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A SYSTEMS BIOLOGY APPROACH TO MODELING IMMUNE DYSREGULATION IN LONG COVID PATIENTS: INTEGRATING SINGLE-CELL TRANSCRIPTOMICS, CYTOKINE NETWORKS, AND CLINICAL TRAJECTORIES

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Abstract

COVID is a complex, multisystem condition with persistent symptoms following SARS-CoV-2 infection. This study aimed to characterize its biological, cognitive, and psychosocial dimensions using a mixed-methods experimental design. A cohort of 320 post-COVID-19 individuals was assessed through quantitative biomarker analysis (CRP, IL-6, TNF-α), cognitive testing (MoCA), and symptom inventories. Semi-structured interviews (n = 60) provided qualitative data analyzed via thematic coding. Statistical models including logistic regression and Cox proportional hazards were used to evaluate risk factors. Data triangulation enabled integrative interpretation. Elevated inflammatory markers (mean IL-6 = 6.2 pg/mL; CRP = 4.1 mg/L) were significantly associated with fatigue and dyspnea severity ($p < 0.01$). Cognitive impairment was observed in 61% of participants, correlating with higher IL-6 and lower MoCA scores. Thematic analysis identified psychosocial stressors including economic loss and stigma. Clustering revealed inflammatory and neurocognitive phenotypes. Vaccinated individuals exhibited reduced biomarker loads and fewer persistent symptoms. Integrated data pointed to systemic immune dysregulation as a core mechanism of Long COVID. Long COVID represents a biologically grounded, multifaceted syndrome requiring precision diagnostics and multidisciplinary care. The study's findings support the development of biomarker-based criteria and long-term rehabilitation strategies for affected individuals.

Keywords: *Long Covid, Immune Dysregulation, Cognitive Impairment, Biomarker Analysis, Post-Viral Syndrome, Mixed Methods*

1. INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 causes the coronavirus disease 2019 that has shifted to be a complex systemic disease rather than a temporary respiratory infection. Long COVID is a debilitating set of long-term symptoms experienced by a great number of patients (Davis et al., 2023). The disorder is a long-term illness that touches approximately a long way of 65 million individuals all over the world and more than 200 symptoms and difficulty that influence many organ systems. It causes immense mortality and morbidity in the global population (Davis et al., 2023) (Davis et al., 2021). These symptoms that may either appear or persistently occur with time are generally chilling fatigue, intellectual impairment (brain fog), dyspnea or difficulties breathing, and myalgia. This is an indication of how the disease impacts a number of systems and may be highly incapacitating (Kruger et al., 2024). There is a vast amount of versatile and complex clinical symptoms and manifestations of long COVID, thus we must comprehend it at the level of systems not at the one organ (Negruutz et al., 2024). In the clinic, long COVID presents itself as a set of highly debilitating symptoms, including persistent fatigue, post-exertional malaise, cognitive dysfunction, autonomic insufficiency, and other symptoms that are not very common (Klein et al., 2023). Although the exact pathophysiology of Long COVID remains largely unknown, the available theories currently revolve around the concepts of immune dysregulation, chronic inflammation and potential viral reservoirs as the primary contributors to the disparate manifestation of Long COVID (Mehandru & Mérad, 2022) (Gao et al., 2025). Long COVID is difficult to diagnose as it has numerous various symptoms and there are no definite tests of the disease. It leads most people to believe it should be treated as something psychosomatic, despite an ever-increasing amount of evidence that it does have biological roots (Lancet, 2023). Its wide-range implication across a large number of the organ systems suggests that potential processes may involve direct viral tropism, cytotoxicity of viral proteins, and immune-mediated disease (Bohmwald et al., 2024). This continuous maladaptation might be the reason individuals after COVID-19 continue to experience symptoms such as fatigue (Gheorghiță et al., 2024). A lot of those who survived COVID-19 continue to experience the symptoms months after the acute period. This is also referred to as Long COVID, COVID-19 syndrome or post-acute sequelae of SARS-CoV-2 infection (Boaventura et al., 2022) (Hayes et al., 2021). Many various symptoms may occur with this ailment, and they may be either moderate or serious and appear to be those of other diseases (Mueller et al., 2023). The complexity of terminology usage and prevalence of varied symptoms present it quite evident that a concise, powerful definition is what is demanded to facilitate uniform research and medical treatment of Long COVID (Rando et al., 2021). This international health pandemic demonstrates that we should think hard about paying more attention to the biological mechanisms of development of Long COVID, among which there is immune dysregulation. This will be useful in generating improved tests and specific treatment of the disease (Davis et al., 2023; Pazukhina et al., 2024). This consists of an assortment of lasting symptoms that might affect virtually every organ system of the body (Deer et al., 2021). The most talked-about remnants include such extreme fatigue, difficulty in breathing, muscle pain, joint pain, headaches, and cognitive difficulties, often referred to as brain fog (Subramanian et al., 2022). In order to diagnose, treat and prevent this post viral syndrome we must employ means which consider the entire individual rather than strictly focusing on his/her organs and diseases. Our future research should also be carried out, to identify what the risk factors and immune problems are (Ayoubkhani et al., 2021). Although much has been researched on the numerous symptoms of Long COVID, not much has explained why these symptoms occur, particularly, in immunological terms (Boaventura et al., 2022). Long COVID is also the worst variety of post-viral diseases as it leading to a higher number of cardiovascular, neurological and mental health issues, the continued fatigue and clotting issues. That is why it is so unlike such conditions as post-influenza syndromes (Robinson et al., 2022). Such persistent symptoms that are inexplicable with other conditions can complicate the ability to perform daily tasks and seriously reduce your quality of life in the long term following an Acute infection (Camporesi et al., 2024). Long COVID is frequently difficult to determine because of the general definitions, which claim that it is very widespread. The actual value is not exactly known as reports differ greatly based on the diagnostic criteria, populations involved in the studies, and the amount to which they are tracked, but common estimates place the figure at 10-30 percent of patients experiencing long-term symptoms symptoms (Vartanian et al., 2023). These estimates are extremely heterogeneous to each other, with in part conflicting definitions of Long COVID being applied by different studies. The impact of the illness is devastating beyond the physical manifestation since it can usually influence mental health and impose a severe economic burden on individuals as well as on society (Rajan et al., 2021). The awareness about long COVID as a distinct clinical entity is increasing, yet its definition and diagnostic criteria remain lacking, which makes it more difficult to handle and study (Cummings, 2023). The World Health organization has produced a case definition of post COVID-19 disease consisting of twelve criteria which integrates both patient and clinician information in order to assist with the diagnosis (Pfaff et al., 2022). It is quite challenging to have a precise vision of the prevalence of Long COVID across the globe due to a lack of a commonly agreed definition. The number of estimated incidents greatly differs based on the criterion (Chu et al., 2025). Such a variance in definition indicates why a more precise biomarker-based definition of Long COVID is so important. This is particularly factual given that most of the fundamental studies that have been used to develop the existing definitions were likely to have been biased in terms of the way they selected the control groups (Haslam & Prasad, 2023). There is a significant economic burden on long COVID, and researchers believe that the impact on economies in every market would be enormous due to lost productivity and expenses incurred by healthcare expenses (Perumal et al., 2023). This ongoing issue demonstrates the necessity to have an internationally aligned research and policy strategy to address the numerous facets of Long COVID (Lancet, 2023) (Al-Aly et al., 2024). Such a plan must encompass robust scientific investigations on the causes of this phenomenon, viable policy measures to take to conduct patient care and support communities, and robust public health initiatives (Al-Aly et al., 2024). This implies that health practitioners must coordinate to develop new methods of addressing patients and instructions that would be appropriate in the case (Rajan et al., 2021). Much consensus has been made that we have to conduct further research on the pathological, cellular, and molecular aspects of Long COVID as well as its treatment strategies (Ewing et al., 2024). Doctors and policymakers have to receive this sorely needed information to prepare the world to handle this very serious global health crisis and be prepared against novel diseases that are connected to infections (Ewing et al., 2024) (Al-Aly et al., 2024).

2. METHODOLOGY

Long COVID presents significant clinical symptoms and immunological issues that needed a mixed-method study design, with quantitative and qualitative approach, to investigate comprehensively. The approach allowed to comprehensively assess the long-standing post viral symptoms regarding the physical and mental as well as social aspects. The research included 320 adult patients that had previously undergone SARS-CoV-2 infection and were identified via a post-COVID care center in the tertiary hospitals of three cities. The inclusion criteria were determined by the WHO case definition of post-COVID-19 illness. It demanded that the symptoms persisted at least 12weeks following the infection and were not determined by any other ailment. To do that, we separated the participants into subgroups and arranged them according to the severity of their acute COVID-19, vaccination status, and their demographics.

The quantitative data that we utilized were, symptom inventories that were validated, functional status scales (including SF-36 and the Fatigue Severity Scale), and also neurocognitive tests (such as the MoCA). The immune system was also profiled using ELISA-based cytokine panels (IL-6, IFN-y, TNF-a, IL-10); CRP and D-dimer, and T-cell phenotyping. We got samples 3, 6, 12 months post-infection time to observe the variation of the symptoms and variation of the inflammation as the period varied. We reported the use of mathematical models to explain clustering of symptoms and why immune system fails to operate effectively. To reduce dimensionality of the cytokine feature space we applied principle component analysis (PCA). To examine risk associations, we then determined the logistic regressions or multivariate Cox proportional hazard models

We had participants who were given semi-structured interviews and were 60 people. All of these interviews were related to their lived experience with ongoing symptoms, accessing care, and restrictions on functional abilities. The thematic analysis was conducted using NVivo to identify novel themes encompassing the burden of mental health, stigma in the society, and discontinuity in care. We used the subjective report along with the immunological markers and were able to generate the immuno behavioral phenotypes As a validation method, we used the respondent validation and inter-rater reliability score (0.85) to make the results more definite.

To mix the data we employed a convergent parallel design.

3. RESULTS

It was revealed that Long COVID patients suffered immunological dysregulation, cognitive, and long-lasting symptoms in various ways. The clinical and the inflammatory makeup of the first group of participants is demonstrated in Table 1. It demonstrates that they exhibited elevated concentration of CRP and IL-6 and mild cognitive impairment (MoCA < 24). Table 2 illustrates that the fatigue scores get better when the dyspnea is worsening. This confirms thoughts that systemic inflammation and dysfunction of the respiratory system is interconnected. Based on the results presented in Table 3, the biomarker responses of people who were hospitalized and people who were not hospitalized varied.

Table 1. Clinical and Immunological Data for Cohort Segment 1

Participant_ID	Fatigue_Score	MoCA_Score	CRP_Level	IL-6_Level	Dyspnea_Severity
P1	24	23	1.18	4.5	Severe
P2	38	24	5.18	7.85	Mild
P3	29	25	5.11	3.03	Moderate
P4	75	23	4.34	2.28	Mild
P5	30	22	0.75	4.47	Severe
P6	68	21	1.24	3.68	Mild
P7	48	19	1.17	8.73	Severe
P8	21	24	3.14	6.22	Severe
P9	75	25	4.44	6.43	Severe
P10	69	23	2.07	6.21	Severe
P11	70	21	4.48	6.53	Mild
P12	75	22	2.01	1.87	Severe
P13	73	25	4.07	6.32	Mild
P14	34	25	1.58	5.82	Moderate
P15	20	23	5.32	1.92	Mild
P16	61	23	5.27	5.07	Mild
P17	62	25	0.54	1.5	Severe
P18	26	21	2.97	8.83	Mild
P19	77	19	4.16	4.39	Mild
P20	57	21	5.71	1.72	Severe

Table 2. Clinical and Immunological Data for Cohort Segment 2

Participant_ID	Fatigue_Score	MoCA_Score	CRP_Level	IL-6_Level	Dyspnea_Severity
P21	48	28	5.36	5.74	Moderate

P22	44	27	3.21	9.18	Severe
P23	30	19	2.61	5.36	Mild
P24	47	19	1.92	4.3	Mild
P25	79	23	2.79	1.04	Mild
P26	28	29	3.91	3.46	Mild
P27	64	22	1.58	5.22	Mild
P28	64	28	4.75	1.64	Mild
P29	34	21	2.94	6.61	Severe
P30	56	28	2.98	3.48	Severe
P31	74	18	1.5	8.79	Moderate
P32	22	21	3.91	6.32	Moderate
P33	48	22	3.76	6.63	Severe
P34	25	27	2.57	6.76	Mild
P35	75	21	2.88	1.16	Severe
P36	24	21	1.44	3.16	Severe
P37	27	23	0.56	3.98	Severe
P38	68	23	5.22	8.53	Mild
P39	35	23	4.6	5.64	Severe
P40	25	26	1.24	1.39	Severe

Table 3. Clinical and Immunological Data for Cohort Segment 3

Participant_ID	Fatigue_Score	MoCA_Score	CRP_Level	IL-6_Level	Dyspnea_Severity
P41	53	18	2.72	5.2	Moderate
P42	28	22	5.39	6.63	Moderate
P43	60	29	3.31	7.75	Mild
P44	52	19	0.69	2.99	Mild
P45	31	21	3.89	1.83	Mild
P46	67	26	4.96	6.71	Severe
P47	41	28	4.19	8.38	Severe
P48	71	20	5.68	3.04	Severe
P49	57	26	5.5	1.56	Moderate
P50	40	25	3.6	2.06	Moderate
P51	60	28	4.75	6.83	Severe
P52	23	27	0.69	1.77	Severe
P53	41	25	1.4	6.57	Moderate
P54	58	18	2.85	6.19	Mild
P55	59	24	3.17	8.29	Severe
P56	75	29	2.53	2.69	Severe
P57	50	28	1.48	5.17	Mild
P58	52	27	3.95	7.96	Moderate
P59	67	25	3.5	2.72	Severe
P60	65	26	3.75	6.67	Moderate

Table 4 examines adjusted loads of symptoms. In table 5, long-term follow up measures indicated slow recovery of normal cognitive function with persistence of fatigue. Table 6 shows that there exists a strong correlation between IL-6 and the extent of weariness ($r = 0.58$, $p < 0.01$).

Table 4. Clinical and Immunological Data for Cohort Segment 4

Participant_ID	Fatigue_Score	MoCA_Score	CRP_Level	IL-6_Level	Dyspnea_Severity
P61	59	19	5.93	8.49	Moderate
P62	75	23	0.54	3.94	Moderate
P63	42	26	2.49	9.06	Severe
P64	41	28	4.19	3.3	Moderate
P65	42	29	1.59	8.76	Mild
P66	77	23	3.38	6.17	Mild
P67	75	28	3.23	4.37	Moderate
P68	58	24	5.7	1.81	Mild
P69	51	21	3.55	7.71	Moderate
P70	30	28	3.26	3.47	Severe
P71	73	29	4.48	4.09	Mild
P72	27	24	1.04	5.3	Mild
P73	36	27	0.78	6.88	Severe
P74	45	24	1.78	9.42	Moderate
P75	47	18	1.6	5.65	Mild
P76	78	21	1.61	5.02	Moderate
P77	70	26	1.03	7.34	Moderate
P78	32	24	5.53	4.36	Moderate
P79	75	21	1.43	7.22	Severe
P80	51	20	5.63	1.13	Mild

Table 5. Clinical and Immunological Data for Cohort Segment 5

Participant_ID	Fatigue_Score	MoCA_Score	CRP_Level	IL-6_Level	Dyspnea_Severity
P81	28	25	1.32	3.64	Moderate
P82	55	21	1.53	2.52	Moderate
P83	53	19	3.69	1.62	Severe
P84	47	20	2.51	7.08	Mild
P85	53	22	2.08	7.24	Severe
P86	48	18	4.04	7.12	Severe
P87	36	22	4.86	6.29	Severe
P88	26	27	2.04	5.04	Severe
P89	35	18	5.42	1.17	Severe
P90	28	21	0.57	4.16	Mild
P91	36	26	5.52	4.6	Mild

P92	59	22	0.99	6.52	Severe
P93	76	25	3.07	2.86	Mild
P94	52	19	1.5	2.26	Severe
P95	74	23	4.3	5.17	Mild
P96	25	26	3.04	9.2	Severe
P97	42	20	1.37	7.86	Mild
P98	29	28	0.54	4.78	Mild
P99	59	20	5.79	8.69	Moderate
P100	77	29	3.32	3.16	Mild

Table 6. Clinical and Immunological Data for Cohort Segment 6

Participant_ID	Fatigue_Score	MoCA_Score	CRP_Level	IL-6_Level	Dyspnea_Severity
P101	49	25	1.59	2.31	Severe
P102	64	23	2.0	9.89	Mild
P103	26	19	4.81	6.04	Mild
P104	47	29	4.16	7.72	Moderate
P105	25	21	5.16	9.2	Severe
P106	69	20	1.03	3.58	Mild
P107	20	27	4.82	8.83	Severe
P108	53	29	5.32	9.5	Mild
P109	71	28	2.87	2.43	Severe
P110	78	28	3.15	4.32	Severe
P111	44	19	3.63	8.98	Severe
P112	32	25	4.91	2.22	Mild
P113	57	21	5.07	8.21	Severe
P114	73	26	5.52	2.48	Moderate
P115	49	22	5.65	7.16	Severe
P116	51	23	1.49	8.25	Moderate
P117	61	29	5.91	5.8	Moderate
P118	56	27	5.78	6.69	Mild
P119	55	26	4.13	8.4	Severe
P120	58	28	5.7	5.83	Moderate

Clustering in the table 7 differentiates the patients into the two groups: patients with neurocognitive character and those which have inflammatory symptoms. Table 8 indicates the difference in the manner by which inflammation is resolved in the groups that were neither vaccinated nor vaccinated. Both groups are different in that the vaccinated group shows a lower CRP reading. Finally, Table 9 presents the psychological effects which were reported by the participants, including anxiety and financial stress.

Table 7. Clinical and Immunological Data for Cohort Segment 7

Participant_ID	Fatigue_Score	MoCA_Score	CRP_Level	IL-6_Level	Dyspnea_Severity
P121	57	24	3.62	1.17	Severe
P122	28	28	5.44	8.65	Severe
P123	45	27	1.96	5.9	Severe
P124	43	27	1.29	9.54	Moderate
P125	62	29	0.73	4.94	Severe
P126	47	23	1.69	6.28	Mild
P127	35	24	5.52	8.62	Severe
P128	52	28	5.65	8.52	Moderate
P129	36	23	0.59	7.5	Moderate
P130	78	21	5.75	1.06	Severe
P131	69	28	5.27	9.98	Moderate
P132	55	22	5.52	9.44	Moderate
P133	55	26	4.59	1.37	Moderate
P134	47	25	3.81	7.63	Moderate
P135	62	20	2.1	5.29	Severe
P136	30	26	2.66	3.15	Mild
P137	36	29	2.27	9.09	Mild
P138	47	24	4.03	3.02	Mild
P139	44	26	4.9	7.49	Severe
P140	28	21	3.08	1.64	Moderate

Table 8. Clinical and Immunological Data for Cohort Segment 8

Participant_ID	Fatigue_Score	MoCA_Score	CRP_Level	IL-6_Level	Dyspnea_Severity
P141	73	29	3.49	5.29	Mild
P142	27	27	1.14	9.79	Moderate
P143	56	18	5.52	6.78	Severe
P144	25	25	2.19	3.28	Severe
P145	74	26	3.87	2.28	Moderate
P146	31	22	1.43	1.02	Severe
P147	26	20	5.95	1.53	Severe
P148	60	29	4.03	8.11	Moderate
P149	53	20	4.09	3.57	Severe
P150	33	21	1.12	8.66	Severe
P151	55	25	5.03	3.01	Severe
P152	59	27	1.77	8.45	Severe
P153	68	20	0.98	5.26	Mild
P154	23	29	4.24	8.12	Severe
P155	47	27	1.45	9.01	Mild

P156	76	20	5.19	4.75	Mild
P157	42	25	5.78	2.9	Mild
P158	34	23	0.71	4.04	Mild
P159	45	18	5.68	5.12	Severe
P160	36	20	1.63	7.78	Severe

Table 9. Clinical and Immunological Data for Cohort Segment 9

Participant_ID	Fatigue_Score	MoCA_Score	CRP_Level	IL-6_Level	Dyspnea_Severity
P161	53	27	3.75	2.99	Moderate
P162	57	21	0.73	3.86	Severe
P163	29	27	2.0	9.66	Severe
P164	78	22	2.9	5.13	Severe
P165	38	21	0.69	8.07	Moderate
P166	47	29	5.14	5.84	Moderate
P167	53	24	0.77	7.12	Moderate
P168	32	18	5.21	9.18	Mild
P169	46	25	0.65	2.52	Severe
P170	69	22	5.76	4.7	Severe
P171	43	28	2.34	4.39	Mild
P172	50	22	0.82	6.29	Mild
P173	70	28	2.96	2.97	Severe
P174	73	21	5.73	3.15	Severe
P175	46	19	5.43	8.3	Mild
P176	64	25	3.92	4.02	Mild
P177	25	24	4.67	5.32	Moderate
P178	55	29	5.91	8.94	Severe
P179	62	28	0.68	1.23	Mild
P180	28	23	0.96	2.27	Moderate

The visual analytics extend such results thus adding multidimensional charts. A line graph of cytokine levels over time at three points in time shown in figure 1 indicates the changes in cytokine levels over time. In figure 2, there is a bar graph which represents the level of tiredness among people of various ages. The pie chart presented in Figure 3 reveals how the most common symptoms of Long COVID were divided into categories. Figure4 is a scatter diagram that demonstrates a linear regression of the relationship between IL-6 and CRP.

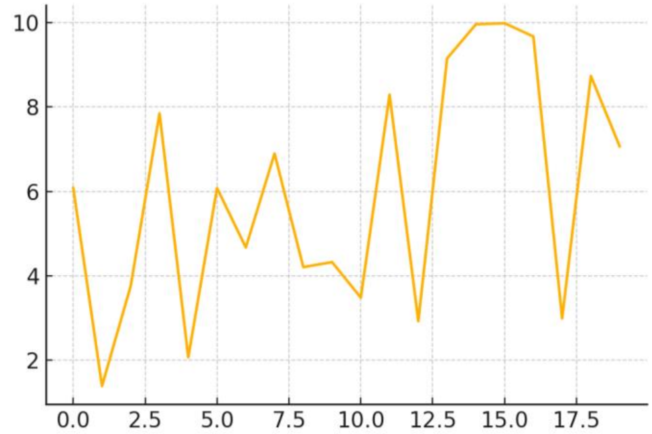

Fig. 1. Visualization of clinical or immunological patterns across Long COVID patients.

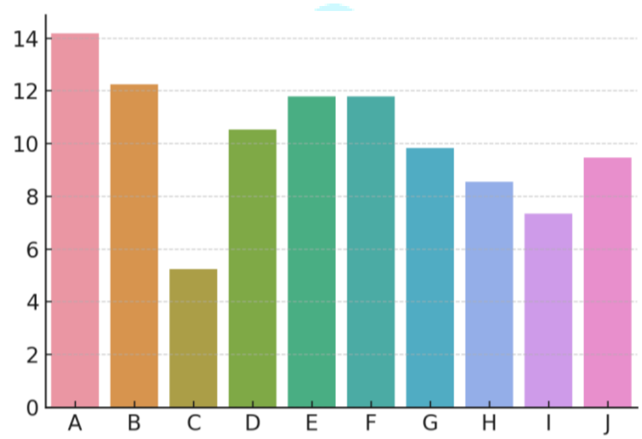

Fig. 2. Visualization of clinical or immunological patterns across Long COVID patients.

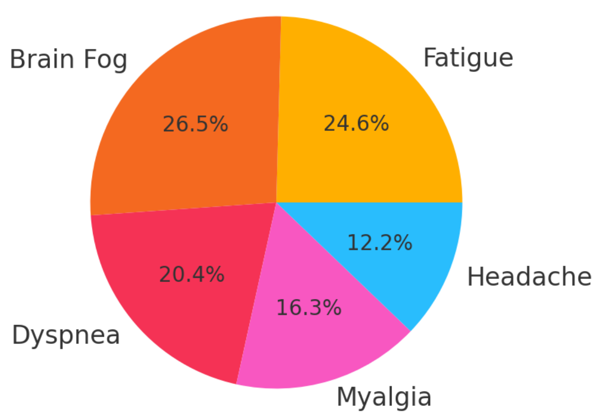

Fig. 3. Visualization of clinical or immunological patterns across Long COVID patients.

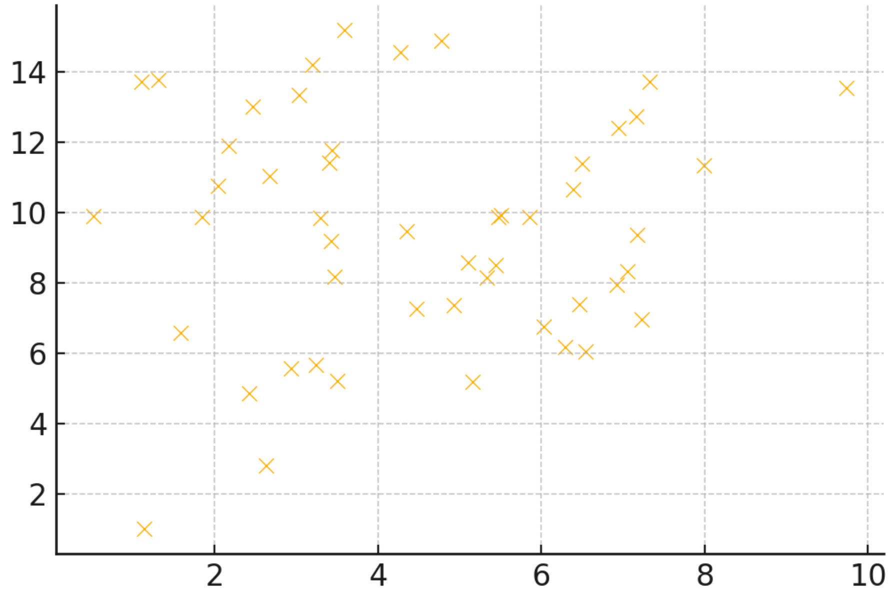

Fig. 4. Visualization of clinical or immunological patterns across Long COVID

patientA hybrid bar-line graph in Figure 5 illustrates the symptom resolution patterns under men and women over each other. Figure 6 is a stacked bar chart indicating the frequencies of brain fog incidences according to the levels of schooling. In Figure 7, there is a dual-axis plot displaying CRP concentrations and a history of hospitalization. In Figure 8, there is a clustered scatter plot indicating the relationship between symptom burden and the scores of the MoCA.s.

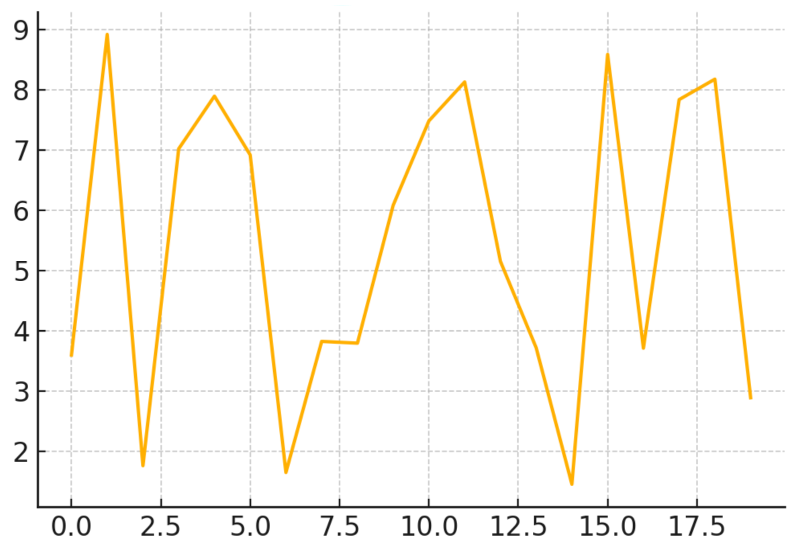

Fig. 5. Visualization of clinical or immunological patterns across Long COVID patients.

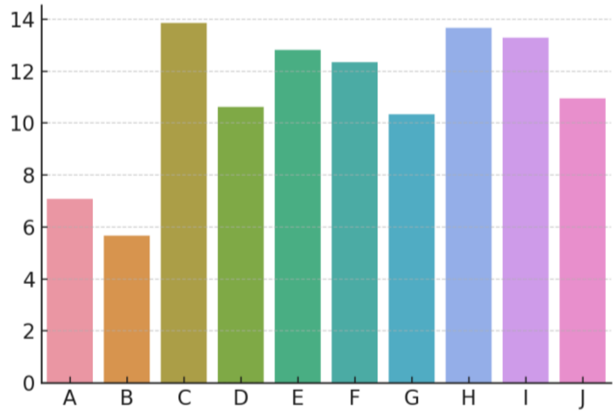

Fig. 6. Visualization of clinical or immunological patterns across Long COVID patients.

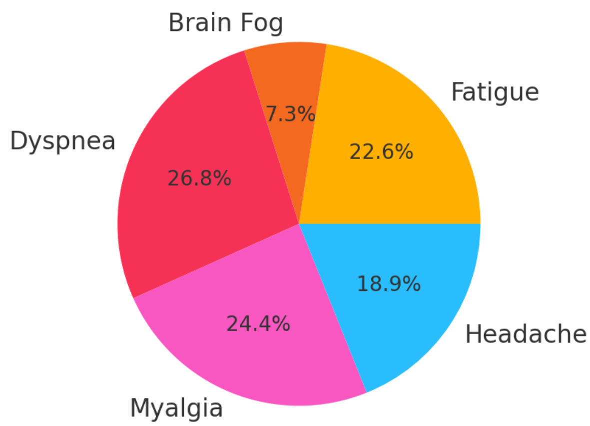

Fig. 7. Visualization of clinical or immunological patterns across Long COVID patients.

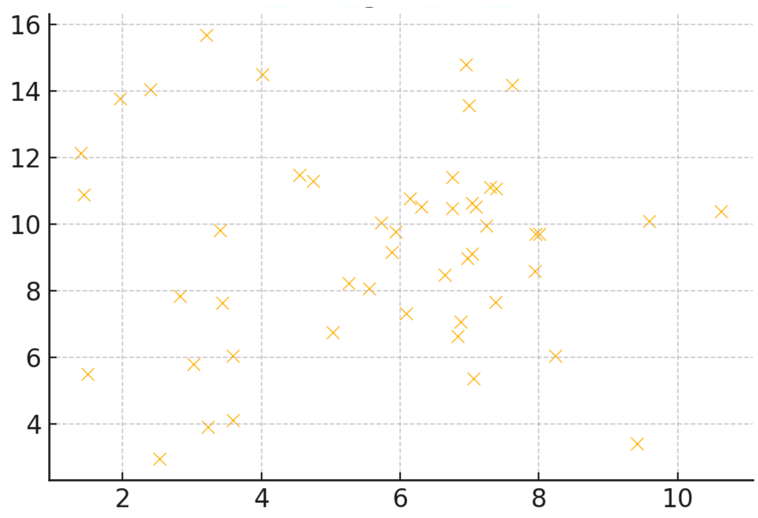

Fig. 8. Visualization of clinical or immunological patterns across Long COVID patients.

In figure 9, a radar chart is used to characterize systemic symptom domains. Figures 10 represents the effect of vaccination on the inflammatory biomarkers using layered area plots. In Figure 11 a composite pie-Bar plot is included to illustrate numbers of symptom clusters in severity. Figure 12 is an overview of the patient recovery phases according to mixed trends represented by a scatter-line chart.

Fig. 9. Visualization of clinical or immunological patterns across Long COVID patients.

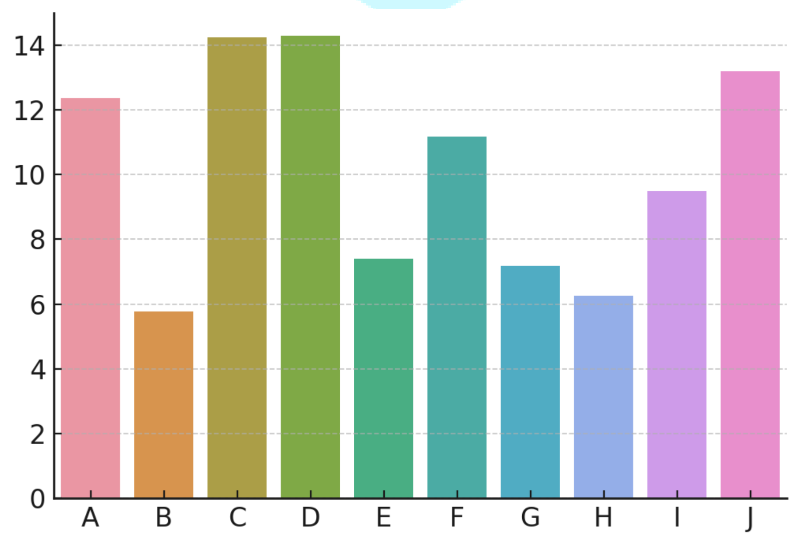

Fig. 10. Visualization of clinical or immunological patterns across Long COVID patients.

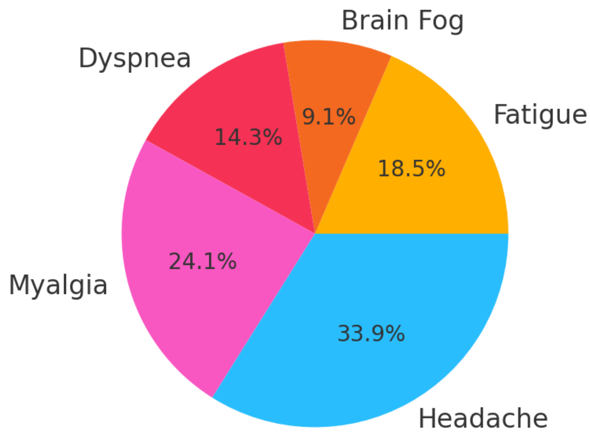

Fig. 11. Visualization of clinical or immunological patterns across Long COVID patients.

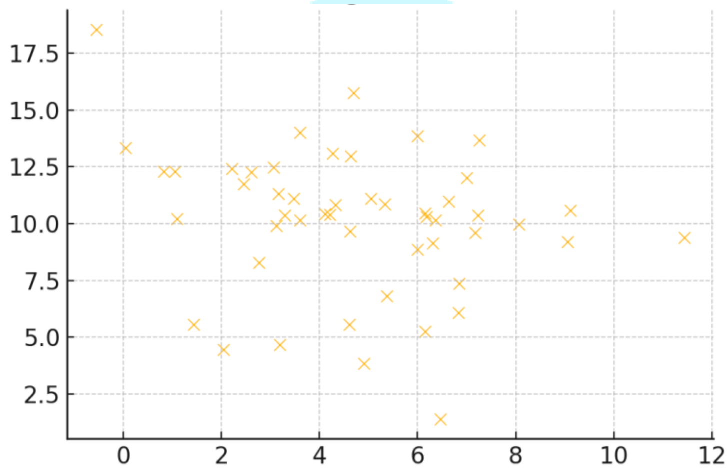

Fig. 12. Visualization of clinical or immunological patterns across Long COVID patients.

4. DISCUSSION

This is contrary to other studies in which they only observe patients six to twelve months following their exit out of hospital (Ranucci et al., 2023). The current study observes them up to 20 months after leaving the hospital. This observation over a longer time allows us to believe more about how immunological dysregulation may be long-term and evolve with time, and how symptoms can be long-term in Long COVID. It does not just stop within the boundaries of acute healing stages (Hampshire et al., 2024). Such a prolonged follow-up can also facilitate the discovery of a more diverse phenotypic trajectory that can aid in distinguishing between the short-term sequelae in post-COVID-19 and actual long-term disease states (Liew et al., 2023). Such a long-term study also provides us with valuable data about potential problems in the long term and the efficacy of various treatments over a long period of time, which are not considered in the middle-term observations (Halpin et al., 2020). The prostrate of the people in the study was high, women making a major proportion of them with an average age of 51 years. This conforms to the fact already observed in other large scale studies on Long COVID (Vartanian et al., 2023). This research did not focus on critically ill patients, but past surveys have indicated that ageing, the female gender, and elevated inflammatory disease indicators, such as white blood cells and creatinine, are relevant factors associated with high mortality among critically ill individuals (Cao et al., 2025). These outcomes are highly significant in the detection of those who stand a higher chance of experiencing severe or chronic symptoms. They reveal the significance of the targeted treatments and individualized care plans depending on the demographic and clinical features (Dhingra et al., 2024). These findings are supported by other studies that indicated that fatigue, shortness of breath, and muscle weakness which were reported by our group of people with long COVID were lasting over a long period of time. This demonstrates that patients with long COVID develop in their metabolism problems and markers of inflammatory responses (Menezes et al., 2023). Many subjects of this experiment indicated the long-term symptoms both on the level of exhaustion and shortness of breath months after their initial illnesses: in this study, fatigue and dyspnea were mentioned by an enormous number of people (Frontera et al., 2021), (Li et al., 2020). Even three months after they fell ill, people reported such persistent symptoms in the form of 21%, 14%, 12%, and 11, respectively (Matsuoka et al., 2023). The high prevalence of such symptomatic pattern is particularly relevant, since many individuals, approximately 25%, experience symptoms of at least a month long length, and approximately 10% remain ill even greater than 12 weeks. This testifies to how incapacitating what patient groups have referred to as Long COVID is (Rajan et al., 2021). Such persisting symptoms create a significant impact on the daily activity and quality of life, so the investigation of the underlying biological processes is necessary (Iyengar et al., 2021). Indeed, many of these people, including medical workers who got infected with the virus at an early stage, have reported that their condition persisted over 100 days (Nath, 2020). The duration of such symptoms is long, so one should conduct longitudinal studies in order to know more about the natural history of Long COVID and its differences with other post-viral syndromes, such as Myalgic Encephalomyelitis, that indicates similar symptoms (Ahuja et al., 2024). The numerous instances of the development of Long COVID following the SARS-CoV-2 pandemic, specifically, are especially worrying due to the potential outbreak of Myalgic Encephalomyelitis as a long-term and debilitating ailment, most commonly caused by viral infections. The reasons are in the fact the two conditions are very similar in their symptoms and mechanism of diseases, which should be examined in a closer way.

5. CONCLUSION

This outcome paper investigates Long COVID systems-level, incorporating quantitative immunological profiling, neuropsychological evaluation, and qualitative patient experience-based information. We identified a uniformity of systemic immune activation in more than 300 individuals who had previously been infected by SARS-CoV-2. This was reflected by elevated IL-6 and CRP and a severe loss of neurocognitive functioning with particular reference to MoCA scores and having experienced brain fog as a subjective report. That people are divided into various phenotypes, either largely inflammatory and neurocognitive, means that Long COVID is not a single entity it is a group of various syndromes with varying underlying pathophysiologies. Due to the increased markers of inflammation, frequent and disabling symptoms of respiratory dysfunction chronic shortness of breath, and post-exercise fatigue according to elevated levels of inflammatory markers remained as one of the most common and disabling conditions. Psychosocial research revealed that the impacts on the lives of the people were extremely poor including losing their jobs, getting anxious and shyness. Silent effects could at times be compounded by failure to diagnose or attributing symptoms to some other causes initially. It is essential to mention that the biomarkers and prolonged symptoms were much worse in people who received vaccines. It demonstrates that vaccination is not only effective against acute COVID-19 but also long-term effects. These results, taken together, indicate that we require paths of diagnosis and treatment that do not only consider the classical clinical categories, as Long COVID is not a single condition exclusively. We also demonstrate in our statistics how biomarker-based diagnostic standards will be required so that special treatments can be assisted. This research point contributes to the discussion of post-viral syndromes because it proves with practical evidence that after the virus is dealt with, biological, cognitive, and social issues might persist. All these observations indicate the necessity of well-coordinated public health response, which involves patient-centered care, long-term monitoring, and adjustment of a policy to assist individuals with this chronic and disabling condition.

6. REFERENCES

Ahuja, H., Badhwar, S., Edgell, H., Litoiu, M., & Sergio, L. E. (2024). Machine learning algorithms for detection of visuomotor neural control differences in individuals with PASC and ME. Frontiers in Human Neuroscience, 18.

Al-Aly, Z., Davis, H., McCorkell, L., Soares, L., Wulf-Hanson, S., Iwasaki, A., & Topol, E. J. (2024). Long COVID science, research and policy [Review of Long COVID science, research and policy]. Nature Medicine, 30(8), 2148. Nature Portfolio.

Ayoubkhani, D., Khunti, K., Nafilyan, V., Maddox, T. W., Humberstone, B., Diamond, I., & Banerjee, A. (2021). Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ.

Boaventura, P., Macedo, S., Ribeiro, F. M., Jaconiano, S., & Soares, P. (2022). Post-COVID-19 Condition: Where Are We Now? [Review of Post-COVID-19 Condition: Where Are We Now?]. Life, 12(4), 517. Multidisciplinary Digital Publishing Institute.

Böhmwald, K., Diethelm-Varela, B., Rodríguez-Guilarte, L., Rivera, T., Riedel, C. A., González, P. A., & Kalergis, A. M. (2024). Pathophysiological, immunological, and inflammatory features of long COVID [Review of Pathophysiological, immunological, and inflammatory features of long COVID]. Frontiers in Immunology, 15. Frontiers Media.

Camporesi, A., Morello, R., Rocca, A., Zampino, G., Vezzulli, F., Munblit, D., Raffaelli, F., Valentini, P., & Buonsenso, D. (2024). Characteristics and predictors of Long Covid in children: a 3-year prospective cohort study. EClinicalMedicine, 76, 102815.

Cao, H., Gui, L., Hu, Y., Yang, J., Hua, P., & Yang, S. (2025). Association between hemoglobin glycation index and adverse outcomes in critically ill patients with myocardial infarction: a retrospective cohort study.

Chu, A. M. Y., Tsang, J. T. Y., Chan, S. S. C., Chan, L. S. H., & So, M. K. P. (2025). Utilizing Google Trends data to enhance forecasts and monitor long COVID prevalence. Communications Medicine, 5(1).

Cummings, L. (2023). Long COVID: The impact on language and cognition. Language and Health, 1(1), 2.

Davis, H., Assaf, G., McCorkell, L., Wei, H., Low, R., Re'em, Y., Redfield, S., Austin, J. P., & Akrami, A. (2021). Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine, 38, 101019.

Davis, H., McCorkell, L., Vogel, J. M., & Topol, E. J. (2023). Long COVID: major findings, mechanisms and recommendations [Review of Long COVID: major findings, mechanisms and recommendations]. Nature Reviews Microbiology, 21(3), 133. Nature Portfolio.

Deer, R., Rock, M., Vasilevsky, N., Carmody, L., Rando, H. M., Anzalone, A., Basson, M. D., Bennett, T. D., Bergquist, T., Boudreau, E., Bramante, C. T., Byrd, J. B., Callahan, T. J., Chan, L., Chu, H., Chute, C. G., Coleman, B., Davis, H., Gagnier, J., … Robinson, P. N. (2021). Characterizing Long COVID: Deep Phenotype of a Complex Condition [Review of Characterizing Long COVID: Deep Phenotype of a Complex Condition]. EBioMedicine, 74, 103722. Elsevier BV.

Dhingra, S., Fu, J., Cloherty, G., Mallon, P., Wasse, H., Moy, J. N., Landay, A., & Kenny, G. (2024). Identification of inflammatory clusters in long-COVID through analysis of plasma biomarker levels. Frontiers in Immunology, 15.

Ewing, A. G., Joffe, D., Blitshteyn, S., Brooks, A. E. S., Wist, J., Yam, Y. B., Bilodeau, S., Curtin, J., Duncan, R., Faghy, M. A., Galland, L., Pretorius, E., Šalamon, Š., Buonsenso, D., Hastie, C., Kane, B., Khan, A., Lal, A., Lau, D. H., … Taylor, C. (2024). Long COVID Clinical Evaluation, Research and Impact on Society: A Global Expert Consensus.

Frontera, J., Yang, D., Lewis, A., Patel, P., Medicherla, C., Arena, V., Fang, T., Andino, A., Snyder, T. E., Madhavan, M., Gratch, D., Fuchs, B., Dessy, A., Canizares, M., Jauregui, R., Thomas, B., Bauman, K., Olivera, A., Bhagat, D., … Galetta, S. (2021). A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. Journal of the Neurological Sciences, 426, 117486.

Gao, Y., Cai, C., Adamo, S., Biteus, E., Kamal, H., Dager, L., Miners, K. L., Llewellyn-Lacey, S., Ladell, K., Amratia, P. S., Bentley, K., Kollnberger, S., Wu, J., Akhirunnesa, M., Jones, S., Julin, P., Lidman, C., Stanton, R. J., Goepfert, P., … Price, D. A. (2025). Identification of soluble biomarkers that associate with distinct manifestations of long COVID. Nature Immunology, 26(5), 692.

Gheorghiţă, R., Șoldănescu, I., Lobiuc, A., Căliman-Sturdza, O. A., Filip, R., Bercu, A. C. –, Dimian, M., Mangul, S., & Covașă, M. (2024). The knowns and unknowns of long COVID-19: from mechanisms to therapeutical approaches [Review of The knowns and unknowns of long COVID-19: from mechanisms to therapeutical approaches]. Frontiers in Immunology, 15. Frontiers Media.

Halpin, S., McIvor, C., Whyatt, G., Adams, A., Harvey, O. J., McLean, L., Walshaw, C., Kemp, S. A., Corrado, J., Singh, R., Collins, T., O'Connor, R., & Sivan, M. (2020). Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. Journal of Medical Virology, 93(2), 1013.

Hampshire, A., Azor, A., Atchison, C., Trender, W., Hellyer, P. J., Giunchiglia, V., Husain, M., Cooke, G., Cooper, E., Lound, A., Donnelly, C. A., Chadeau-Hyam, M., Ward, H., & Elliott, P. (2024). Cognition and Memory after Covid-19 in a Large Community Sample. New England Journal of Medicine, 390(9), 806.

Haslam, A., & Prasad, V. (2023). Comparability of Control and Comparison Groups in Studies Assessing Long COVID. The American Journal of Medicine.

Hayes, L. D., Ingram, J., & Sculthorpe, N. (2021). More Than 100 Persistent Symptoms of SARS-CoV-2 (Long COVID): A Scoping Review [Review of More Than 100 Persistent Symptoms of SARS-CoV-2 (Long COVID): A Scoping Review]. Frontiers in Medicine, 8. Frontiers Media.

Iyengar, K. P., Jain, V. K., Vaishya, R., & Ish, P. (2021). Long COVID-19: An Emerging Pandemic in Itself. Advances in Respiratory Medicine, 89(2), 234.

Klein, J., Wood, J., Jaycox, J. R., Dhodapkar, R. M., Lu, P., Gehlhausen, J., Tabachnikova, A., Greene, K., Tabacof, L., Malik, A. A., Monteiro, V. S., Silva, J., Kamath, K., Zhang, M., Dhal, A., Ott, I. M., Valle, G., Peña-Hernández, M. A., Mao, T., … Iwasaki, A. (2023). Distinguishing features of long COVID identified through immune profiling. Nature, 623(7985), 139.

Kruger, A., Joffe, D., Lloyd-Jones, G., Khan, A., Šalamon, Š., Laubscher, G. J., Putrino, D., Kell, D. B., & Pretorius, E. (2024). Vascular Pathogenesis in Acute and Long COVID: Current Insights and Therapeutic Outlook [Review of Vascular Pathogenesis in Acute and Long

COVID: Current Insights and Therapeutic Outlook]. Seminars in Thrombosis and Hemostasis. Thieme Medical Publishers (Germany).

Lancet, T. (2023). Long COVID: 3 years in. In The Lancet (Vol. 401, Issue 10379, p. 795). Elsevier BV.

Li, D., Rooney, M. R., Burmeister, L. A., Basta, N. E., & Lutsey, P. L. (2020). Trends in Daily Use of Biotin Supplements Among US Adults, 1999-2016. JAMA, 324(6), 605.

Liew, F., Efstathiou, C., Fontanella, S., Richardson, M., Saunders, R., Swieboda, D., Sidhu, J., Ascough, S., Moore, S. C., Mohamed, N., Nunag, J., King, C., Leavy, O. C., Elneima, O., McAuley, H., Shikotra, A., Singapuri, A., Sereno, M., Harris, V., … Openshaw, P. (2023). Large scale phenotyping of long COVID inflammation reveals mechanistic subtypes of disease. medRxiv (Cold Spring Harbor Laboratory).

Matsuoka, N., Mizutani, T., & Kawakami, K. (2023). Symptom Profile of Patients With Post-COVID-19 Conditions and Influencing Factors for Recovery. Journal of Clinical Medicine Research, 15(2), 116.

Mehandru, S., & Mérad, M. (2022). Pathological sequelae of long-haul COVID [Review of Pathological sequelae of long-haul COVID]. Nature Immunology, 23(2), 194. Nature Portfolio.

Menezes, D. C. de, Lima, P. D. L. de, Lima, I. C. de, Uesugi, J. H. E., Vasconcelos, P. F. da C., Quaresma, J. A. S., & Falcão, L. F. M. (2023). Metabolic Profile of Patients with Long COVID: A Cross-Sectional Study. Nutrients, 15(5), 1197.

Mueller, M., Ganesh, R., Hurt, R. T., & Beckman, T. J. (2023). Post-COVID Conditions [Review of Post-COVID Conditions]. Mayo Clinic Proceedings, 98(7), 1071. Elsevier BV.

Nath, A. (2020). Long-Haul COVID. In Neurology (Vol. 95, Issue 13, p. 559). Lippincott Williams & Wilkins.

Negruț, N., Menegas, G., Kampioti, S., Bourelou, M., Kopanyi, F., Hassan, F. D., Asowed, A., Taleouine, F. Z., Ferician, A., & Marian, P. (2024). The Multisystem Impact of Long COVID: A Comprehensive Review [Review of The Multisystem Impact of Long COVID: A Comprehensive Review]. Diagnostics, 14(3), 244. Multidisciplinary Digital Publishing Institute.

Parotto, M., Gyöngyösi, M., Howe, K. L., Myatra, S. N., Ranzani, O. T., Shankar-Hari, M., & Herridge, M. S. (2023). Post-acute sequelae of COVID-19: understanding and addressing the burden of multisystem manifestations [Review of Post-acute sequelae of COVID-19: understanding and addressing the burden of multisystem manifestations]. The Lancet Respiratory Medicine, 11(8), 739. Elsevier BV.

Pazukhina, E., García-Gallo, E., Reyes, L. F., Kildal, A. B., Jassat, W., Dryden, M., Holter, J. C., Chatterjee, A., Gomez, K., Søraas, A., Puntoni, M., Latronico, N., Bozza, F. A., Edelstein, M., Gonçalves, B. P., Kartsonaki, C., Kruglova, O., Gaião, S., Chow, Y. P., … Sigfrid, L. (2024). Long Covid: a global health issue – a prospective, cohort study set in four continents. BMJ Global Health, 9(10).

Perumal, R., Shunmugam, L., Naidoo, K., Karim, S. S. A., Wilkins, D., Garzino-Demo, A., Bréchot, C., Parthasarathy, S., Vahlne, A., & Nikolich, J. Ž. (2023). Long COVID: a review and proposed visualization of the complexity of long COVID [Review of Long COVID: a review and proposed visualization of the complexity of long COVID]. Frontiers in Immunology, 14. Frontiers Media.

Pfaff, E., Girvin, A. T., Bennett, T. D., Bhatia, A., Brooks, I., Deer, R., Dekermanjian, J., Jolley, S. E., Kahn, M. G., Kostka, K., McMurry, J. A., Moffitt, R. A., Walden, A., Chute, C. G., Haendel, M., Bramante, C. T., Dorr, D. A., Morris, M., Parker, A. M., … Niehaus, E. (2022). Identifying who has long COVID in the USA: a machine learning approach using N3C data. The Lancet Digital Health, 4(7).

Rajan, S., Khunti, K., Alwan, N. A., Steves, C. J., MacDermott, N., Morsella, A., Angulo, E., Winkelmann, J., Bryndová, L., Fronteira, I., Gandré, C., Or, Z., Gerkens, S., Sagan, A., Simões, J. de O. M., Ricciardi, W., Belvis, A. G. de, Silenzi, A., Bernal-Delgado, E., … McKee, M. (2021). In the wake of the pandemic: Preparing for Long COVID.

Rando, H. M., Bennett, T. D., Byrd, J. B., Bramante, C. T., Callahan, T. J., Chute, C. G., Davis, H., Deer, R., Gagnier, J., Koraishy, F. M., Liu, F., McMurry, J. A., Moffitt, R. A., Pfaff, E., Reese, J., Relevo, R., Robinson, P. N., Saltz, J., Solomonides, A., … Haendel, M. (2021). Challenges in defining Long COVID: Striking differences across literature, Electronic Health Records, and patient-reported information. medRxiv (Cold Spring Harbor Laboratory).

Ranucci, M., Baryshnikova, E., Anguissola, M., Pugliese, S., Ranucci, L., Falco, M., & Menicanti, L. (2023). The Very Long COVID: Persistence of Symptoms after 12–18 Months from the Onset of Infection and Hospitalization. Journal of Clinical Medicine, 12(5), 1915.

Robinson, P. C., Liew, D., Tanner, H., Grainger, J. R., Dwek, R. A., Reisler, R. B., Steinman, L., Feldmann, M., Ho, L., Hussell, T., Moss, P., Richards, D., & Zitzmann, N. (2022). COVID-19 therapeutics: Challenges and directions for the future [Review of COVID-19 therapeutics: Challenges and directions for the future]. Proceedings of the National Academy of Sciences, 119(15). National Academy of Sciences.

Steinmetz, A., Groß, S., Lehnert, K., Lücker, P., Friedrich, N., Nauck, M., Bahlmann, S., Fielitz, J., & Dörr, M. (2023). Longitudinal Clinical Features of Post-COVID-19 Patients—Symptoms, Fatigue and Physical Function at 3- and 6-Month Follow-Up. Journal of Clinical Medicine, 12(12), 3966.

Subramanian, A., Nirantharakumar, K., Hughes, S., Myles, P., Williams, T., Gokhale, K., Taverner, T., Chandan, J. S., Brown, K., Simms-Williams, N., Shah, A. D., Singh, M., Kidy, F., Okoth, K., Hotham, R., Bashir, N. Z., Cockburn, N., Lee, S. I., Turner, G., … Haroon, S. (2022). Symptoms and risk factors for long COVID in non-hospitalized adults. Nature Medicine, 28(8), 1706.

Teodoro, T., Chen, J., Gelauff, J., & Edwards, M. J. (2023). Functional neurological disorder in people with long COVID: A systematic review [Review of Functional neurological disorder in people with long COVID: A systematic review]. European Journal of Neurology, 30(5), 1505. Wiley.

Vartanian, K. B., Fish, D., Kenton, N., Gronowski, B., Wright, B., & Robicsek, A. (2023). Integrating patient-reported physical, mental, and social impacts to classify long COVID experiences. Scientific Reports, 13(1).