NEUROSCIENCE RESEARCH NOTES

OPEN ACCESS | MINI-REVIEW ISSN: 2576-828X

Bibliometric analysis on potential biomarkers for long COVID

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Received: 22 August 2025; **Accepted:** 7 June 2026; **Published:** 28 June 2026
Edited by: Pike See Cheah (Universiti Putra Malaysia, Malaysia)
Reviewed by: Nurfaizatul Aisyah Ab Aziz (Universiti Malaysia Sarawak, Malaysia); Kumitaa Theva Das (Universiti Sains Malaysia, Malaysia)
https://doi.org/10.31117/neuroscirn.v9i2.502

Abstract: Long COVID has emerged as a significant public health challenge due to its diverse and often debilitating symptoms that affect various bodily systems. Identifying reliable diagnostic biomarkers for long COVID is crucial for early detection, prevention, and the development of treatment strategies. The aim of this study was to perform a bibliometric analysis of available biomarkers associated with long COVID published in the literature between 2020 and 2024. We searched the Scopus database for English-language research articles and reviews published between 2020 and 2024 that contained the terms “long COVID” and “biomarkers.” After excluding publications unrelated to the topic, we applied bibliometric techniques using the bibliometrix package in R and VOSviewer to analyse the final set of 398 articles. Publication trends, collaborative networks, keyword co-occurrence, and citation impact were systematically evaluated to identify the most frequently reported biomarkers and map the research landscape. Inflammatory factors, including interleukin 6, C-reactive protein, and tumour necrosis factor-alpha, were frequently highlighted. Additionally, cardiac function markers (troponin and N-terminal pro B-type natriuretic peptide) and neurological indicators (neurofilament light chain and glial fibrillary acidic protein) were identified. Although numerous studies have emphasised the multisystem pathology of long COVID, the published literature has not yet converged on a single biomarker with sufficient evidence for the clinical diagnosis of long COVID. This bibliometric analysis indicates that, while a unified diagnostic biomarker for long COVID remains elusive, multiple recurring patterns have emerged across immunological, cardiovascular, neurological, and metabolic domains. These findings may advance pathophysiological understanding and inform future research and clinical translation.

Keywords: Long COVID; Diagnostic biomarkers; SARS-CoV-2; Bibliometric analysis

1.0 INTRODUCTION

Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), commonly referred to as long COVID or long COVID-19, refers to the persistence of symptoms and health issues in some patients long after the acute phase of COVID-19 infection has resolved (Nalbandian et al., 2021; Davis et al., 2023). This condition has emerged as a significant public health challenge due to its diverse and often

debilitating symptoms that affect various bodily systems, including respiratory, cardiovascular, and neurological functions (Carfì et al., 2020; Greenhalgh et al., 2020).

However, the definition of this condition has not yet been well described. For example, the U.S. Centers for Disease Control and Prevention uses the term "PASC" to describe the wide range of health consequences that can persist for four weeks or more following SARS-CoV-2 infection (Centers for Disease Control and Prevention, 2024). Furthermore, the European Society of Clinical Microbiology and Infectious Diseases defines long COVID as the persistence or recurrence of one or more symptoms beyond 12 weeks after a confirmed COVID-19 infection, which cannot be explained by alternative diagnoses (Yelin et al., 2022). Similarly, the National Institute for Health and Care Excellence in the United Kingdom differentiates between ongoing symptomatic COVID-19, occurring from 4 to 12 weeks post-infection, and post-COVID-19 syndrome, which includes symptoms persisting beyond 12 weeks (National Institute for Health and Care Excellence, 2020). These definitions emphasise that long COVID is not a single disease but rather a condition with a broad spectrum of clinical manifestations (World Health Organization, 2021).

Identifying reliable diagnostic biomarkers for long COVID is crucial for early detection, patient stratification, and the development of personalised treatment strategies. Biomarkers, which are measurable indicators of biological states or conditions, can provide valuable insights into the underlying pathophysiological mechanisms of long COVID (Espín et al., 2023; Lai et al., 2023; Nalbandian et al., 2021). However, it remains unclear whether a specific diagnostic biomarker for long COVID exists or which markers are most reliably associated with this condition.

A bibliometric analysis involves quantitatively examining scientific publications to measure research output, influence, and collaboration patterns. This approach can help identify high-impact studies, leading researchers, significant research institutions, and most frequently used keywords, providing a detailed overview of the research dynamics (Guler et al., 2016; Ninkov et al., 2022; Pritchard, 1969).

Although several bibliometric analyses of long COVID have been published (Lai et al., 2024), these studies primarily focused on mapping general publication trends and collaborative networks without systematically categorising the identified biomarkers into pathophysiological domains. The present study addresses this gap by not only mapping the bibliometric landscape of long COVID biomarker research but also proposing a four-system biomarker framework encompassing immune-inflammatory, cardiovascular, neurological, and metabolic systems, thereby providing a structured conceptual model for understanding the multisystem pathophysiology of long COVID.

Specifically, this study aims to: (1) characterise publication trends, geographic distributions, and collaborative networks in long COVID biomarker research from 2020 to 2024; (2) identify the most frequently cited biomarkers and their clinical associations through keyword co-occurrence and citation analysis; and (3) propose a systematic biomarker classification framework based on convergent findings across high-impact studies.

2.0 METHODS

2.1 Initial data collection

2.1.1 Data source

The Scopus database was selected as the sole data source for this bibliometric analysis. Scopus was chosen over Web of Science and PubMed due to its broader multidisciplinary journal coverage, comprehensive citation tracking capabilities, and adherence to Bradford's law, making it particularly suitable for bibliometric research (Burnham, 2006). Furthermore, Scopus provides robust analytical metadata, including author affiliations, funding information, and keyword indexing, which facilitated the extraction of variables necessary for network and trend analyses (van Eck & Waltman, 2014).

This approach can help identify high-impact studies, leading researchers, and significant research institutions, providing a detailed overview of the research dynamics (Ninkov et al., 2022; van Eck & Waltman, 2014). The Scopus database is exclusively used for literature search due to its comprehensive coverage of global academic information across multiple disciplines and its adherence to Bradford's law, making it particularly suitable for bibliometric analysis (Burnham, 2006).

2.1.2 Keyword search

A literature search was conducted using the following specific keyword string: (TITLE-ABS-KEY("Long COVID" OR "Post-acute Sequelae of SARS-CoV-2 infection" OR "Post-COVID-19 Syndrome" OR "PASC" OR "Chronic COVID" OR "COVID-19 long-term effects" OR "Long haul

COVID" OR "Long-term COVID" OR "Long term effects of COVID") AND TITLE-ABS-KEY("Diagnostic markers" OR "Biomarkers" OR "Markers" OR "Indicators" OR "Diagnostic indicators" OR "Prognostic markers" OR "Prognostic indicators" OR "Clinical markers")). The initial search yielded 815 documents (**Figure 1**).

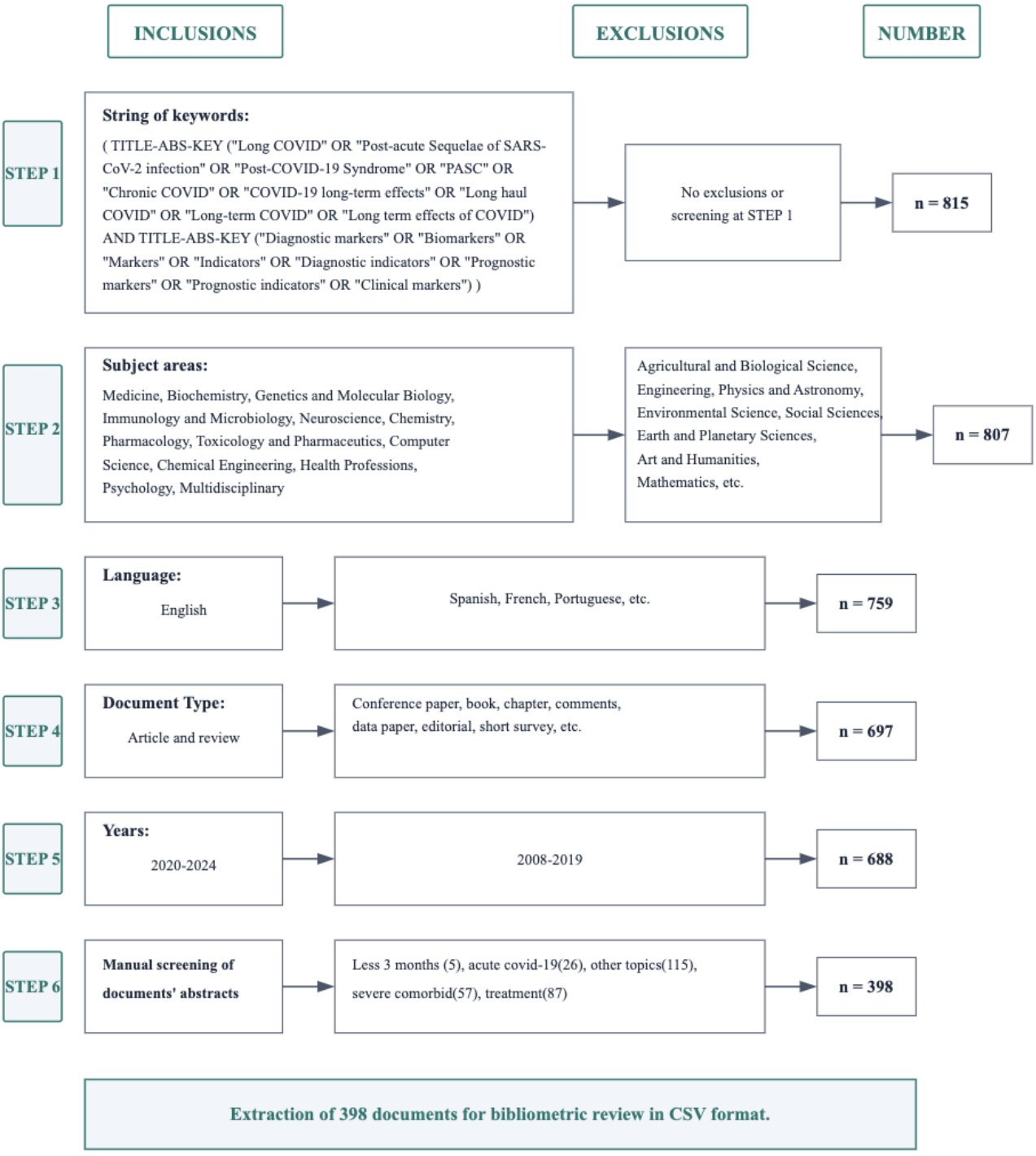

Figure 1: Flow diagram of the literature search and selection process for Long COVID diagnostic biomarker studies. This flowchart illustrates the screening process starting from an initial set of 815 documents identified by the specified keywords (step 1). Subsequent steps include selecting only documents from specific subject areas (step 2), limiting the language to English (step 3), restricting document types (step 4), and filtering by publication years (step 5). Finally, a manual screening of abstracts (step 6) was performed. A total of 398 documents that met the "Long COVID" and biomarker research requirements remained for the bibliometric analysis. In the figure, "n" indicates the number of documents remaining after each screening step.

2.1.3 Literature screening and selection

A systematic screening process was implemented to identify relevant literature. Initial exclusion removed documents from non-relevant fields, including Agricultural and Biological Sciences, Engineering, Physics and Astronomy, Environmental Science, Social Sciences, Earth and Planetary Sciences, Arts and Humanities, and Mathematics (n=807). Subsequently, non-English articles were excluded (n=759), followed by the removal of non-article and non-review types such as conference papers, book chapters, comments, data papers, editorials, and short surveys (n=697). The search was then restricted to publications from January 2020 to May 2024 (n=688). Finally, manual screening excluded studies focusing on acute COVID-19, treatments, or other unrelated topics, as well as those with follow-up periods of less than 3 months, yielding 398 articles for the final analysis. Given this exclusion criterion, the dataset predominantly reflects biomarker profiles associated with post-COVID-19 syndrome (>12 weeks post-infection); a sub-analysis distinguishing the 4–12 week phase was not feasible.

2.2 Data extraction and analysis

In this study, the R package "bibliometrix" was utilised for conducting bibliometric analysis. Additionally, "biblioshiny", an app providing a web interface for bibliometric analysis, was employed to extract variable data (Aria & Cuccurullo, 2017). We analysed and visualised various aspects, including publication trends, journal distributions, author distributions, countries and institutions, collaborative networks, citation impact, and the most frequently cited papers globally, and conducted keyword clustering analysis. Journal impact factors and category information were based on the "2024 Journal Citation Reports" (JCR, 2024).

For visualisation, Bibliometrix (version 4.1.2) and VOSviewer (version 1.6.19) were used to map co-authorship and keyword co-occurrence among countries, institutions, and authors to enhance the understanding of long COVID research (Lai et al., 2024; Yu et al., 2020). Biomarkers were selected based on frequency of citation (>5% of articles analysed), clinical relevance in cited studies, and confirmed associations with persistent long COVID symptoms identified in high-impact literature (citation threshold: >50 citations).

3.0 RESULTS

3.1 Document types and source analysis

From January 2020 to May 2024, research on diagnostic biomarkers for long COVID has increased significantly (**Figure 2**). A total of 398 documents were published across 212 sources. The annual growth rate of publications is 208.01%, highlighting rapidly growing interest and the urgent need to understand long COVID diagnostics. As depicted in **Figure 3**, the number of articles published per year has increased steadily, with a jump starting from 2021. In 2023, approximately 175 articles were published, and the predicted values for 2024 indicate a continued upward trend, with an estimated 200 articles. This suggests a sustained and growing interest in the field.

Figure 2: Overview of bibliometric indicators for long COVID diagnostic biomarker research (2020–2024). This dashboard summarises key descriptive statistics derived from 398 documents, including author counts, collaboration metrics, keyword diversity, and citation impact. Generated using the bibliometrix package (version 4.1.2) in R via biblioshiny.

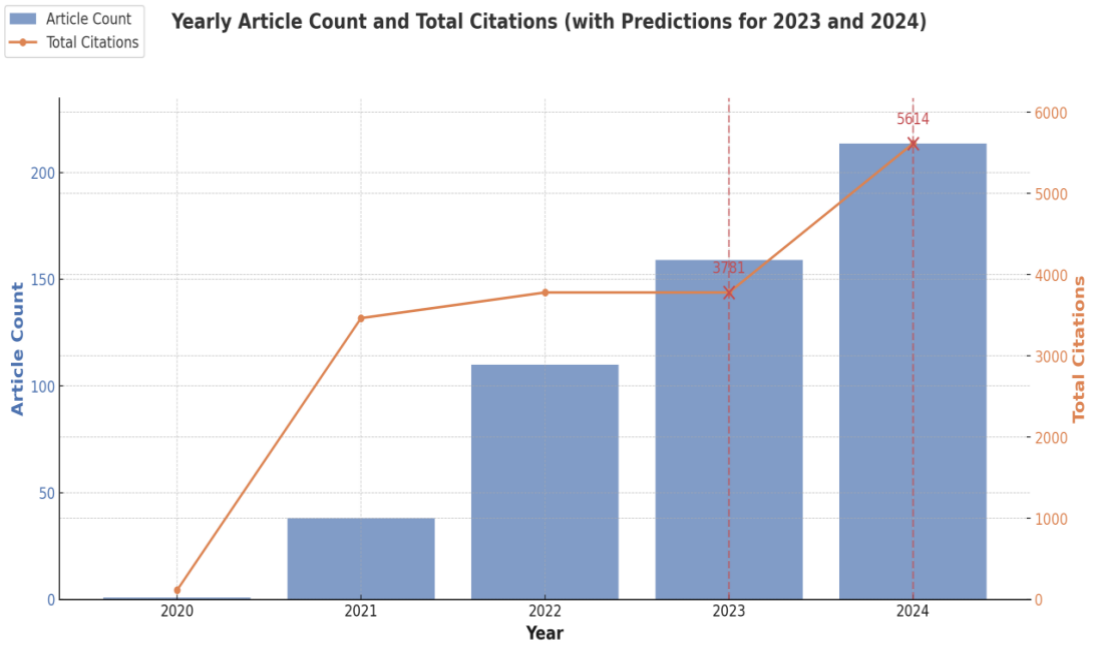

Figure 3: Annual publication and citation trends for long COVID diagnostic biomarker research (2020–2024). Blue bars represent annual article counts (left axis); the orange line shows cumulative citations (right axis). Values for 2023 and 2024 (dashed lines) are projected estimates based on data available at the time of collection. Generated using the bibliometrix package (version 4.1.2) in R via biblioshiny.

3.2 Author and authorship analysis

A total of 4,286 authors contributed to the body of work on long COVID biomarkers, reflecting the breadth of research engagement in this field (**Figure 2**).

3.3 Document age and research impact

The average age of the documents is 1.25 years, indicating the recent and rapidly evolving nature of research on long COVID biomarkers. This metric underscores the ongoing advancements and the up-to-date nature of the research outputs. Additionally, the high citation counts for key publications reflect the significant impact of these studies within the scientific community (**Figure 2**).

3.4 Geographic and institutional contributions

The United States emerged as the leading contributor, with 114 publications, and institutions such as Harvard University, which had 11 publications and 417 citations. Other notable contributors included Germany, Italy, and the United Kingdom, with Charité – Universitätsmedizin Berlin and University College London being key institutions in these countries (**Table 1**).

Table 1: The 10 most productive countries and institutions in long COVID diagnostic markers research

No.	Country	TP	TC
1	United States	114	3390
2	Germany	60	1261
3	Italy	51	685
4	United Kingdom	43	1440
5	Spain	26	456
6	Brazil	23	230
7	Canada	23	819
8	China	22	852
9	Australia	18	868
10	France	15	442
No.	**The most productive institution**	**TPi**	**TCi**
1	Harvard University	11	417
2	Charité – Universitätsmedizin Berlin	16	604
3	University of Rome La Sapienza	9	144
4	University College London	15	832
5	Centro de Investigación Biomédica en Red	6	174
6	Universidade de São Paulo	11	84
7	University of Alberta	5	57
8	University of Zurich	5	131
9	Barwon Health	6	65
10	Institut national de la santé et de la recherche médicale	12	438

TP = total publications; TC = total citations; TPi = total publication by institutions; TCi = total citations by institution

3.5 Author productivity and impact

An analysis of author productivity and impact revealed significant contributions from several key researchers in the field of long COVID diagnostic biomarkers. **Figure 4** illustrates the relationship between the number of publications and the total citations received by individual authors, providing insight into both the quantity and influence of their research output. This visualisation helps identify the most prolific and impactful researchers in the field. The analysis revealed that 4,286 authors contributed to the body of work on long COVID biomarkers, with an average of 12.3 co-authors per document. Only 11 documents were single-authored, indicating a strong preference for collaborative research efforts. International co-authorship accounted for 30.15% of the publications, underscoring the global nature of research in this field. The most productive authors in this field included Peluso Michael J. from the University of California at San Francisco and Scheibenbogen Carmen M. from Charité – Universitätsmedizin Berlin, each with 7 publications (**Table 2**). These authors have significantly influenced the field, as evidenced by their high citation counts and h-indices (**Figure 4**).

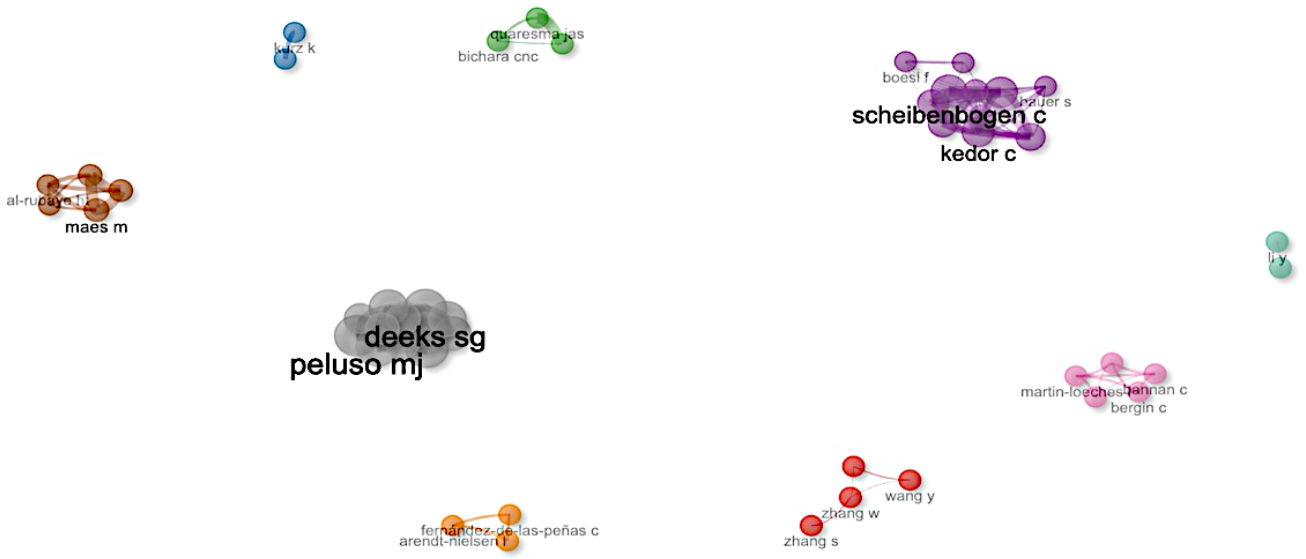

Figure 4: Author productivity and impact in the field of long COVID diagnostic biomarker research. This network visualisation illustrates co-authorship clusters among researchers in this field. Each colour-coded node represents an author, with larger nodes indicating higher productivity or citation impact. The proximity of the nodes reflects how often the authors collaborate, while larger labels denote authors with greater influence in the network. Generated using the bibliometrix package (version 4.1.2) in R via biblioshiny.

Table 2: The 10 most productive authors in long COVID diagnostic markers research

No.	Authors	TP	TC	h-index	Affiliation	Country
1	Peluso, Michael J.	7	359	41	University of California at San Francisco	United States
2	Scheibenbogen, Carmen M.	7	303	71	Charité – Universitätsmedizin Berlin	Germany
3	Quaresma, Juarez A.S.	7	124	33	Universidade Federal do Pará	Brazil
4	Magno Falcão, Luiz F.	7	124	12	Universidade do Estado do Pará	Brazil
5	Maes, Michael H.J.	7	91	149	University of Electronic Science and Technology of China	China
6	Deeks, Steven G.	6	359	155	University of California at San Francisco	United States
7	Bellmann-Strobl, Judith T.	6	284	36	Charité – Universitätsmedizin Berlin	Germany
8	Al-Hakeim, Hussein K.	6	65	23	University of Kufa	Iraq
9	Almulla, Abbas F.	6	65	17	The Islamic University, Najaf	Iraq
10	Fernández De Las Peñas, César	6	34	85	Universidad Rey Juan Carlos	Spain

TP = total publications; TC = total citations; h-index = Hirsch Index

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3.6 Journal analysis

The top journals publishing research on long COVID diagnostic biomarkers include "Frontiers in Immunology," "International Journal of Molecular Sciences," and "Journal of Clinical Medicine" (**Table 3**). These journals have consistently published high-impact articles, with "Frontiers in Immunology" leading with 29 publications and a high citation score. Based on the 2024 Journal Citation Reports, the majority of the top ten publishing journals in this dataset are classified as Q1 or Q2, reflecting the high academic standing of the publication venues. Open-access status was not systematically recorded; because open-access publications generally attract higher citation rates, this may be a potential source of citation bias to consider when interpreting journal-level findings.

Table 3: The 10 most productive journals in long COVID diagnostic markers research.

No.	Journal	TP	TC	Cite Score 2024	The most cited articles	Publisher
1	Frontiers in Immunology	29	358	9.8	Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning	Frontiers Media S.A.
2	International Journal of Molecular Sciences	20	138	6.2	Selenium deficiency due to diet, pregnancy, severe illness, or COVID-19—a preventable trigger for autoimmune disease	MDPI
3	Journal of Clinical Medicine	15	187	4.9	Biomarkers of post-COVID depression	MDPI
4	Viruses	9	65	5.4	Persistent SARS-CoV-2 Infection, EBV, HHV-6 and Other Factors May Contribute to Inflammation and Autoimmunity in Long COVID	MDPI
5	Scientific Reports	8	31	5.6	Extended coagulation profile of children with Long COVID: a prospective study	Nature Publishing Group
6	Brain, Behavior, and Immunity	7	811	7.7	Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis	Elsevier
7	Journal of Medical Virology	7	60	4.2	Persistence of neutrophil extracellular traps and anticardiolipin auto-antibodies in post-acute phase COVID-19 patients	Wiley-Blackwell
8	Cells	6	59	6.9	Role of SARS-CoV-2 Spike-Protein-Induced Activation of Microglia and Mast Cells in the Pathogenesis of Neuro-COVID	MDPI
9	Frontiers in Medicine	6	130	5.1	Serum Metabolic Profile in Patients With Long-COVID (PASC) Syndrome: Clinical Implications	Frontiers Media S.A
10	Journal of Personalised Medicine	6	22	5.2	Long COVID: Clinical Framing, Biomarkers, and Therapeutic Approach	MDPI

TP = total publications; TC = total citations.

3.7 Highly cited articles

The article titled "Long COVID or Post-COVID-19 Syndrome: Putative Pathophysiology, Risk Factors, and Treatments" by Yong et al. (2021) stands out as the most cited, with an impressive 653 citations. Other highly cited works delve into the pathophysiology, risk factors, and long-term effects of COVID-19, underscoring the pivotal role these studies play in advancing understanding and driving progress in the field (**Table 4**).

3.8 Keyword and citation analysis

The documents featured 1,019 unique keywords, suggesting a diverse range of research topics and approaches within the field. The total number of references cited across all documents is 27,294, indicating extensive academic dialogue and foundational research underpinning current studies. The average number of citations per document is 22.08, demonstrating the high impact and relevance of these studies within the scientific community (**Figure 2**).

3.9 Network analysis

The keyword co-occurrence network provided insights into the interconnectedness of various research themes. Central nodes such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) indicate a predominant focus on inflammatory processes. The network also highlighted significant associations with clinical symptoms such as fatigue, dyspnea, and myalgia, underscoring the multifaceted nature of long COVID and the need for a comprehensive diagnostic approach (**Figure 5**).

Table 4: Top 10 articles on the Scopus database ordered by citation score.

No.	Citation	Title	Journal	Publisher	TC 2024
1	Yong et al. (2021)	Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments	Infectious Diseases	Sunway University	653
2	Ceban et al. (2022)	Fatigue and cognitive impairment in Post-COVID-19 Syndrome: A systematic review and meta-analysis	Brain, Behavior, and Immunity	University Health Network	581
3	Mandal et al. (2021)	Long-COVID': A cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19	Thorax	Royal Free London Nhs Foundation Trust	531
4	Phetsouphanh et al. (2022)	Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection	Nature Immunology	University of New South Wales	444
5	Guedj et al. (2021)	18F-FDG brain PET hypometabolism in patients with Long COVID	European Journal of Nuclear Medicine and Molecular Imaging	Aix-Marseille University	258
6	Schou et al. (2021)	Psychiatric and neuropsychiatric sequelae of COVID-19 – A systematic review	Brain, Behavior, and Immunity	Aarhus University	226
7	Spudich et al. (2022)	Nervous system consequences of COVID-19	Science	Yale School of Medicine	219
8	Fogarty et al. (2021)	Persistent endotheliopathy in the pathogenesis of Long COVID syndrome	Journal of Thrombosis and Haemostasis	School of Pharmacy and Biomolecular Sciences	176
9	Gassen et al. (2021)	SARS-CoV-2-mediated dysregulation of metabolism and autophagy uncovers host-targeting antivirals	Nature Communications	University of Bonn	155
10	Swank et al. (2023)	Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae	Clinical Infectious Diseases	Harvard Medical School	146

TC = total citations.

3.10 Collaborative networks

The co-authorship network map revealed strong collaborative ties among researchers and institutions across different countries. Major collaborative hubs were identified in the United States and Europe, with extensive links to Asia and Australia. This global collaboration is essential to addressing the complex, multifaceted challenges of long COVID (**Figure 6**).

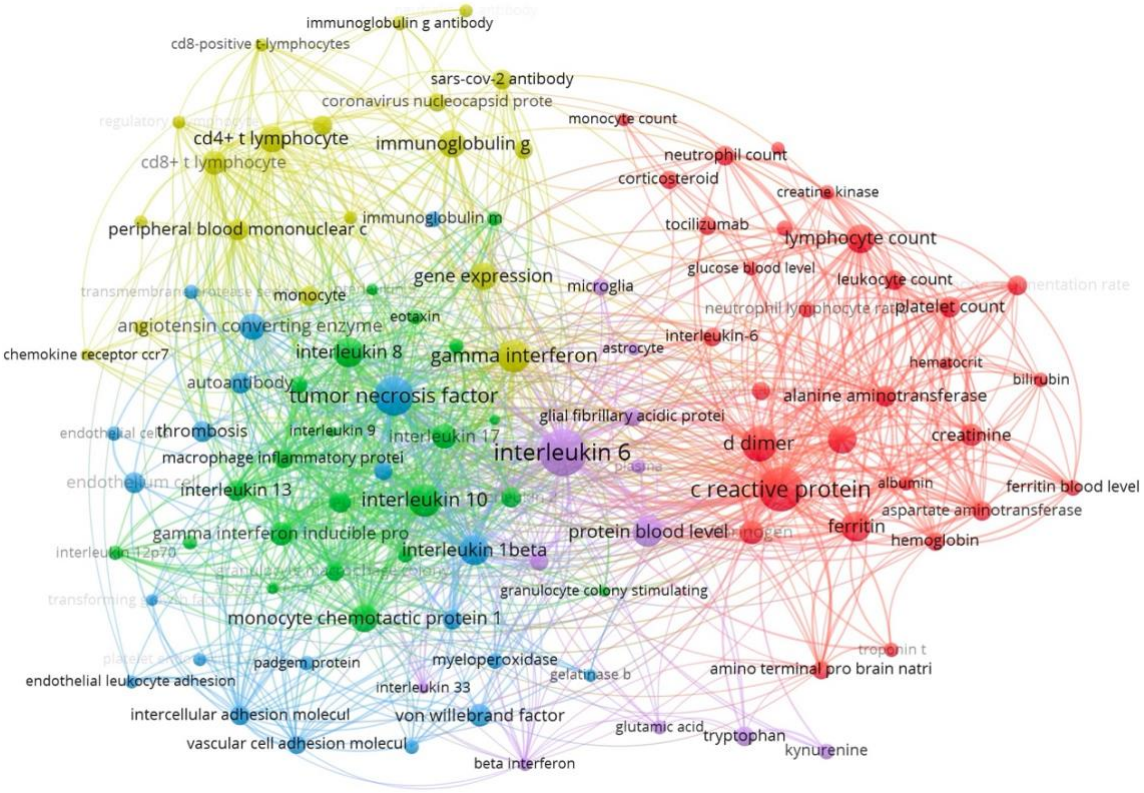

Figure 5: Keyword co-occurrence network analysis in the long COVID diagnostic biomarker research field. This network visualisation shows the co-occurrence relationships among frequently cited keywords in this field. Each node represents a specific keyword, with larger nodes indicating higher usage frequency. Colours group terms into clusters of closely related concepts, while the connecting lines (edges) reflect how often the keywords appear together—thicker lines denote stronger co-occurrence. Notably, immune and inflammatory terms (e.g., interleukin-6, C-reactive protein) form dense clusters, suggesting a strong research focus on immune dysregulation in long COVID. Generated using VOSviewer (version 1.6.19).

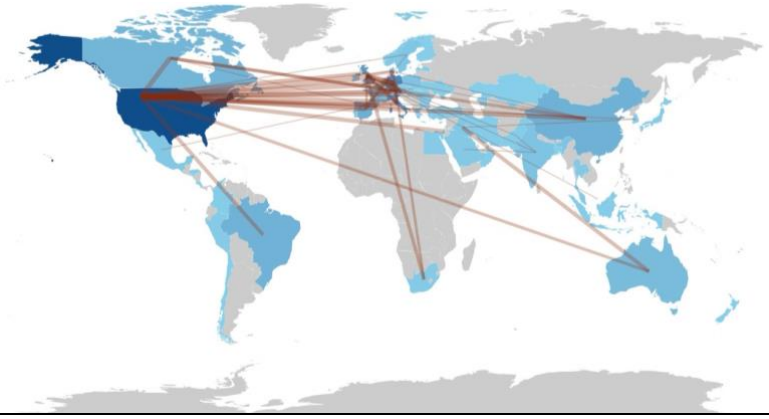

Figure 6: Global Collaboration Network in the long COVID diagnostic biomarker research field. This world map depicts the global collaboration network in this field. Countries are colour-coded by publication volume (dark shading indicates more publications). Lines between countries represent co-authorship links, with thicker lines denoting more frequent or extensive collaborations. Countries without relevant publications appear in a lighter or neutral tone. Generated using VOSviewer (version 1.6.19).

3.11 Analysis of the ten most representative studies in the field of long COVID from 2020.1 to 2024.5

The ten most representative studies in long COVID biomarker research were selected based on rigorous criteria emphasising both scientific impact and methodological quality. These studies were selected from the highest-cited original research articles (excluding reviews and meta-analyses) in our dataset, with impact factors ranging from 5.5 to 54.4, ensuring the inclusion of only the most influential clinical

investigations. The selection prioritised prospective and cross-sectional studies that provided robust evidence for biomarker associations with long COVID symptoms, with sample sizes ranging from 42 to 384 patients and follow-up periods ranging from a median of 54 days to over 8 months post-infection.

Table 5 was constructed to systematically present the clinical characteristics and biomarker profiles from these ten pivotal studies, enabling direct comparison of findings across different research groups and methodologies. The table consolidates critical information, including study design, sample demographics, symptom prevalence, and specific biomarker measurements, providing a comprehensive overview of the current evidence base.

Analysis of **Table 5** reveals consistent patterns across multiple independent investigations. The most frequently reported clinical manifestations include fatigue (ranging from 51% to 100% across studies), cognitive impairment and brain fog (49% to 87%), and respiratory symptoms, including breathlessness and persistent cough (34% to 80%). Regarding biomarker findings, inflammatory markers were persistently elevated, with interleukin-6, tumour necrosis factor-alpha, and C-reactive protein remaining abnormal months after acute infection. Cardiovascular biomarkers, including D-dimer, troponin, and natriuretic peptides, indicated ongoing cardiac and vascular dysfunction. Neurological markers, particularly neurofilament light chain and glial fibrillary acidic protein, correlated with cognitive symptoms and sensory disturbances.

Based on the convergent findings from **Table 5** and the broader literature analysis, we established a four-system biomarker framework that captures the multisystem pathophysiology of long COVID. This categorisation was developed because the identified biomarkers clustered into distinct pathophysiological domains: immune-inflammatory, cardiovascular, neurological, and metabolic. This systematic approach provides a structured framework for understanding the complex, interconnected nature of long COVID pathophysiology while facilitating clinical translation and future research directions. Beyond the core findings presented in **Table 5**, a comprehensive analysis of the broader literature reveals an extensive array of biomarkers spanning multiple biological systems (Supplementary Materials 1).

The immune-inflammatory system demonstrates the most extensive dysregulation, with elevated levels of numerous cytokines, chemokines, and acute-phase proteins. Complement system activation markers, including C1s-C1 inhibitor complex and terminal complement complex, indicate persistent immune activation. Adaptive immune dysfunction manifests through altered T-cell populations and autoantibody production against various self-antigens.

The four-system biomarker framework encompasses distinct but interconnected pathophysiological domains. The immune-inflammatory system, characterised by persistently elevated IL-6, TNF-α, and CRP, correlates with fatigue, persistent cough, and depressive symptoms. Research by Peluso et al. (2021) and Phetsouphanh et al. (2022) demonstrates that these inflammatory mediators remain elevated months after acute infection, suggesting fundamental disruption of immune resolution processes.

Cardiovascular system biomarkers, including troponin, NT-proBNP, and D-dimer, reflect ongoing cardiac injury and endothelial dysfunction. Studies by Mandal et al. (2021) and Townsend et al. (2021) document a persistent elevation of these markers that correlates with breathlessness, chest pain, and exercise intolerance. The work of Fogarty et al. (2021) specifically demonstrates endothelial activation via elevations in von Willebrand factor and thrombomodulin, indicating persistent vascular dysfunction.

Neurological system involvement is evidenced through neurofilament light chain and glial fibrillary acidic protein abnormalities, markers that directly correlate with brain fog, cognitive impairment, and sensory symptoms, including anosmia and ageusia. Research by Klein et al. (2023) and imaging studies by Guedj et al. (2021) provide convergent evidence for widespread nervous system involvement extending beyond the acute phase of infection. Metabolic system dysregulation manifests as markers of insulin resistance (HOMA2-IR) and lipid metabolic abnormalities, reflecting disruption of cellular energy metabolism. These findings, combined with markers of mitochondrial dysfunction, suggest fundamental alterations in cellular bioenergetics that may underlie the persistent fatigue and exercise intolerance characteristic of long COVID.

Table 5: Top 10 cited original articles on biomarkers in long COVID.

No.	Title	First Author, Year, Journal	IF; TC	Study design, sample number	Clinical findings and symptoms	Biomarkers
1	Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection	Phetsouphanh et al., 2022, Nat Immunol. 23(2):210-216.	28.3; 597	Cross-sectional study with matched controls, 62	Long COVID: 21.08%; persistent symptoms at 4 months, including fatigue, dyspnea, or chest pain.	BT: IFN-β ↑; IFN-λ1 ↑; IL-8 ↓; CXCL9 ↓; CXCL10 ↓; PTX3, IFN-γ, IFN-λ2/3, and IL-6 associated with long COVID
2	Long-COVID: A cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19	Mandal, 2021, Thorax. 76(4):396-398.	9; 587	Cross-sectional study, 384	Persistent breathlessness: 53%; persistent cough: 34%; persistent fatigue: 69%; depression: 14.6%	BT: D-dimer ↑; CRP ↑; lymphocytes ↑; ferritin ↓; ALT ↓; AST ↓
3	18F-FDG brain PET hypometabolism in patients with long COVID	Guedj, 2021, Eur J Nucl Med Mol Imaging. 48(9):2823-2833.	8.6; 308	Cross-sectional study with matched controls, 79	Dyspnea: 80%; pain: 66%; memory/cognitive impairment: 49%; insomnia: 46%; hyposmia/anosmia: 29%; dysgeusia/ageusia: 26%	PET: hypometabolism in bilateral rectus/orbital gyrus, right temporal lobe, bilateral pons/ medulla brainstem, and bilateral cerebellum
4	Distinguishing features of long COVID identified through immune profiling	Klein et al., 2023, Nature. 623(7985):139-148.	54.4; 291	Cross-sectional study, 275	Fatigue: 87% Brain fog: 78% Memory difficulty: 62% Confusion: 55%	BT: non-conventional monocytes ↑; cDC1 cells ↓; CD4+ IL-4/IL-6 double-positive T cells ↑; anti-S1 IgG ↑; anti-N IgG ↑; EBV gp23 antibodies ↑; cortisol ↓; complement C4b ↑; CCL19 ↑; galectin-1 ↑
5	Persistent Circulating Severe Acute Respiratory Syndrome Coronavirus 2 Spike Is Associated With Post-acute Coronavirus Disease 2019 Sequelae	Swank, 2023, Clin Infect Dis. 76(3):e487-e490.	8.2; 246	Retrospective pilot study with controls, 63	Cardiovascular symptoms: NQ; systemic symptoms: NQ; head/eye/ear/nose/throat symptoms: NQ; musculoskeletal symptoms: NQ	BT: spike ↑; S1 subunit ↑; nucleocapsid ↑

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6	Persistent endotheliopathy in the pathogenesis of long COVID syndrome	Fogarty, 2021, J Thromb Haemost. 19(10):2546-2553.	5.5; 211	Cross-sectional study with controls, 67	Hospitalisation: 74%; ICU admission: 16%; comorbidities: 62%	BT: factor VIII: C ↑; von Willebrand factor antigen ↑; von Willebrand factor propeptide ↑; soluble thrombomodulin ↑; thrombin generation abnormalities, including lag time ↓, endogenous thrombin potential ↑, and peak thrombin ↑
7	Markers of Immune Activation and Inflammation in Individuals With Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection	Peluso, 2021, J Infect Dis. 224(11):1839-1848.	5; 173	Prospective cohort study, 121	Concentration problems: 57.5%; Fatigue: 56.2%; Sleep problems: 43.8%; Anosmia/ dysgeusia: 37.0%	BT: TNF-α ↑; IP-10 ↑; IL-6 ↑
8	A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity	Kedor et al., 2022, Nat Commun. 13(1):5104.	16.1; 164	Prospective observational cohort study, 42	Fatigue: 100%; Post-exertional malaise: 100%; Need for rest: 96-100%; Cognitive impairment: 91%; Mental fatigue: 100%; Sleep disturbances: 83-89%	BT: erythrocyte IL-8 ↑; ACE1 ↓; mannose-binding lectin ↓; antinuclear antibodies ↑
9	Long -term SARS-CoV-2-specific immune and inflammatory responses in individuals recovering from COVID-19 with and without post-acute symptoms	Peluso, 2021, Cell Rep. 36(6):109518.	7.5; 149	Prospective observational cohort study, 70	Persistent symptoms at first visit: 45.8%; Persistent symptoms at 4 months: 53.8%; Neurological symptoms: >70%; Fatigue and reduced exercise tolerance: >70%; Loss/change in smell or taste: >70%; Pulmonary symptoms: >70%	BT: CD4+ T cells ↑; N-specific interferon-γ producing CD8+ T cells ↓; CD8+ T cells expressing CD107a ↓; IP-10 ↑; Neutralizing antibodies ↓
10	Prolonged elevation of D-dimer levels in convalescent COVID-19 patients is independent of the acute phase response	Townsend, 2021, J Thromb Haemost. 19(4):1064-1070.	5.5; 135	Cross-sectional observational study, 150	Fatigue: 51%; breathlessness and reduced exercise tolerance: NQ; abnormal chest X-rays: NQ	BT: D-dimer ↑

IF = impact factor; TC, total citations; BT = blood test; PET = positron emission tomography; NQ = not quantified in the original study.

The four-system framework was derived empirically from the convergent findings of keyword co-occurrence clustering, citation network analysis, and the biomarker profiles reported in the ten most representative studies. These four domains: immune-inflammatory, cardiovascular, neurological and metabolic, consistently emerged as the dominant and most densely interconnected clusters in both the VOSviewer network analysis and the literature synthesis. Although autonomic dysfunction and coagulation abnormalities were also identified in the broader literature, they were not designated as independent domains because the associated biomarkers substantially overlapped with the immune-inflammatory and cardiovascular categories, respectively. Specifically, coagulation biomarkers such as D-dimer and fibrinogen are functionally linked to endothelial dysfunction, which is already captured within the cardiovascular domain. In contrast, autonomic markers such as heart rate variability and catecholamine levels represent functional outputs of both the neurological and cardiovascular systems rather than a distinct pathophysiological entity.

4.0 DISCUSSION

Our bibliometric analysis reveals a heterogeneous and rapidly expanding research landscape in which no single biomarker has emerged as a consensus diagnostic indicator for long COVID. Instead, the citation structure and keyword co-occurrence patterns of the 2020–2024 literature converge on four interrelated biomarker domains: immune-inflammatory, cardiovascular, neurological and metabolic, each anchored by a small number of high-centrality markers (**Figure 7**). The following discussion interprets this structure, contextualises it against the underlying pathophysiological literature, and identifies translational and methodological implications.

Figure 7 summarises the biomarker–symptom relationships emerging from our 2020–2024 bibliometric dataset, organised into four parallel domains: immune-inflammatory, cardiovascular, neurological, and metabolic. Each domain is anchored by a small set of frequently cited biomarkers: IL-6, TNF-α, and CRP in the immune domain; troponin, NT-proBNP, and D-dimer in the cardiovascular domain; neurofilament light chain and glial fibrillary acidic protein in the neurological domain; and HOMA2-IR and triglycerides in the metabolic domain — each linked to a characteristic symptom cluster. While this four-domain representation provides a useful organisational framework, it inevitably simplifies the dense cross-domain interactions evident in the underlying literature, which the following sections examine in detail (Nalbandian et al., 2021; Ceban et al., 2022).

The evolution of SARS-CoV-2 variants introduces heterogeneity that the present dataset cannot formally stratify. Earlier variants, such as Delta, with greater lower respiratory tract tropism, may have driven the early prominence of IL-6 and cardiovascular markers in the 2020–2021 literature, while Omicron's upper respiratory tropism may partly explain the stabilisation of respiratory cluster keywords and the proportional growth of neurological keywords in our post-2022 data. Vaccination status and reinfection history further modulate biomarker profiles in ways that bibliometric methods cannot capture. Future primary studies should explicitly account for these variables.

The most consistently reported biomarkers in long COVID are inflammatory mediators, particularly IL-6, TNF-α, and CRP. These markers are closely associated with fatigue, persistent cough, post-exertional malaise, and depressive or cognitive symptoms. Their persistent elevation beyond the acute phase indicates fundamental disruption of immune resolution processes, establishing a pathological cycle where initial tissue damage promotes ongoing inflammation (Davis et al., 2023; Lai et al., 2023). The keyword centrality of IL-6 and TNF-α in our keyword co-occurrence network reflects not only their biological importance but also their status as widely available standardised assays, facilitating their early and extensive incorporation into long COVID research.

At the molecular level, IL-6 activates the JAK-STAT signalling pathway, affecting hypothalamic-pituitary-adrenal axis function, potentially providing a biochemical basis for fatigue symptoms. Similarly, sustained elevation of TNF-α correlates with inhibition of hippocampal neurogenesis and decreased neuroplasticity, offering a neurobiological explanation for depressive symptoms (Almulla et al., 2024; Arish et al., 2023). The production of autoantibodies, such as antinuclear antibodies, may explain symptom persistence after viral clearance through "molecular mimicry" mechanisms (Chang et al., 2021; Son et al., 2023). Crucially, these inflammatory mediators do not remain confined to the immune domain: IL-6 and TNF-α also drive endothelial activation in the cardiovascular cluster and prime microglial responses in the neurological cluster, foreshadowing the cross-system interactions discussed below.

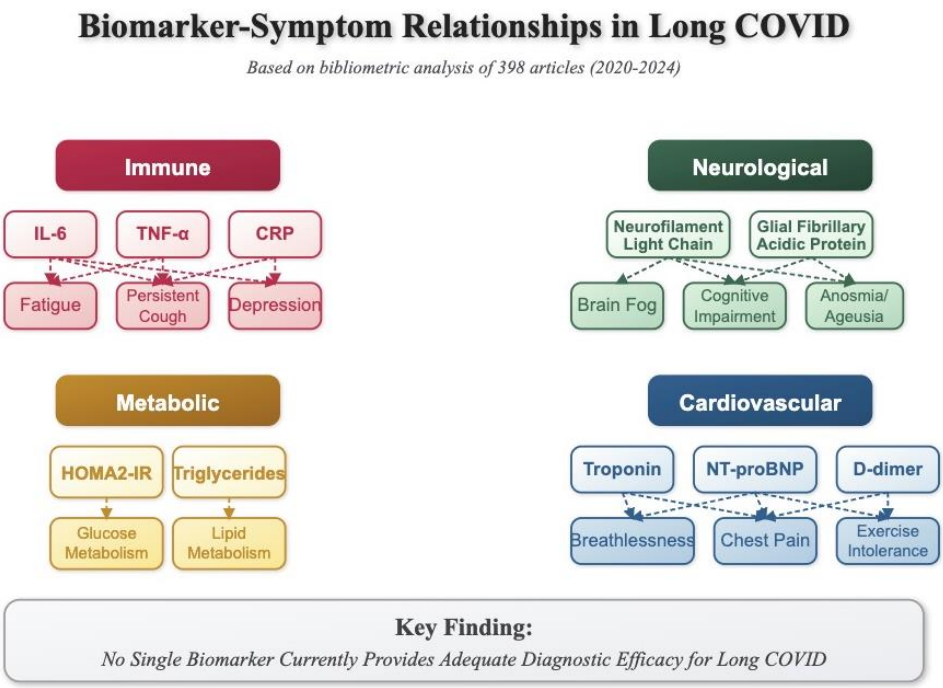

Figure 7: Biomarker-Symptom Relationships in long COVID. This schematic illustrates the associations between specific biomarkers and clinical manifestations of long COVID across four primary pathophysiological domains identified through bibliometric analysis of 398 articles (2020–2024): immune-Inflammatory, neurological, metabolic, and cardiovascular. Autonomic dysfunction and coagulation abnormalities, discussed in the text as cross-cutting pathological features, are not depicted as independent domains due to their substantial biomarker overlap with the neurological and cardiovascular systems, respectively (see Discussion for details). The four domains are presented as parallel structures for clarity; cross-domain interactions (e.g., immunothrombosis, neuro-autonomic coupling, metabolic convergence) are discussed in the text.

Neurological biomarkers, including neurofilament light chain and glial fibrillary acidic protein, directly reflect neuronal damage and astrocytic activation, correlating with brain fog, cognitive impairment, and anosmia/ageusia (Bark et al., 2023; Plantone et al., 2024). Abnormal brain metabolism patterns on FDG-PET imaging further corroborate these findings (Guedj et al., 2021; Gutman et al., 2024). Consistent with this, the neurological cluster in our keyword network has grown proportionally from 2022 onward, reflecting expanding assay availability and increasing clinical recognition of post-COVID cognitive impairment.

These neurological biomarkers are closely linked to microglial activation and neuroinflammatory responses, particularly in cognitive-critical regions including the hippocampus, prefrontal cortex, and insula (Díez-Cirarda et al., 2023; Frontera et al., 2022). Notably, these patterns share similarities with those observed in certain neurodegenerative disorders, suggesting long COVID may share common neural injury mechanisms (Douaud et al., 2022; Rogers et al., 2020). Importantly, neuroinflammation in brainstem autonomic centres may simultaneously drive the autonomic dysregulation discussed in the following paragraph, illustrating that neurological biomarkers cannot be interpreted in isolation from cardiovascular and autonomic findings.

Autonomic nervous system dysfunction occupies a bridging position between the neurological and cardiovascular domains in our framework, rather than constituting a separate biomarker category. Autonomic-related terms [postural orthostatic tachycardia syndrome (POTS), heart rate variability, orthostatic intolerance] co-occur with both neurological markers (reflecting central autonomic control) and cardiovascular markers (reflecting peripheral hemodynamic consequences) in our bibliometric dataset. Biomarkers, including altered catecholamine levels, reduced heart rate variability, and abnormal vasomotor responses, reflect a sympathetic-parasympathetic imbalance (Akbarialiabad et al., 2021; Phetsouphanh et al., 2022), while interactions with endothelial dysregulation explain orthostatic intolerance, dizziness, and palpitations (Su et al., 2022). This cross-domain positioning supports our broader interpretation that long COVID biomarker categories should be understood as interconnected rather than discrete.

The cardiovascular domain in our framework comprises two tightly linked sub-clusters: myocardial injury markers and coagulation markers. High-sensitivity troponin and NT-proBNP reflect myocardial injury and endothelial dysfunction, associated with breathlessness, chest pain, and exercise intolerance (Aboughdir et al., 2020; Yaluri et al., 2023), while D-dimer, fibrinogen, and platelet factor 4 reflect a persistent hypercoagulable state (Gameil et al., 2021; Mohd Zawawi et al., 2023). Mechanistically, endothelial cells become direct targets for SARS-CoV-2 via ACE2 receptors, leading to microvascular dysfunction and impaired tissue perfusion (Lindner et al., 2020; Tavazzi et al., 2020), and the resulting endothelial activation confirmed by elevated von Willebrand factor, promotes microthrombus formation that further exacerbates tissue hypoxia and organ dysfunction (Ackermann et al., 2020; Tang et al., 2020). This "endotheliopathy" provides a unifying framework for multi-organ involvement, as microcirculatory dysfunction simultaneously affects cardiac, pulmonary, and cerebral tissues (Bellone et al., 2024; van den Berg et al., 2023). Complex interactions between coagulation and inflammatory responses form the "immunothrombosis" phenomenon (Sollini et al., 2021; Son et al., 2023), which directly links the cardiovascular cluster back to the immune-inflammatory cluster discussed above and helps explain the coexistence of fatigue, dyspnea, and cognitive impairment across patients (Bellone et al., 2024; Guedj et al., 2021).

Metabolic dysregulation biomarkers HOMA2-IR and triglycerides reflect cellular energy metabolism disruption in long COVID patients, associated with glucose and lipid metabolism abnormalities (Al-Hakeim et al., 2023; Szögi et al., 2024). Mitochondrial dysfunction represents a core mechanism, manifesting as reduced ATP production, altered membrane potential, and increased oxidative stress (Ayola-Serrano et al., 2021). Although metabolic markers occupy a less central position in our keyword network, their rising citation frequency since 2022 suggests an emerging research focus.

Metabolomic studies further reveal alterations in tricarboxylic acid cycle intermediates and lipid peroxidation products, patterns that significantly overlap with those reported in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (Fernández-Lázaro et al., 2021; Haque & Pant, 2022), explaining the prevalent fatigue and post-exertional malaise in long COVID. Notably, metabolic dysregulation may represent a downstream convergence point of the three preceding domains, as immune-mediated cellular damage, microcirculatory hypoxia, and neuroinflammation all ultimately impair mitochondrial function, positioning the metabolic cluster as an integrator rather than an independent system.

The convergent publication trends across the four biomarker domains suggests several translational directions. Multi-marker panels combining immune-inflammatory, cardiovascular, neurological, and metabolic markers may enable more precise patient stratification than any single biomarker. The most consistently cited markers in our dataset including IL-6, CRP, D-dimer, and NfL, represent candidate surrogate endpoints for clinical trials evaluating immunomodulatory or neuroprotective therapies. Integration of these biomarker categories into post-COVID follow-up protocols could also facilitate earlier identification of patients at risk for progressive multi-organ dysfunction. These applications require prospective clinical validation prior to implementation.

Previous studies are in line with our findings. Lai et al. (2023) conducted a systematic review identifying persistent immune dysregulation including elevated IL-6, TNF-α, and autoantibody production, as central to long COVID pathophysiology. Furthermore, Gao et al. (2025) employed ultrasensitive proteomic profiling to identify a plasma biomarker signature linking persistent breathlessness with apoptotic and inflammatory signalling networks centred on CCL3, CD40, IL-18, and IRAK1 (Yin et al., 2024). Although these specific proteomic markers did not feature prominently in our 2020–2024 dataset — as the study falls outside our search window and its citation impact has yet to propagate through the literature — the broader emphasis on immune-inflammatory dysregulation is well aligned with our findings. Moreover, Yang et al. (2025) applied dose-response modelling and identified CXCL8 as the most sensitive proinflammatory marker (lowest ED_{50}), followed by IL-6, IL-1β, and TNF-α, which corresponds to the high citation frequency of these markers in our dataset. Notably, a key distinction between these studies and the present work is that they evaluated clinical or mechanistic evidence for specific biomarkers directly. In contrast, our bibliometric analysis maps the structural organisation and temporal evolution of the research landscape as a whole.

As the preceding paragraphs have progressively shown, the four biomarker domains in our framework do not operate in isolation but interact through shared pathophysiological mechanisms — interactions that are

themselves visible in the cross-cluster keyword links of our network. Three integrative axes emerge from this analysis. First, immunothrombosis is a paradigmatic example of immune-cardiovascular coupling: persistent elevations of IL-6 and TNF-α drive endothelial activation, von Willebrand factor release, and subsequent microthrombus formation, thereby linking the immune-inflammatory and cardiovascular domains (Bellone et al., 2024; Son et al., 2023). Second, autonomic dysfunction bridges the cardiovascular and neurological domains, as microglial activation in brainstem autonomic centres evidenced by neuroinflammatory markers, may simultaneously drive sympathetic-parasympathetic imbalance and cardiovascular dysregulation (Su et al., 2022; Phetsouphanh et al., 2022). Third, metabolic disruption, particularly mitochondrial dysfunction reflected in altered HOMA2-IR and tricarboxylic acid cycle intermediates, represents a downstream convergence point where immune-mediated cellular damage, microcirculatory hypoxia, and neuroinflammation ultimately manifest as the fatigue and exercise intolerance that cut across all four domains (Szögi et al., 2024; Fernández-Lázaro et al., 2021). Taken together, these three axes argue against a domain-by-domain reading of long COVID biomarkers.

The bibliometric structure of our 2020-2024 dataset in which cross-cluster keyword co-occurrences are nearly as dense as within-cluster links, supports this interpretation at the level of the research field itself: investigators have often implicitly framed their work around system interactions rather than isolated markers. This interconnected pathophysiology underscores the need for composite multi-system biomarker panels rather than single-marker diagnostic approaches. It suggests that future validation studies should prioritise cross-domain marker combinations that simultaneously capture immunothrombotic, neuro-autonomic, and metabolic-convergence signatures.

5.0 LIMITATIONS

This bibliometric analysis is subject to several limitations. First, our investigation was confined to articles indexed in the Scopus database, potentially excluding pertinent publications, especially those in non-English languages or in journals not covered by Scopus. Second, given the rapidly evolving nature of long COVID research, with continuous updates and an influx of new publications, our analysis represents only a snapshot of the research landscape as of the search date. Third, although bibliometric analysis provides valuable quantitative insights into research trends and collaborative networks, it does not capture qualitative dimensions, such as the clinical significance of findings or the methodological rigour of study designs.

Our analysis, while comprehensive, relies on bibliometric data limited to published and highly cited literature, potentially overlooking emerging biomarkers or those only recently gaining attention. Future reviews could overcome these limitations by integrating bibliometric methods with systematic review approaches, thereby offering a more comprehensive appraisal of biomarker research in long COVID. Moreover, expanding the scope to include additional databases and employing more advanced analytical techniques may further elucidate the evolving research landscape in this field. Future primary research studies should validate biomarkers identified here, especially those showing strong theoretical support but limited current citation impact. Additionally, the geographic concentration of publications in high-income, English-speaking countries may also introduce a country-level citation bias, potentially underrepresenting contributions from low- and middle-income countries.

6.0 CONCLUSIONS

Our bibliometric analysis of 398 publications from 2020 to 2024 reveals a heterogeneous research landscape characterised by a lack of consensus on a single diagnostic biomarker for long COVID; this reflects the structure of the published literature as captured by bibliometric methods rather than a definitive clinical determination. Despite this heterogeneity, the recurrent prominence of immune-inflammatory markers, alongside cardiovascular, neurological, and metabolic biomarkers, suggests that research on long COVID biomarkers is increasingly organised around a multisystem pathophysiological framework. Notably, the four-system biomarker framework proposed in this study encompassing immune-inflammatory, cardiovascular, neurological, and metabolic domains, provides a structured conceptual model for interpreting the diverse biomarker evidence and for understanding the multisystem nature of long COVID. Future studies should move beyond isolated biomarker evaluation toward prospective validation of composite biomarker panels, with careful attention to disease stage, symptom phenotype, and follow-up duration. Such efforts may support the transition from descriptive biomarker cataloguing to more clinically informative diagnostic strategies.

Acknowledgements: This work was supported by JSPS KAKENHI Grant-in-Aid for Scientific Research (JP22K07480).

Author Contributions: XL: Data acquisition, data curation, statistical analysis, visualization, literature search, writing (original draft and editing); TS: writing (review and editing); NS: methodology, writing (review and editing); BL: methodology, writing (review and editing), supervision.

Conflict of Interest: The author declares no conflict of interest.

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