dyspnea, 37.5% persistent fatigue, 30.6% hair loss, 14% arthralgia and 11% memory and attention deficits. The rate of these symptoms reduced at the 12 month follow-up. At least 50% of the patients reported anxiety and depression symptoms. At 6 months 57.4% of patients showed reduced DLCO and 21.3% reduced FVC% and improvement at 12 months was noted for FVC but not for DLCO and TLC. Persistent radiographic



						abnormalities, most commonly ground-glass opacities and interstitial changes, were observed at both timepoints in many patients.
6.	Shah (2022)	Post-COVID syndrome: A prospective study in a tertiary hospital of Nepa	Plos One	: A prospective The post-COVID status of 300 patients	A prospective. This study was conducted prospectively in Tribhuvan University Teaching Hospital	During the post-COVID phase, fatigue was the most common persistent symptom, with 34% experiencing fatigue after 60 days and 28.3% even after 90 days from the onset of symptoms. Univariate logistic regression showed sore throat (OR 4.6; 95% CI (2.8-7.6)), rhinitis (OR 3.6; 95% CI (2.1-5.9)), fatigue (OR 3.7; 95% CI (1.8-7.6)), diarrhea (OR 4.1; 95% CI (2.4-6.9)), anosmia (OR 6.7; 95% CI (3.9-11.3)), ageusia (OR 7.8; 95% CI (4.5-13.4)) and shortness of breath (OR 14.9; 95% CI (1.8-119.6)) at admission were all predictors of post-COVID syndrome after three months
7.	Willi (2021)	COVID-19 sequelae in adults aged less than 50 years: A systematic review	Travel Medicine and Infectious Disease	A total of 31 papers were included.	A systematic literature search	Sequelae persistence since infection spanned 14 days to three months. Sequelae included persistent fatigue (39-73% of assessed persons), breathlessness (39-74%), decrease in



						quality of life (44-69%), impaired pulmonary function, abnormal CT findings including pulmonary fibrosis (39-83%), evidence of peri-/perimyo-/myocarditis (3-26%), changes in microstructural and functional brain integrity with persistent neurological symptoms (55%), increased incidence of psychiatric diagnoses (5.8% versus 2.5-3.4% in controls), incomplete recovery of olfactory and gustatory dysfunction (33-36% of evaluated persons).
8.	Lam (2023)	Long-term post-acute sequelae of COVID-19 infection: a retrospective, multi-database cohort study in Hong Kong and the UK	eClinicalMedicine	A total of 535,186 and 16,400 patients were diagnosed with COVID-19 from HKHA and UKB, of whom 253,872 (47.4%) and 7613 (46.4%) were male	Retrospective, multi-database cohort study	Patients with COVID-19 incurred greater risk of heart failure (HR 1.82; 95% CI 1.65, 2.01), atrial fibrillation (1.31; 1.16, 1.48), coronary artery disease (1.32; 1.07, 1.63), deep vein thrombosis (1.74; 1.27, 2.37), chronic pulmonary disease (1.61; 1.40, 1.85), acute respiratory distress syndrome (1.89; 1.04, 3.43), interstitial lung disease (3.91; 2.36, 6.50), seizure (2.32; 1.12, 4.79), anxiety disorder (1.65; 1.29, 2.09), post-traumatic stress disorder (1.52; 1.23, 1.87), end-



						stage renal disease (1.76; 1.31, 2.38), acute kidney injury (2.14; 1.69, 2.71), pancreatitis (1.42; 1.10, 1.83), cardiovascular (2.86; 1.25, 6.51) and all-cause mortality (4.16; 2.11, 8.21) mortality during their post-acute phase of infection
9.	Dryden (2022)	Post-COVID-19 condition 3 months after hospitalisation with SARS-CoV-2 in South Africa	Lancet Glob Health	Of 241 159 COVID-19 admissions reported 3094 patients that we were able to contact, 2410 (77.9%) consented to participate in the study at 1 month after discharge	Prospective cohort study	The most common symptoms reported at 3 months were fatigue (50.3%), shortness of breath (23.4%), confusion or lack of concentration (17.5%), headaches (13.8%), and problems seeing or blurred vision (10.1%).
10.	Mclaughlin (2023)	A Cross-Sectional Study of Symptom Prevalence, Frequency, Severity, and Impact of Long COVID in Scotland: Part II	The American Journal of Medicine	The survey was completed by 253 respondents	A Cross-Sectional Study	Severe impact on work and study were predicted by more severe and more frequent fatigue, more severe pain, and more severe cognitive impairmen
11.	Almas (2022)	Post-acute COVID-19 syndrome and its prolonged effects: An updated systematic review	Annals of Medicine and Surgery	Twenty-one articles qualified for the final analysis	systematic review Relevant databases were searched for extraction of articles	The most common persistent clinical manifestations were fatigue (54.11%), dyspnea (24.38%), alopecia (23.21%), hyperhidrosis (23.6%), insomnia (25.98%), anxiety (17.29%), and arthralgia (16.35%)
12.	Sigfrid (2021)	Long Covid in adults discharged from UK hospitals	The Lancet Regional Health - Europe	327 hospitalised participant	cohort study at least 3 months post-discharge.	93% reported persistent symptoms, with fatigue the most

		after Covid-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol				common (83%), followed by breathlessness (54%)
13.	Darcis (2021)	Long-term clinical follow-up of patients suffering from moderate-to-severe COVID-19 infection: a monocentric prospective observational cohort study	International Journal of Infectious Diseases	199 individuals were included in the analysis	Prospective observational cohort study	Six months after discharge, 47% and 32% of patients still had exertional dyspnoea and fatigue.
14.	Todt (2021)	Clinical outcomes and quality of life of COVID-19 survivors: A follow-up of 3 months post hospital discharge	Respiratory Medicine	251 participants	cohort study	At 3 months of follow-up, 6 patients had died, 51 (20.3%) had visited the emergency department again and 17 (6.8%) had been readmitted to hospital. Seventy patients (27.9%) persisted with increased dyspnoea and 81 had a positive screening for anxiety/depression. Similarly, patients reported an overall worsening of EQ-5D-3L single summary index at 3 months compared to before the onset of COVID-19 symptoms

Table 1. Summary of references post COVID-19 sequelae

DISCUSSION

It is clear that some patients, regardless of disease severity, continue to have symptoms weeks and months after the onset of COVID-19.¹⁴ Try to distinguish between “post-acute Covid-19” and “chronic Covid-19”, which can last more than 3 weeks and 12 weeks respectively after the first symptoms appear. We chose the term post-Covid syndrome instead of post-acute Covid-19 syndrome because symptoms persist for more than three months.¹⁵ SARS-CoV-2 can infect lung, heart, liver and kidney tissues, gastrointestinal mucosa, vascular endothelium, macrophages, T cells, and neurons. Therefore, in each affected organ, whether directly or indirectly, there is a

possibility of persistent damage with specific sequelae. WHO recommends a recovery time of up to two weeks for mild illness and up to six weeks for severe illness.¹³ Those with comorbidities reported post-COVID complications such as mobility problems, pain, anxiety, and depression, as well as more significant signs of dementia. In post-COVID-19 syndrome studies, relatively high rates of fatigue, dyspnea, or physical intolerance, and psychological symptoms have been consistently documented in all studies.¹⁶ A longitudinal cohort consisting of 91% of participants with mild disease detected persistent symptoms in 33% of outpatients and 31% of hospitalized patients.¹⁷ Studies with shorter follow-up (≤ 2 months) reported higher frequency of acute symptoms such as cough, fever, and acute gastrointestinal symptoms, which might indicate persistent infection,¹⁷⁻²⁰ whereas studies with follow-up beyond 3 months reported fatigue, shortness of breath, and musculoskeletal symptoms more frequently.¹⁸

The range of symptoms reported include those which may be related to direct lung damage, such as breathlessness, and also those for which an underlying pathophysiological mechanism may be less clear such as fatigue, muscle pain and cognitive complaints. The latter group are also features of other post infectious syndromes and post intensive care syndrome, and may have a similar aetiology, such as infection triggered autoimmunity, dysautonomia or other mechanism.¹⁹ or some individuals, COVID-19 can cause symptoms that last for weeks or months after the infection has gone. Post-COVID conditions are being seen in a growing number of patients reporting a constellation of symptoms after SARS-CoV-2 infection that are persistent, debilitating, and have yet to be fully explained by known or measurable mechanisms.²⁰ At 3 months, more than a quarter of our cohort reported feeling persistently more breathless than before the onset of COVID-19 symptoms. Previous studies had already identified dyspnoea as a frequent symptom among patients recovering from COVID-19 up to 6 months following hospital discharge.²¹

There is evidence of chronic fatigue as a long-term consequence, particularly in people under 30 years of age, following outbreaks of influenza A(H1N1), SARS-CoV, Ebola virus and West Nile virus. In some of these cases, the diagnostic criteria for chronic fatigue syndrome were met (13). Fatigue has been identified as one of the most common symptoms of post-COVID syndrome and among survivors of the 2003 SARS-CoV-1 pandemic.³ The term "myalgic encephalomyelitis" is used to describe a broad-spectrum condition with symptoms such as fatigue, postexertional malaise, sleep disturbances, cognitive impairment, and nonprovoked pain that persist for more than 6 months with substantial intensity and not completely explained by a medical condition.^{4,5} It is a heterogeneous, multifactorial etiology involving immune, virologic, psychological, musculoskeletal, and endocrine factors. Nutritional deficiencies could be a major challenge in some patients who have poor oral intake due to debility, lack of taste and smell, and medication sideeffects, leading to negative protein balance and a lack of nutrients essential to proper musculoskeletal functioning. These factors are augmented in the elderly with previously existing chronic health issues. Persistent low-grade neuroinflammation in a vulnerable population is a potential cause of chronic fatigue.²²

Misinformation about inflammatory response pathways, particularly in the cytokine network, may be the underlying cause.¹³ Findings regarding longer-term sequelae are similar to those from prior coronavirus outbreaks, with 40% of severe acute respiratory syndrome (SARS) survivors reporting chronic fatigue up to four years after infection. Similar chronic symptoms, in particular, fatigue, have been also described in other viral (e.g. Ebola virus, Epstein-Barr virus, Dengue virus), and bacterial (e.g. *Borrelia burgdorferi*) infection.¹⁰ Fatigue, persistent cough, exertional dyspnea, and body discomfort or vertigo were seen in 28.3%, 2%, 6.7%, and 17.7% of cases, respectively, in our study. The underlying cause of fatigue is still largely unknown. Fatigue can be caused by changes in the immune system due to viral infections.²³

Post-COVID pathophysiologic changes that predispose to glucose intolerance are being actively investigated. Three prominent pathophysiologic mechanisms that have emerged relate to a heightened proinflammatory state, the role of angiotensin converting enzyme (ACE)-2 receptors, and pancreatic beta cell dysfunction.²² As seen in the results section, abnormalities in pulmonary function were observed in the lung function examination (e.g. as decrease in aerobic capacity or

reduction in diffusion capacity) as well as radiologically. Although the majority of patients have fully recovered or are in the process of radiological and/or clinical recovery, it would not be surprising if residual pulmonary fibrosis persists for a long time. This could also be a plausible explanation for why some patients experience shortness of breath even up to 12 weeks after admission.^{13,15} The most frequently reported radiographic abnormalities at 6 and 12 months were opacities and reticular opacities. Although the proportion of patients with abnormalities is relatively high, a small number of lung parenchyma are often involved and, more importantly, abnormalities that are not suggestive of the fibrotic interstitial lung disease phenotype.⁵

Myocarditis, perimyocarditis and pericarditis were diagnosed as late as 11 weeks after symptom of infection onset.²⁴ Our study revealed that 28.75% of patients, asymptomatic and symptomatic together, had a raised troponin level and it is assumed that this is owing to myocarditis, microangiopathy, myocardial infarction and cytokine storm.²⁵ Some authors believe that SARS-CoV-2 may cause long-term neurodegenerative diseases such as multiple sclerosis, Parkinson's disease, and narcolepsy in predisposed individuals.²⁶

Nevertheless, Mongioi et al. hypothesize a role of SARS-CoV-2 in pancreatic damage and subsequent development of diabetes, in hypothalamic-pituitary-adrenal axis dysfunction and adrenal insufficiency and in hypothalamic-pituitary-thyroid axis dysfunction with thyroid damage, as seen in SARS-CoV infection.²⁶ Endocrine perturbations stemming from pituitary malfunction, hypothyroidism or hypothalamic-pituitary-adrenal axis disruption might be potential components that delay or prevent post-COVID recovery.^{27,28} Additionally, there is emerging data that a scenario of insulinopenic hyperglycemia resembling type 1 diabetes (T1DM), possibly via immunologic pathways, might be associated with acute COVID-19 and its aftermath.²⁸

Elevated liver enzyme, alanine transaminase, was also found in 36.83 patients in this study, which is also consistent with many other review articles.²⁹ SARS-CoV-2 has been shown to persist in the small intestine of 7 out of 14 people. Since the intestine is the largest lymphatic organ, virus particles remaining in the intestine can cause long-term effects.³⁰

Lam et al studies have reported that respiratory failure caused by fibrosis, interstitial thickening and vascular abnormalities may still persist in COVID-19 survivors 12 months following their acute infections.⁵ Despite the gradual improvement in pulmonary physiology and exercise capacity, persistent physiological and radiographic abnormalities may still persist 12 months beyond hospital discharge.^{6,8,9}

Anosmia is a well-known symptom in COVID-19 patients which appears to be more common in women and improves with time. Anosmia's pathophysiological mechanisms aren't entirely known. Injury to the olfactory neuroepithelium is possible because SARS-CoV-2 accesses the nasal epithelium via the Angiotensin-converting enzyme-2 (ACE-2) receptor.³ Impact of long COVID on daily activities, work and caring. Interestingly, both severity and frequency of neurological symptoms, including lack of attention, loss of smell, impaired sense of smell, loss of taste, impaired sense of taste, and loss of appetite, associated most strongly with negative mood. Previous research has found that a loss of taste and smell attributed to COVID-19 infection has strong detrimental impacts on psychological well-being and quality of life.³¹

Persistent squeal lung injury can explain cough and respiratory difficulty. Detected shortness of breath and anosmia in the context of post-COVID syndrome may be attributed to SARS-CoV-2 pathomechanism: vascular angiogenesis was observed at a higher frequency in the lungs of patients with COVID-19 when compared to individuals infected with influenza virus.³² Hypertension, diabetes mellitus-II, chronic lung disease, and malignancies were the most common concomitant conditions before SARS-CoV-2 infection. They thus reflected the most common concomitant diseases in the general population.^{3,7,9}

Post-COVID pathophysiologic changes that predispose to glucose intolerance are being actively

investigated. Three important pathophysiological mechanisms have emerged involving increased inflammation, the role of angiotensin-converting enzyme (ACE)-2 receptors, and pancreatic beta-cell dysfunction.^{3,4} The post-COVID pathophysiological changes that lead to glucose intolerance are under active investigation.¹² Three prominent pathophysiological mechanisms that have emerged relate to a heightened proinflammatory state, the role of angiotensin converting enzyme (ACE)-2 receptors, and pancreatic beta cell dysfunction.³³

Similar to chronic fatigue syndrome, the etiology, and pathophysiology of neuropsychiatric symptoms in COVID-19 are multifactorial and unclear.²² In a cohort of 355 patients in Bangladesh, and 143 patients in Italy, a cumulative 63% of the patients were screened positive in at least one of the domains evaluated for neuropsychiatric sequelae (depression, anxiety, insomnia, obsessive-compulsive disorders, etc.) Clinical depression and anxiety were reported in approximately 17% of patients following COVID-19.^{33,34} Memory loss in the form of dementia and ageusia is also reported in a few studies, including cognitive impairment with or without fluctuations.³³

In addition to highly complex health symptoms, organ-specific complications and the emergence of new chronic non-communicable diseases may be long-term consequences of SARS-CoV-2 infection, particularly in people with severe COVID-19 illness.^{6,8}

CONCLUSIONS

Particular attention should be paid to residual multi-organ dysfunction, particularly persistent pulmonary impairment, function and inflammatory heart disease, as well as mental health and neurological sequelae including post-viral fatigue syndrome. There are many sequelae in post Covid-19 sufferers, this will affect the target organs in the body. Fatigue is the most reported sequelae symptom.

REFERENCES

1. Heidemann C, Sarganas G, Du Y, Gaertner B, Poethko-Müller C, Cohrdes C, Schmidt S, Schlaud M, Scheidt-Nave C (2023) Long-term health consequences among individuals with SARS-CoV-2 infection compared to individuals without infection: results of the population-based cohort study CoMoLo Follow-up. *BMC Public Health*.21;23(1):1587.
2. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, W. H. O.(2022) Clinical case definition working group on post-COVID-19 condition a clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*.22(4):e102-7.
3. Afrin L.B., Weinstock L.B., Molderings G.J., (2020) Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome, *Int. J. Infect. Dis.* 100 327. <https://doi.org/10.1016/j.ijid.2020.09.016>
4. Martino GP, Benfaremo D, Bitti G, Valeri G, Postacchini L, Marchetti A, Angelici S, Moroncini G. (2022) 6 and 12 month outcomes in patients following COVID-19-related hospitalization: a prospective monocentric study. *Internal and Emergency Medicine*. 7(6):1641-9.
5. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A et al (2021) More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 11(1):16144
6. Talman S, Boonman-de Winter LJM, de Mol M, Hoefman E, van Etten RW et al (2021) Pulmonary function and health-related quality of life after COVID-19 pneumonia. *Respir Med* 176:106272
7. Menges D, Ballouz T, Anagnostopoulos A, Aschmann HE, Domenghino A, Fehr JS, Puhan MA.

- (2021) Burden of post-COVID-19 syndrome and implications for healthcare service planning: A population-based cohort study. *PloS one* e0254523.
8. Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q et al (2021) 3 month, 6 month, 9 month, and 12 month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med* 9(7):747-754
9. Shah S, Bhattarai SR, Basnet K, Adhikari YR, Adhikari TB, Bhatta N, Chamlagain R, Aryal S, Sah SK, Bhandari G, Bhandari B. (2022) Post-COVID syndrome: A prospective study in a tertiary hospital of Nepal. *Plos one* 17(8):e0272636.
10. Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, et al. (2021) Sequelae in Adults at 6 Months After COVID-19 Infection. *JAMA Netw Open*; 4: e210830. <https://doi.org/10.1001/jamanetworkopen.2021.0830> PMID: 33606031
11. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. (2020) Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. *medRxiv*. 12.24.20248802. <https://doi.org/10.1101/2020.12.24.2024880>
12. Willi S, Lüthold R, Hunt A, Hänggi NV, Sejdiu D, Scaff C, Bender N, Staub K, Schlagenhauf P. (2021) COVID-19 sequelae in adults aged less than 50 years: a systematic review. *Travel medicine and infectious disease*. 1;40:101995.
13. Eiros R, Barreiro-Perez M, Martin-Garcia A, Almeida J, Villacorta E, Perez-Pons A, et al. (2021) Pericarditis and myocarditis long after SARS-CoV-2 infection: a cross-sectional descriptive study in health-care workers. *MedRxiv* <https://doi.org/10.1101/2020.07.12.20151316>.
14. AM B. (2021) Chronic COVID syndrome: Need for an appropriate medical terminology for long-COVID and COVID long-haulers. *J. Med. Virol.* 93 2555-2556. <https://doi.org/10.1002/JMV.26624>
15. Moldofsky H., Patcai J., (2011) Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. *BMC Neurol.* 11 <https://doi.org/10.1186/1471-2377-11-37> PMID: 2143523
16. Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, et al. (2021) Sequelae in Adults at 6 Months After COVID-19 Infection. *JAMA Netw Open*.; 4: e210830.
17. Sudre C.H., Murray B., Varsavsky T., Graham M.S., Penfold R.S., Bowyer R.C., et al., (2021) Attributes and predictors of long COVID. *Nat. Med.* 2021 274. 27 626-631. <https://doi.org/10.1038/s41591-021-01292-y>
18. McLaughlin M, Cerexhe L, Macdonald E, Ingram J, Sanal-Hayes NE, Meach R, Carless D, Sculthorpe N. (2023) A cross-sectional study of symptom prevalence, frequency, severity, and impact of long-COVID in Scotland: part I. *The American journal of medicine*.
19. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. (2020) Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. *medRxiv*. 12.24.20248802. <https://doi.org/10.1101/2020.12.24.20248802>.
20. Todt BC, Szlejf C, Duim E, Linhares AO, Kogiso D, Varela G, Campos BA, Fonseca CM, Polesso LE, Bordon IN, Cabral BT. (2021) Clinical outcomes and quality of life of COVID-19 survivors: A follow-up of 3 months post hospital discharge. *Respiratory medicine*. 1;184:106453.
21. Badinlou F, Forsström D, Jansson-Fröjmark M, Abzhandadze T, Lundgren T. (2021) Impairments following COVID-19 infection: Manifestations and investigations of related factors.



ScientificReports. 13(1):6564.

22. Boddu SK, Aurangabadkar G, Kuchay MS. (2020) New onset diabetes,type 1 diabetes and COVID-19. *Diabetes Metab Syndr* 14:2211-2217.

23. Ackermann M., Verleden S.E., Kuehnel M., Haverich A., Welte T.,Laenger F., et al., (2020) Pulmonary Vascular Endothelialitis,Thrombosis, and Angiogenesis in Covid-19., *N. Engl. J. Med.* 383 120-128.<https://doi.org/10.1056/NEJMoa2015432> PMID: 32437596

24. Mongioi LM, Barbagallo F, Condorelli RA, Cannarella R, Aversa A,La Vignera S, et al. (2020) Possible long-term endocrine-metabolic complications in COVID-19: lesson from the SARS model. *Endocrine*68:467-70. <https://doi.org/10.1007/s12020-020-02349-7>.LK.

25. Kumar -MP, Mishra S, Jha DK, Shukla J, Choudhury A, Mohindra R,et al. (2020) Coronavirus disease (COVID-19) and the liver: a comprehensive systematic review and meta-analysis. *Hepatol Int*:1-12.

26. Mannan A, Mehedi HM, Chy NU, Qayum MO, Akter F, Rob MA, Biswas P,Hossain S, Ayub MI. (2021) A multi-centre, cross-sectional study oncoronavirus disease 2019 in Bangladesh: clinical epidemiology andshort-term outcomes in recovered individuals. *New Microbes New Infect* ;40: 100838.

27. Greer N, Bart B, Billington CJ, Diem SJ, Ensrud KE, Kaka A, etal. (2022) COVID-19 postacute care major organ damage: a systematicreview. *BMJ* ;12(8): e061245.

28. Lam IC, Wong CK, Zhang R, Chui CS, Lai FT, Li X, Chan EW, Luo H,Zhang Q, Man KK, Cheung BM. (2023) Long-term post-acute sequelae ofCOVID-19 infection: a retrospective, multi-database cohort study in HongKong and the UK. *EClinicalMedicine*.

29. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. (2021)6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* ; 397: 220-232. [https://doi.org/10.1016/S0140-6736\(20\)32656-8](https://doi.org/10.1016/S0140-6736(20)32656-8) PMID: 33428867

30. Rizvi AA, Kathuria A, Al Mahmeed W, Al-Rasadi K, Al-Alawi K,Banach M, Banerjee Y, Ceriello A, Cesur M, Cosentino F, Galia M. (2020)Post-COVID syndrome, inflammation, and diabetes. *Journal of Diabetes andits Complications* 108336.

31. Almas T, Malik J, Alsubai AK, Zaidi SM, Iqbal R, Khan K, Ali M,Ishaq U, Alsufyani M, Hadeed S, Alsufyani R. (2022) Post-acute COVID-19syndrome and its prolonged effects: An updated systematic review. *Annalsof Medicine and Surgery* ;80:103995.

32. Mowat A.M., Agace W.W., (2014) Regional specialization within theintestinal immune system, *Nat. Rev. Immunol.* 14 667-685.<https://doi.org/10.1038/nri3738>

33. Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS,Gillesen A, Berry C, Lowe DJ, McPeake J, Lone N. (2021) Long Covid inadults discharged from UK hospitals after Covid-19: A prospective,multicentre cohort study using the ISARIC WHO Clinical CharacterisationProtocol. *The Lancet Regional Health-Europe*.

34. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, BowyerRC, et al. (2021) Attributes and predictors of long COVID. *Nat Med.*; 27:626-631. <https://doi.org/10.1038/s41591-021-01292-y> PMID: 33692530