Identifying subtypes of Long COVID: a systematic review

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Summary

Background **Long COVID, a persistent condition following SARS-CoV-2 infection, exhibits diverse symptoms across multiple organ systems. This study aims to summarize the existing clustering and classification approaches to support the management of Long COVID.**

Methods **Following PRISMA guidelines, we systematically searched PubMed, Embase, Web of Science, and Google Scholar from their inception to January 21, 2025, and updated the search on October 1, 2025, to identify studies that presented a way to categorize Long COVID patients or symptoms. Data extraction and quality assessment were conducted for eligible studies. We presented symptom co-occurrence networks, and performed meta-analysis to estimate the percentage of different organ system-based symptom clusters. In addition, we conducted an exploratory analysis of the determinants of different symptom clusters. The protocol was registered in OSF (https://doi.org/10.17605/OSF.IO/J483F).**

Findings **Forty-seven cohort studies and 17 cross-sectional studies categorizing Long COVID subtypes or symptoms were included, encompassing 2.43 million participants across 20 countries. The methodological quality of the cohort studies was on average high (mean Newcastle–Ottawa scale score: 7.5/9), and of the 17 cross-sectional studies moderate (mean Joanna Briggs Institute tool score: 0.61/1.00). Patients or symptoms were categorized either according to the co-occurrence of symptoms (n = 30 studies, 46.9%); by the affected organ system (n = 16, 25.0%); by severity stratification (n = 9, 14.1%); by clinical indicators (n = 3, 4.7%); or by using other ways of**

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classification (n = 6, 9.4%). Among the 30 studies defining patient clusters by the co-occurrence of symptoms, fatigue was the most frequently used descriptor for a cluster, either alone or together with other symptoms (n = 15 studies). Pairwise co-occurrence analysis revealed some commonly used symptom dyads, including olfactory–gustatory dysfunction (n = 10 times), anxiety–depression (n = 10) and joint pain/swelling–muscle pain (n = 9). Fatigue was a recurrent core symptom, frequently co-occurring with joint pain/swelling (n = 9 times) or muscle pain (n = 7), cognitive symptoms (n = 7), and dyspnea (n = 7). Meta-analysis of the organ system-based subtypes showed that respiratory symptom cluster had the highest pooled percentage (47% [95% CI: 29%–65%]), followed by neurological (31% [95% CI: 3%–60%]) and gastrointestinal clusters (28% [95% CI: 0%–57%]). These percentages represent the proportion of Long COVID patients with each symptom cluster within the 16 included organ system-based subtyping studies, not population-level prevalence of Long COVID. Exploratory analysis indicated that symptom subtypes were influenced by factors such as sex, age, virus variant, and comorbidities.

Interpretation This review identified four major approaches for categorizing Long COVID patients and their symptoms. Symptom co-occurrence and organ system were the most commonly used subtypes used in categorization. Fatigue and olfactory–gustatory dysfunction emerged as recurrent core symptoms across multiple subtypes of Long COVID.

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Keywords: Long COVID; Symptoms; Subtypes; Cluster; Classification; Systematic review

Research in context

Evidence before this study

Long COVID is recognized as a highly heterogeneous condition with a wide range of symptoms affecting multiple organ systems. Although individual studies have attempted to categorize or cluster Long COVID patients or symptoms, a comprehensive synthesis of these findings is lacking. A systematic search of PubMed, Embase, Web of Science, and Google Scholar from their inception to January 21, 2025, and updated the search on October 1, 2025, using terms related to Long COVID and clustering or subtyping (e.g., "Long COVID," "PASC," "cluster," "subtype," "phenotype"), revealed an overview of existing Long COVID subtypes. Existing literature primarily consisted of studies focusing on specific symptom clusters or patient subgroups, but no overarching framework had been established to integrate these findings. The need for a systematic review to synthesize and evaluate the different approaches to categorizing Long COVID patients and symptoms was evident.

Added value of this study

This systematic review is the first to comprehensively synthesize evidence on the categorization and clustering of Long COVID patients and their symptoms, including 64 studies with over 2.43 million participants across 20 countries. This study identifies four major subtype classification principles: symptom co-occurrence (46.9%), organ system (25.0%), severity stratification (14.1%), and clinical indicators (4.7%). The review highlights fatigue as a central symptom, with a pooled percent of 37% [95% CI: 19%–55%] among patients with Long COVID, frequently co-occurring with other symptoms such as joint pain, cognitive issues, and dyspnea. Meta-analysis of organ system-based symptom clusters revealed that respiratory (47% [95% CI: 29%–65%]), neurological (31% [95% CI: 3%–60%]), and gastrointestinal (28% [95% CI: 0%–57%]) clusters were the most prevalent. Exploratory analyses further indicated that factors such as sex, age, and comorbidities influence the distribution of these subtypes. This study provides a novel framework for understanding Long COVID's complexity and offers a foundation for future research and clinical practice.

Implications of all the available evidence

The findings underscore the multisystem nature of Long COVID. By systematically identifying the subtypes of Long COVID, this study clarifies the landscape of symptom clustering and patient stratification, and provides a basis for generating hypotheses about potential shared pathophysiological mechanisms. It also highlights common classification methods and symptom clusters, supporting targeted management and personalized care. Future research should focus on standardizing classification methods, integrating multi-omics data to uncover underlying mechanisms, and validating subtype-specific interventions. This will be crucial for advancing precision medicine and improving outcomes for Long COVID patients.

Introduction

Long COVID is a postviral condition, estimated to affect over 65 million individuals worldwide based on global COVID-19 infections.[1] In October 2021, the World Health Organization (WHO) defined Long COVID as a condition characterized by symptoms that occur within three months of the initial SARS-CoV-2 infection, persist for at least two months, and cannot be explained by an alternative diagnosis.[2]

The clinical manifestations of Long COVID involve different organ systems (respiratory, neurological, and cardiovascular, amongst others), and present complex and individualized symptom patterns. This complexity, compounded by limited mechanistic insight and diagnostic testing, contributes to ambiguity in diagnostic criteria.[1]

Among individuals with Long COVID, the different manifestations do not occur randomly but are associated with specific demographic or clinical characteristics (e.g., age or comorbidities). Moreover, the patterns of co-occurrence and severity of symptoms vary significantly across different population groups. Identifying subtypes, classifying the patients in a clinically or pathophysiologically meaningful way into categories, can help clarify the sources of phenotypic heterogeneity, uncover potential shared pathological mechanisms underlying the different patterns,[3] support differential diagnosis, and enable the development of subtype-specific therapeutic strategies.[4]

Although there have been attempts to categorize Long COVID patients and their symptoms, to date, no comprehensive review has synthesized the different approaches for such categorizations. Furthermore, the extent to which demographic characteristics and a range of host- and virus-related factors are consistently associated with different Long COVID phenotypes is still unknown.[5] This study aims to systematically review the characteristics of studies on subtypes of Long COVID regardless of the classification method, integrate existing evidence, identify a framework of classification approaches, estimate the percentage of common symptom clusters, and explore their associations with specific population features.

Methods

This study was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) 2020 statement[6] (Appendix 1) and registered with the Open Science Framework (OSF) (https://doi.org/10.17605/OSF.IO/J483F).

Inclusion and exclusion criteria

We included original studies that explicitly reported patient or symptom clusters or subtypes of Long COVID, regardless of the method (e.g., clustering algorithms, descriptive grouping, or expert-based classification). We excluded (1) conference abstracts without sufficient data; (2) duplicate publications (preprints were excluded if the article was already officially published); and (3) studies whose clustering results were not derived solely from symptom datasets of Long COVID patients (e.g., symptom groups identified based on combined Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long COVID data). Although review articles were excluded, we screened their reference lists to identify potentially eligible studies.

Search strategy

We systematically searched PubMed, Embase, Web of Science, and Google Scholar from their inception to January 21, 2025, and updated the search on October 1, 2025. Additional relevant articles were identified by screening the reference lists of included studies. The search strategy combined MeSH terms (e.g. "Post-Acute COVID-19 Syndrome") and free-text terms (e.g., "PASC", "long COVID", "post COVID", "cluster*", "subtype*", "subphenotype*", "phenotype*", "pattern*", and "endotype*"). Detailed search strategies and results are provided in Appendix 2.

Study selection

Search results from all databases were imported into EndNote 21.4 (Bld 18113) for deduplication. Four investigators screened the articles independently in two steps: in the first step, titles and abstracts were screened to exclude clearly irrelevant records and ineligible publication types; and in the second step, full texts were reviewed against the pre-specified inclusion criteria. A fifth investigator reviewed all excluded articles to minimize the risk of erroneous exclusion. Before the formal screening, we randomly selected 100 studies for a pilot screening to ensure consistency in the screening standards among the investigators. All investigators completed the screening of these studies and subsequently discussed the results until consensus on the inclusion and exclusion was reached. Reasons for exclusion and their frequencies were documented according to PRISMA guidelines. Discrepancies were resolved through team discussion and consensus.

Data extraction and quality assessment

Data extraction was performed by one of four investigators, with independent verification by a fifth investigator. Before the formal data extraction, we randomly selected five included studies for a pilot test. All investigators extracted data from these studies based on the predefined items and then cross-checked and discussed the results to ensure the consistency and accuracy of the extraction process. The following information was extracted: (1) General study characteristics: publication year, country, and study setting; (2) Study design: study population, definition of Long

COVID used, sample size, methods of symptom assessment during follow-up (e.g., patient self-reports, clinical assessments) and data collection period; (3) Symptom classification methods: clustering method (e.g., hierarchical clustering, k-means), number of clusters, cluster names and categories, and clustering criteria; and (4) Patient-related factors potentially associated with clusters: demographic characteristics, clinical features and disease course, comorbidities, mental health and quality of life, and biomarkers.

The methodological quality of the studies was assessed using the Newcastle–Ottawa Scale (NOS) for cohort studies[7] and the Joanna Briggs Institute (JBI) tool for cross-sectional studies.[8] NOS considers three domains—selection (0–4 points), comparability (0–2 points), and outcome assessment (0–3 points)—with a total score ranging from 0 to 9. Studies with scores of 7–9, 4–6, and <4 points were categorized as of high, moderate, and low quality, respectively. The JBI tool evaluates nine methodological items for cross-sectional studies (e.g., sampling representativeness, measurement validity, confounding control), with each item rated as "Yes," "No," "Unclear," or "Not Applicable." Overall quality was calculated as the percentage of "Yes" responses (Responses with "Not Applicable" were not counted in the denominator). Two investigators conducted the quality assessments independently, with disagreements resolved by a third senior researcher.

Data analysis

Analysis of clusters

We synthesized and summarized the clustering results of Long COVID symptoms and other patient features from the included studies to construct a cross-study Long COVID subtype classification framework. We identified major approaches of categorizations and their hypothesized underlying mechanisms. Based on these categorizations, we analyzed the corresponding Long COVID subtypes defined according to the symptom or patient clusters, as well as the frequencies of their use across studies.

We conducted additional analyses for different categorization approaches. Based on preliminary findings, we expected to see at least categorizations based on common co-occurrence and organ system of the symptoms. For studies focusing on co-occurrence of symptoms, we calculated the frequencies of all possible pairs of co-occurring symptoms within each same multisymptom cluster. Based on these data, hierarchical clustering (Ward's method with Euclidean distance) was employed to regroup the symptoms. The findings were visualized using ChiPlot software (https://www.chiplot.online/, accessed on April 8, 2025). For studies grouping symptoms according to organ system, we extracted the numbers of patients with each symptom cluster. For each outcome, we reported proportions (percentages) with 95% confidence intervals (CIs), calculated as the number of Long COVID patients presenting with the symptom divided by the total number of Long COVID patients assessed. These percentages are distinct from "prevalence" (a population-level epidemiological indicator) and specifically describe within-study symptom cluster frequencies. Percentages were used because the study objective was to describe the frequency of each symptom cluster rather than to compare intervention and control groups. No transformation or standardisation was applied before synthesis. Meta-analysis was then performed using the metaprop function in R (version 4.4.3) to calculate pooled percentage estimates for each symptom cluster among Long COVID patients. The meta-analysis estimated the pooled percentage of patients with symptoms in each organ system-based cluster among those with Long COVID in the relevant studies, using random-effects models to account for high heterogeneity.

Exploratory analysis

Based on the original studies that categorized Long COVID symptoms by organ system, we identified and qualitatively summarized potential factors associated with different symptom clusters. We examined whether specific symptom clusters were more prevalent in certain subgroups. These exploratory analyses may consider factors such as demographic characteristics (e.g., age, sex, ethnicity), clinical features and disease course (e.g., severity of illness, length of hospitalization, management modalities, stage of illness), as well as mental health and quality, depending on the data available from the original studies.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the manuscript for publication.

Results

Literature screening

A total of 4004 potentially relevant studies were initially identified. After a multistage screening process, 64 studies[3–5,9–69] were included in the final analysis. The detailed screening flowchart is presented in Fig. 1.

Basic characteristics of included studies

Among the 64 included studies,[3–5,9–69] prospective cohort studies were the most common (n = 26, 40.6%), followed by retrospective cohort studies (n = 20, 31.2%) and cross-sectional studies (n = 17, 26.6%). One study (1.6%) employed a mixed cohort design. Study sizes varied by design: prospective cohorts (n = 26) had a median sample size of 594 (range: 97–73,727); retrospective cohorts (n = 20) had a median sample size of

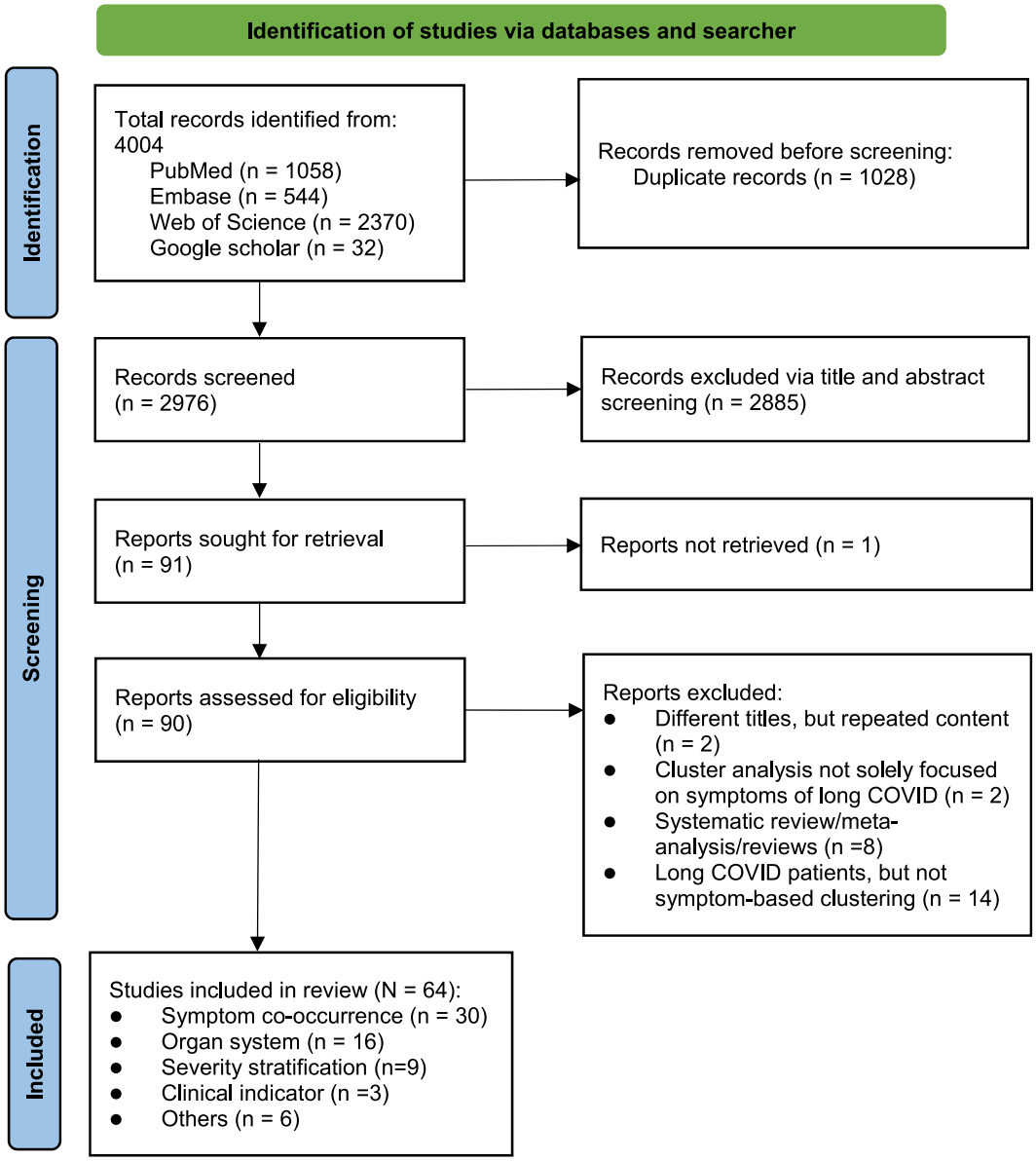

Fig. 1: **PRISMA flow chart for study selection**.

23,974 (range: 95–907,391); cross-sectional studies (n = 17) had a median sample size of 909 (range: 127–8630); mixed/hybrid cohort (n = 1, hybrid cohort study) had a sample size of 1297. The studies were published between 2021 and 2025, with the number of publications increasing every year.

Nine studies (14.1%) were multinational collaborations. The remaining 55 studies (85.9%) were conducted within a single country. The studies spanned 20 countries, with the United States (n = 25), the Netherlands (n = 5), and Canada, Italy, and Germany (each n = 4) being the top contributors.

The total sample size across all studies was 2,430,177 participants, ranging from 95 to 907,391 individuals per study. The majority focused on adult populations (n = 49, 76.6%), with only four (6.2%) targeting children. Twenty-five (39.1%) studies used the WHO criteria, while another 25 (39.1%) applied definitions from other authorities (e.g., the U.S. Centers for Disease Control and Prevention [CDC], the UK National Institute for Health and Care Excellence [NICE]), ten (15.6%) applied modified criteria, and four (6.2%) did not report any specific definition.

Data sources primarily included patient self-reports (n = 36 studies, 56.3%) and electronic health records (n = 25, 39.1%), with some studies integrating multiple data sources. Most studies (n = 60, 93.8%) covered the full spectrum of symptoms, whereas the remaining four (6.2%) focused on specific symptom subgroups.

Regarding clustering methods, hierarchical clustering (n = 24, 37.5%) and K-means (n = 12, 18.8%) were the most commonly used techniques. The number of identified clusters was typically three or four (n = 39 studies, 60.9%). Key characteristics of the studies are summarized in Table 1, with detailed features of each included study provided in Appendix 3.

Quality assessment of included studies

Methodological quality was assessed using NOS for cohort studies and the JBI checklist for cross-sectional studies. The methodological quality of the 47 included cohorts was on average high, with a mean score of 7.5 out of 9. Thirty-four studies (72.3%) were rated as having high quality (score ≥7). Representativeness of the exposed cohort, accurate assessment of exposure, and control of important confounding factors were all each considered adequately in 40 of the 47 studies. However, limitations were noted in the selection of non-exposed cohorts (adequately done in 15 of the 47 studies), and in completeness of follow-up (29 of the 47 studies meeting the criteria).

The 17 cross-sectional studies exhibited moderate overall quality, with a mean score of 0.61 out of 1.00. Comprehensive descriptions of study populations, effective disease identification methods, and robust statistical analyses were adequately considered in all 17 studies. Key weaknesses were related to sampling validity: 14 of the 17 studies employed non-representative sampling frameworks, and seven studies used non-probabilistic sampling methods, indicating potential selection bias. Only ten of the studies used standardized methods for disease measurement, and ten studies had insufficient data coverage. None of the studies adequately reported response rates, leading to unclear management of non-response bias. Detailed quality assessment results are provided in Appendix 4.

Long COVID subtypes

This study synthesized and identified four major ways to categorize symptoms or patients into clusters, as well as their hypothesized underlying mechanisms (Table 2). The main classification types were by symptom co-occurrence (n = 30, 46.9%), organ system (n = 16, 25.0%), severity (n = 9, 14.1%), and clinical indicators (n = 3, 4.7%). The remaining six (9.4%) studies used various ways that could not be grouped to any of the main classification types.

Among the 30 studies categorized by symptom co-occurrence, olfactory-gustatory dysfunction (n = 6

Category	Number (Percentage)
Year of publication	
2021	3 (4.7%)
2022	13 (20.3%)
2023	18 (28.1%)
2024	20 (31.3%)
2025	10 (15.6%)
Country of origin	
United States	25 (39.1%)
The Netherlands	5 (7.8%)
Canada	4 (6.3%)
Germany	4 (6.3%)
Italy	4 (6.3%)
United Kingdom	3 (4.7%)
Japan	3 (4.7%)
Others	16 (25.0%)
Study design	
Prospective cohort	26 (40.6%)
Retrospective cohort	20 (31.2%)
Cross-sectional	17 (26.6%)
Mixed cohort	1 (1.6%)
Study population	
Adults	49 (76.6%)
Children/adolescents	4 (6.2%)
Adults and children	5 (7.8%)
Unspecified	6 (9.4%)
Definition	
WHO	25 (39.1%)
Other established definition	25 (39.1%)
Adapted definition	10 (15.6%)
Not specified	4 (6.2%)
Sample size	
<500	19 (29.7%)
500–10,000	26 (40.6%)
>10,000	19 (29.7%)
Data sources for follow-up[ab]	
Patient self-report	36 (56.3%)
EHR/EMR[e]	25 (39.1%)
Clinical assessment	14 (21.9%)
Multicenter medical database	4 (6.2%)
Other sources	4 (6.2%)
Symptoms classified	
All symptoms	60 (93.8%)
Specific symptoms[c]	4 (6.2%)
Clustering method[a]	
Hierarchical clustering analysis	24 (37.5%)
K-means clustering	12 (18.8%)
Latent class analysis	7 (10.9%)
Exploratory factor analysis	5 (7.8%)
PAM (k-medoids)[e]	5 (7.8%)
Topic modeling	4 (6.3%)
Multiple correspondence analysis	3 (4.7%)
HDBSCAN[e]	3 (4.7%)
Principal component analysis	2 (3.1%)
Louvain community detection algorithm	2 (3.1%)
Other methods[d]	11 (17.2%)

(Table 1 continues on next page)

Category	Number (Percentage)
(Continued from previous page)	
Number of clusters[a]	
2 clusters	9 (14.1%)
3 clusters	20 (31.3%)
4 clusters	19 (29.7%)
5 clusters	8 (12.5%)
≥6 clusters	10 (15.6%)

[a]The analysis encompassed a total of 64 studies, with two studies involving dual cohort clusters and some classifications permitting multiple selections (e.g., data sources, clustering algorithms), resulting in potential percentage totals exceeding 100%. [b]Patient self-reported data incorporated structured questionnaires (online/paper-based surveys, WHO symptom questionnaires, EQ5D quality of life scales, mental health assessments), mobile applications/digital tools (e.g., COVID RADAR app, mobile symptom trackers, administrative portals), symptom diaries/scales (self-reported symptoms such as Long COVID manifestations, dyspnea scores, orthostatic vital signs, and management feedback). Electronic Health Records (EHR/EMR) included hospital and outpatient records, diagnostic tests (e.g., electrocardiograms, chest X-rays), laboratory results, and management documentation. Clinical assessments utilized standardized tools such as physical examinations, neuropsychological testing, pulmonary function tests, olfactory evaluations (Sniffin' Sticks), and the SF-36 questionnaire. Multicenter medical databases, such as the N3C platform (OMOP data model), INSIGHT Network, OneFlorida+ Consortium, and PEDSnet, provided regional/national healthcare data. [c]Specific symptoms: Focusing on specific symptom systems, such as neurological symptoms, or olfactory disorders. [d]Other Methods: Includes methods with ≤1 occurrence across studies (e.g., K-modes, fuzzy C-means. [e]EHR/EMR: Electronic Health Record/Electronic Medical Record; HDBSCAN: Hierarchical Density-Based Spatial Clustering of Applications with Noise; PAM: Partitioning Around Medoids (k-medoids).

Table 1: **Characteristics of the included Long COVID subtype studies.**

studies), fatigue and dyspnea (n = 5), and fatigue with cognitive and/or neurological symptoms (n = 5) were frequently reported as symptoms clusters. Notably, fatigue was the most commonly reported symptom, in some cases defining its own cluster, or co-occurring with other symptoms (n = 15). Proposed underlying mechanisms included autonomic dysfunction and microglial activation.

Among the 16 studies using organ system-based categorization, neurological symptoms (n = 12), respiratory symptoms (n = 11), and gastrointestinal symptoms (n = 7) were the most frequently mentioned symptom clusters. The occurrence of these symptoms is thought to involve mechanisms such as localized tissue damage (e.g., pulmonary fibrosis), neuroinflammation, and endothelial dysfunction.

Five of the nine studies using severity-based categorization classified symptoms into mild, moderate, and severe based on symptom scores, symptom counts, or quality of life assessments. Potential mechanisms included differential immune response intensity and persistent viral antigen presence.

Three studies that categorized patients based on clinical indicators identified subtypes using molecular features (e.g., abnormal triglyceride levels) and imaging patterns (e.g., restrictive lung function). The first study revealed that microvascular abnormalities (e.g., pulmonary capillaritis or thrombosis) cause impaired gas exchange, the second study that some symptoms are caused by persistent immune activation and metabolic dysregulation, and the third study identified four inflammatory subtypes.

The six studies that used other types of categorization primarily focused on sociodemographic heterogeneity without a clearly defined clustering nomenclature.

Symptom co-occurrence classification and re-co-occurrence analysis

We integrated results from the 30 clustering studies using symptom co-occurrence for classification and presented how often the different symptoms occur with each other using heatmaps and network co-occurrence diagrams (see Fig. 2A and B). This pairwise co-occurrence analysis reflects how frequently symptoms were clustered together across the 30 studies (study-level), not the prevalence of co-occurrence at the patient level. Pairwise co-occurrence analysis revealed that the most frequent co-occurring symptom pairs were olfactory-gustatory dysfunction (n = 10 times) and anxiety-depression (n = 10), followed by joint pain/swelling-muscle pain (n = 9), and joint pain/swelling-fatigue (n = 9). Fatigue-muscle pain, fatigue-cognitive symptoms, and fatigue-dyspnea co-occurred seven times each, underscoring fatigue's central role in multisystem involvement. Headache-cognitive symptoms (n = 5) and palpitations-chest pain (n = 5) were also frequent pairs, the latter linking cardiovascular and respiratory symptom domains. Fig. 2B underscores the multisystem nature of Long COVID, with interconnected nodes across systems.

Our analysis revealed distinct symptom clusters, with the following clusters being particularly evident: a group centered around chronic physical decline, consisting of fatigue, dyspnea, exercise intolerance, muscle pain, and chest pain; a neuropsychiatric symptom group including cognitive symptoms, insomnia, anxiety, and depression; and a group of upper respiratory symptoms resembling post-acute infection, with olfactory and gustatory dysfunction, runny nose/nasal congestion, sneezing, and cough.

Meta-analysis of percentages of different symptom clusters generated based on organ system

The overall percentage of respiratory-related symptoms in studies using organ system-based categorization was 47% [95% CI: 29%–65%]. The percentage of neurological symptom cluster (including sensory abnormalities and cognitive impairments) was 31% [95% CI: 3%–60%]. The overall percentage with gastrointestinal symptom cluster (containing symptoms such as nausea, diarrhea, and abdominal pain.) was 28% [95% CI: 0%–57%]; and the percentage with olfactory/gustatory disorder cluster 41% [95% CI: 0%–94%]. The meta-analysis further revealed a 37% [95% CI: 19%–55%]

Subtype classifications	Number of studies (Percentage)	Representative patient or symptom clusters (number and proportion of studies that defined this as a distinct subtype/cluster)	Potential mechanisms[b]
Symptom co-occurrence[4,9–37]	30 (46.9%)	- Olfactory–gustatory dysfunction (6, 20.0%) - Fatigue–dyspnea (5, 16.7%) - Fatigue–cognitive/neurological symptoms (5, 16.7%) - Cardiopulmonary symptoms (4, 13.3%)	Autonomic dysfunction, microglial activation, peripheral nerve sensitization
Organ system[3,5,38–51]	16 (25.0%)	- Neurological symptom cluster (12, 75.0%) - Respiratory symptom cluster (11, 68.8%) - Gastrointestinal symptom cluster (7, 43.8%) - Fatigue cluster (5, 31.3%) - ENT Symptom cluster (3, 18.8%) - Cardiopulmonary symptom cluster (3, 18.8%) - Olfactory and/or gustatory dysfunction cluster (3, 18.8%)	Local tissue damage (e.g., pulmonary fibrosis), neuroinflammation, endothelial dysfunction
Severity stratification[52–60]	9 (14.1%)	- Mild/moderate/severe (5, 55.6%) - Recovery/persistent clusters (2, 22.2%) - Quality of life/physical and mental health grading (2, 22.2%)	Differences in immune response intensity, persistent viral antigens, metabolic exhaustion, vascular injury (hypercoagulability)
Clinical indicator[61–63]	3 (4.7%)	- Molecular features resembling healthy populations, no clear Long COVID risk factors; triglyceride and organic acid-based clusters, high molecular heterogeneity linked to severe symptoms and poor prognosis (1, 33.3%) - Normal MRI with minor gas retention; reduced RBC/Mem but normal PFT; slight Mem/Gas increase with normal PFT; significantly increased Mem/Gas with reduced RBC/Mem; restrictive PFT pattern (1, 33.3%) - Younger group without comorbidities, elevated CRP and D-dimer, low lymphocytes; older group with multiple comorbidities, highest inflammation, lowest lymphocytes; older group with multiple comorbidities, high lymphocytes, low CRP; older group with only hypertension, high lymphocytes, moderate CRP (1, 33.3%)	Microvascular abnormalities (e.g., pulmonary capillaritis or thrombosis) causing impaired gas exchange; persistent immune activation and metabolic dysregulation
Other[a,64–69]	6 (9.4%)	No standardized clustering terminology defined	Social health disparities, heterogeneity in study design, limitations of data-driven methods

[a]"Other" includes studies without clearly defined cluster classification, such as those based on sociodemographic variables (e.g., race, insurance status), key limitations in patient-reported outcomes (PROs), general health conditions, and patterns of social connectedness. ENT: Ear, Nose, and Throat; RBC: Red Blood Cells; Mem: Membrane Conductance; PFT: Pulmonary Function Test. [b]The "Potential mechanisms" presented here are hypothetical and based on interpretations from the cited literature. They are provided to aid conceptual understanding and should not be regarded as conclusions drawn from the current systematic review.

***Table 2*: Distribution and hypothesized mechanisms of the identified Long COVID subtype classifications.**

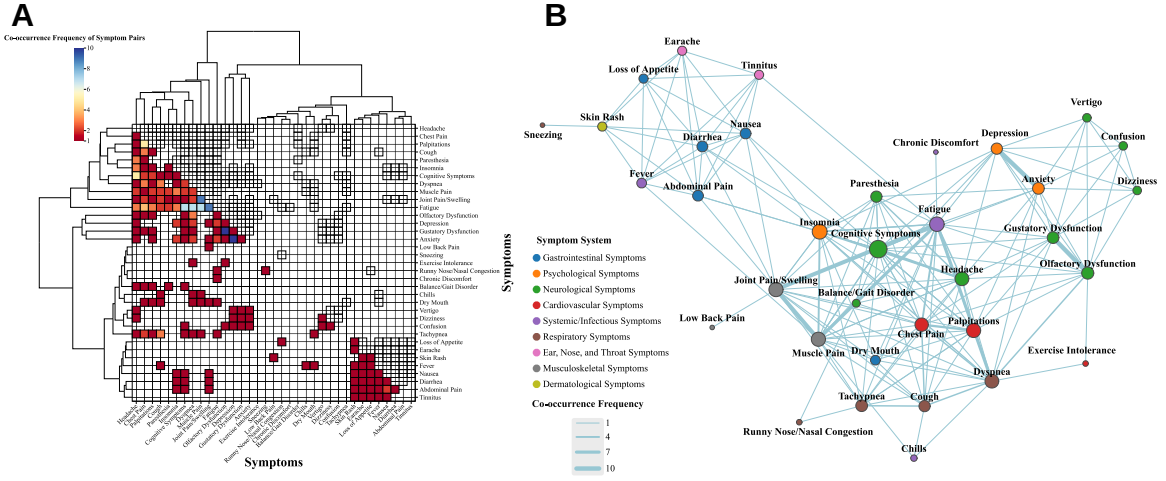

***Fig. 2*: A. Hierarchical clustering heatmap of co-occurrence of Long COVID symptoms**. Each cell represents the frequency of co-occurrence between two symptoms in the studies. Blue corresponds to high co-occurrence frequency (maximum of 10), and red to low frequency (minimum of 1). Combinations with a co-occurrence frequency of 0 are omitted. Blank cells indicate no reported co-occurrence in the included studies. **B. Co-occurrence network of Long COVID symptoms**. The network diagram illustrates the co-occurrence relationships between symptoms. Nodes represent symptoms, with colors indicating the system to which the symptom belongs. The thickness of the edges reflects the frequency of co-occurrence.

percentage of fatigue symptom cluster (i.e. as a separate cluster). Musculoskeletal symptoms, including muscle pain and joint pain and stiffness, had a pooled percentage of 28% [95% CI: 0%–57%]. Although the number of studies on dermatological symptom cluster was limited, the overall percentage of skin symptoms (such as rash or itching) was 17% [95% CI: 0%–50%]. The overall percentage of the Ear, Nose, and Throat (ENT) symptom cluster, including tinnitus and sore throat, was 19% [95% CI: 0%–54%] (see Fig. 3).

Exploratory analysis

Exploratory analyses revealed that factors such as sex, age, race/ethnicity, host characteristics, and socioeconomic background significantly influence the formation of different symptoms. Females had a significantly higher risk of neuropsychiatric symptoms[3,5,41–46] and fatigue[5,42,43] than males, while males were more likely to experience respiratory symptoms.[41,45,46] Older individuals were more prone to respiratory symptoms, cardio-renal manifestations, and ENT symptoms.[4,39,40,46]

In terms of racial or ethnic differences, Hispanic and African American populations were more likely to develop respiratory/cardiac and neuropsychiatric clusters, whereas white individuals had a higher percentage of fatigue and musculoskeletal symptoms.[43,64] Regarding viral variants, the Alpha variant was strongly associated with olfactory and respiratory symptoms,[38] while the Delta variant increased the risk of ENT-related symptoms.[5] Among host factors, a high BMI, socioeconomic deprivation, and comorbidities such as COPD were significantly associated with an increased risk of cardiopulmonary symptom clusters and Long COVID symptom burden.[5,43]

Discussion

This study systematically synthesized evidence from 64 studies on subtypes of Long COVID patients and their symptoms, presenting an overview of patient and symptom categorizations and their determinants. Four distinct categorization approaches for patients and symptoms were identified, based on symptom co-occurrence, organ system, severity, and clinical indicators. Among these, symptom co-occurrence-based and organ system-based categorizations were the most common, used in 70% of all studies. These two subtypes emphasize the concurrent presentation of multiple symptoms within individual patients, reflecting the complex and overlapping phenotypes of Long COVID. Within the co-occurrence-based categorizations, olfactory and gustatory dysfunction was the most frequently reported cluster, likely attributable to the high risk of smell and taste loss among Long COVID patients.[70] Notably, cardiopulmonary symptoms and olfactory-gustatory dysfunction were commonly defined as clusters in both co-occurrence and organ system-based approaches. Fatigue, as a central symptom, demonstrated dual attributes, it could exist as an independent subtype of Long COVID,[5,9,10] or form a cluster with joint/muscle pain, cognitive symptoms, or dyspnea. This phenotypic complexity suggests that fatigue may lie at a critical intersection of multisystem interaction or represent different pathophysiological stages depending on the timing of symptom presentation. The overlapping nature of symptoms, such as fatigue, which may arise from multiple underlying pathologies (e.g., inflammation, neurological dysfunction), complicates the identification of distinct subtypes when relying solely on clinical symptomatology. This highlights the need for integrating mechanistic and diagnostic data to refine subtype classification. In the Global Burden of Disease (GBD) study,[71] fatigue, cognitive dysfunction, and respiratory symptoms are categorized as three distinct symptom clusters. However, the findings indicated that approximately 38% of Long COVID patients experienced two or all three clusters concurrently, underscoring the frequent clinical co-occurrence of these symptoms. The symptoms of Long COVID are also not static but can fluctuate in response to various internal and external stimuli, reflecting the complex pathological underpinnings of the condition. Nonetheless, the study analyzed the clusters separately, primarily due to their high individual prevalence, more frequent reporting in the literature, and distinct clinical management needs. While we identified distinct clusters, Long COVID often presents as a multisystem disease with symptom co-occurrence across categories (e.g., fatigue in respiratory and neurological clusters). Subtypes are not mutually exclusive, as evidenced by studies like Caspersen et al.[41] and RECOVER,[37] highlighting overlapping phenotypes.

Most studies using organ system-based categorization classified the symptoms directly into clusters according to the organ system to which each symptom belongs, and then calculated the occurrence of symptoms within each system. Therefore, in our meta-analysis, we estimated the percentage of each cluster in the entire Long COVID population, rather than by subpopulations clustered based on dominant symptom presentations in a specific organ system. In other words, the analysis aggregated symptom data by organ system unit, not by distinct patient subgroups exhibiting predominant organ-specific manifestations. This approach allows for a comprehensive overview of the burden across different physiological systems, although it does not reflect mutually exclusive patient subtypes.

In all studies, the neurological cluster, respiratory, olfactory and/or gustatory dysfunction cluster, cardiopulmonary cluster, gastrointestinal cluster, and fatigue cluster were found to be the most prevalent regardless of the subtyping approach. The internal consistency observed across symptom clusters suggests shared biological underpinnings, such as autonomic nervous

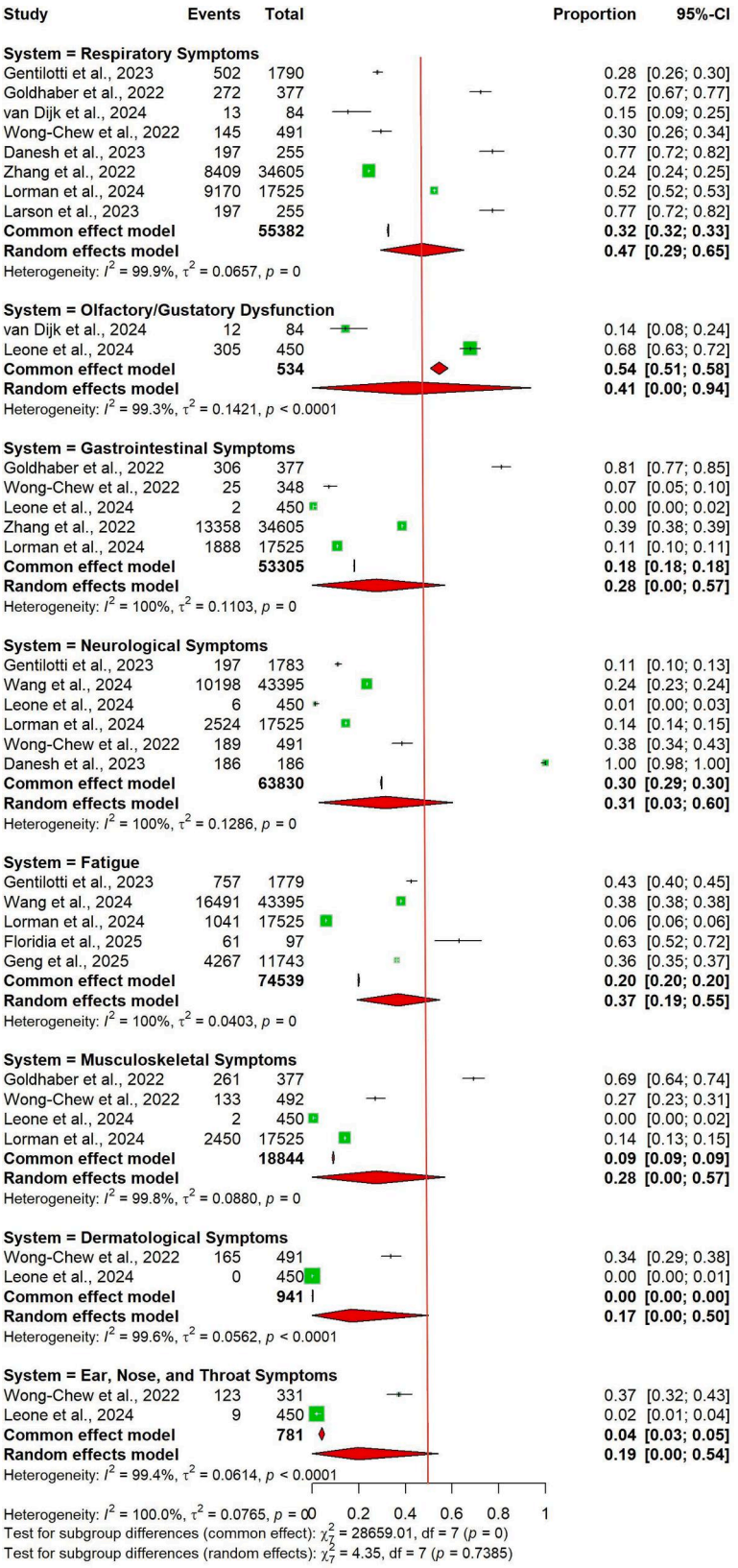

Fig. 3: **Meta-analysis of percentage of different symptom clusters generated based on organ system.** The vertical line at 50% highlights symptom clusters affecting more than half of the Long COVID patients in the studies.

system dysfunction, persistent inflammatory responses, and microglial activation.[72] This is consistent with findings from Kuodi et al.,[73] who identified three typical Long COVID symptom groups (neurological, cardiopulmonary, and systemic inflammatory) based on seven studies, although those studies were not specifically focusing on symptom subtyping. The cardiopulmonary cluster, typically characterized by symptoms such as breathlessness and chest discomfort, may also occasionally include fatigue. However, fatigue is frequently reported as an independent cluster in other studies and may share overlapping mechanisms with cardiopulmonary manifestations. This cluster may arise from various underlying issues, including pulmonary microvasculature damage, cardiovascular dysfunction, or impaired oxygen utilization. Distinguishing between these causes is crucial for targeted intervention but requires advanced diagnostic tools beyond symptom assessment.

While the categorizations based on severity stratification and clinical indicators were not very common, they are particularly valuable for risk stratification and identifying high-risk individuals.[74] Furthermore, clustering outcomes were found to be influenced by a variety ethnicity/ethnicity, SARS-CoV-2 variant, and comorbidities, further underscoring the highly individualized nature of Long COVID. In this context, highly individualized approaches are essential for managing Long COVID. Clustering can help identify common symptom patterns which in turn can be used to guide tailored management strategies, such as referral to appropriate specialists or rehabilitation services, based on individual risk profiles.

Across all included studies, three main clustering methods were observed: (1) applying clustering algorithms to group patients into subtypes based on similarity, (2) grouping symptoms based on variable correlation (e.g., combining dyspnea and chest pain), and (3) classifying patients based on temporal patterns in self-reported symptoms. These methodologies help uncover latent subgroups with potentially significant diagnostic and therapeutic relevance. While many studies used data-driven clustering methods, others relied on descriptive or tabular approaches, reflecting the diversity in subtyping Long COVID without requiring advanced algorithms.

Therefore, despite the heterogeneity in the categorization approaches, findings from existing studies can be dialectically integrated into clinical practice. Based on the evidence, we propose a symptom subtype–oriented management framework for Long COVID (see Fig. 4). This framework suggests that clinicians should first classify patients based on symptom co-occurrence, then map those phenotypes to corresponding organ system symptom clusters using demographic characteristics and coding systems (e.g., mapping symptoms to ICD-10 codes and subsequently to Clinical Classifications Software Refined [CCSR] categories, thereby aligning them with specific clinical domains or organ systems), and finally refer patients to relevant specialists for targeted management. This approach addresses the current gap in Long COVID–specific clinics or rehabilitation services in many healthcare settings. In cases where symptoms are too heterogeneous to be matched to a single organ system subtype, therapeutic strategies should be developed based on the pathophysiological mechanisms associated with particular symptom clusters. In the absence of clear mechanistic pathways, patients should be managed using a severity-based stratification model (e.g., using symptom severity scores, frequency, impact on quality of life, or relevant biomarkers[53–55,61]). Mild cases may be managed by general practitioners in community healthcare centers; if management is ineffective, patients should be referred to community-based Long COVID specialty clinics or rehabilitation centers for intermediate-level care. For severe or complex cases, comprehensive multidisciplinary diagnosis and treatment (MDT) at tertiary care centers should be implemented, integrating physical therapy, occupational rehabilitation, psychological support, and targeted pharmacological interventions.[52] A bidirectional referral system should be established to ensure that patients who do not respond to lower-level care can be rapidly transferred to higher-level MDT centers via expedited "green channels". While symptom-based clustering facilitates practical management, it does not fully elucidate underlying pathologies. For instance, symptoms like fatigue and breathlessness may arise from pulmonary microvascular damage, cardiovascular inefficiencies, or impaired oxygen utilization, each necessitating distinct interventions. To better understand these complex relationships, future studies should integrate multi-omics and imaging data to link symptom clusters to specific pathophysiological mechanisms. In this context, hypothesized mechanisms, drawn from included studies and broader literature, include autonomic dysfunction and microglial activation for co-occurrence clusters (e.g., fatigue–dyspnea[72,74]), local tissue damage for organ system clusters (e.g., pulmonary fibrosis[75]), and persistent viral antigens for severity-based ones.[72] These mechanisms remain hypothetical and warrant further mechanistic research.

This study is to our knowledge the first to focus specifically on the categorization and clustering of Long COVID patients. Drawing on data from 19 countries, we systematically reviewed existing studies to outline the current landscape of different subtypes of Long COVID and integrated recurring symptom clusters to develop a nomenclature framework for classification approaches. The study conducted an in-depth analysis of the major categorization approaches, illustrated specific co-occurring symptom patterns reported in the literature, and quantified the

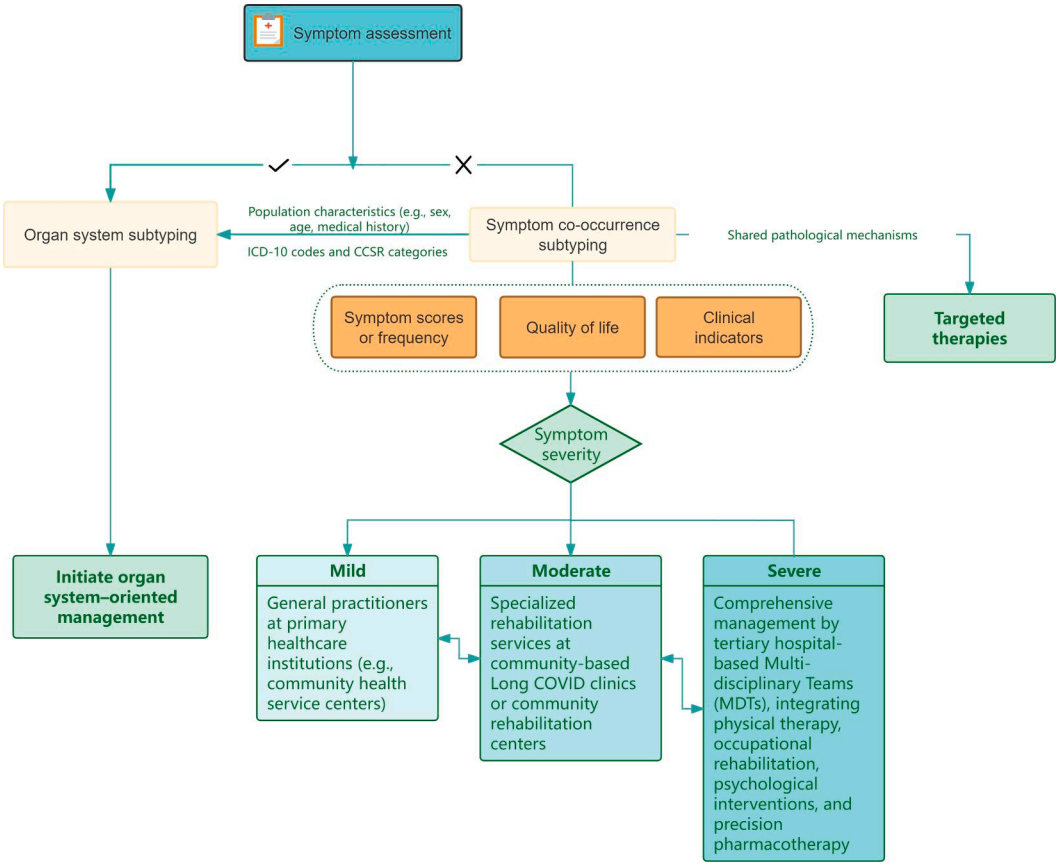

Fig. 4: **Management framework for Long COVID based on subtype**.

percentage of organ system-based symptom clusters. These findings provide evidence-based support for future research and offer a basis for new clinical pathways for the diagnosis and management of Long COVID.

However, the study also has several limitations. First, the included studies exhibited a high degree of heterogeneity: the studies used different definitions of Long COVID and its symptoms, resulting in inconsistencies in defining the symptoms and disease stages in the different study populations. Moreover, differences in symptom naming conventions and clustering algorithms further increased the complexity of the results. Although we attempted to mitigate this heterogeneity through the use of random-effects models in the meta-analysis we conducted, it is important to note that high heterogeneity is common in meta-analyses of percentages and does not necessarily indicate inconsistency in findings (unlike in conventional meta-analyses of clinical outcomes). This heterogeneity weakens the reliability of pooled percentage estimates, as they may not accurately reflect symptom cluster frequencies in all Long COVID populations. Additionally, since our meta-analysis is limited to studies using organ system categorization, it does not represent all Long COVID literature, further restricting the generalizability of percentage estimates. Despite these limitations, the aggregated results remain valuable for reference.[76] However, the meta-analysis is limited to studies using organ system categorization and therefore does not represent all Long COVID literature. In addition, the observed high heterogeneity (I^2 = 100%) reflects variability in definitions and study populations; thus, the results should be interpreted as descriptive summaries rather than definitive prevalence estimates. Furthermore, studies without subtyping were excluded, which may have led to an underrepresentation of broader symptom data. Second, there are limitations related to population representativeness and data sources. Pediatric populations were underrepresented (only 6% of the studies specifically targeted children). Additionally, the reliance on self-reported symptoms in many studies poses challenges for accurately subtyping Long COVID, as this approach is subject to bias and variability. Symptom capture bias may exist across different data sources, for instance, structured electronic health records (EHRs) may underreport subjective symptoms,[75] while survey-based

data are susceptible to recall bias.[77] Third, there are methodological limitations. We did not explore temporal trends across different time periods. Only 4% of the studies included in this review used biomarkers or objective clinical indicators as the basis for symptom subtyping, thereby limiting insights into mechanistic validation and the identification of therapeutic targets. Due to limited availability of data, in-depth analyses were restricted to categorizations by symptom co-occurrence and organ system, and we were unable to quantitatively assess the influence of demographic factors on subtype formation. In studies employing organ system-based classification, respiratory and neurological symptom clusters were observed to be the most prevalent. However, it is important to note that in a subset of studies, these frequencies reflected the symptom burden within subgroups already assigned to specific organ system clusters. As a result, the reported figures may slightly overestimate the percentage of these symptoms in the overall Long COVID population, potentially obscuring the true extent of cross-system symptom co-occurrence. This, in turn, may limit a comprehensive understanding of the full spectrum of symptoms and the multisystem interplay underlying Long COVID. Furthermore, such an approach may underestimate the presence of certain symptoms within non-dominant systems, thereby affecting the clinical recognition of the heterogeneous phenotypes of Long COVID and impeding the development of holistic management strategies.

It is also worth noting that the principles for clustering and categorization in the different approaches vary substantially. The co-occurrence based and organ system-based approaches categorized primarily symptoms, and therefore the term "symptom cluster" can be used well to describe the results; however, such system clusters do not necessarily form a mutually exclusive categorization of Long COVID cases, and patients may manifest with symptoms from multiple clusters simultaneously. Our co-occurrence analysis is limited to study-level data, which may not capture patient-level variability; future work should prioritize patient-level meta-analyses where possible. In contrast, some approaches, like severity based and those based on patients' demographic characteristics, classify patients strictly into mutually exclusive categories, often referring also to factors not related to the actual symptoms. Additionally, the episodic and fluctuating nature of Long COVID symptoms presents challenges for static classification models, as symptoms can change rapidly. Therefore, our study does not intend to find a universal or optimal categorization method, but rather should be seen as a general overview of the different ways to categorize both Long COVID patients and symptoms. Future research should integrate longitudinal data to better capture the dynamic and evolving nature of the condition.

Future research should prioritize the standardization of symptom clustering methodologies, including the harmonization of core symptom assessment tools and clustering techniques such as algorithm selection. More targeted clustering strategies, particularly those centered on the patient as the primary unit of analysis, should be adopted to better capture clinically meaningful symptom groupings. Building on this foundation, commonly co-occurring symptoms should be integrated with multi-omics data, such as inflammatory markers, metabolomics, and neuroimaging, to facilitate mechanism-oriented phenotypic modeling. This approach would enable more precise alignment between patient and symptom clusters, underlying mechanisms, and targeted management, thereby supporting optimal resource allocation and precision care strategies. Furthermore, incorporating time-series clustering and trajectory modeling could help elucidate the dynamic evolution, stability, and progression of Long COVID phenotypes. Data collaboration and standardization of terminology should be also strengthened internationally, for example, through the adoption of standardized phenotype vocabularies such as the Human Phenotype Ontology, to enhance cross-national and inter-institutional integration and comparability of research findings.

We systematically synthesized global evidence on symptom clustering in Long COVID, identifying four major classification approaches and highlighting fatigue, neurological, and respiratory symptom clusters as core phenotypes. The findings underscore the complex, multisystem nature of Long COVID and the influence of demographic and viral factors on symptom subtype distribution. By proposing a subtype-oriented diagnostic and therapeutic framework, this study provides a conceptual basis for individualized care. Future work should focus on standardizing the definitions and measures of symptoms integrating multi-omics data to enable mechanism-based precision interventions.

Contributors

B.W., X.L.: Data curation, Investigation, Formal analysis, Visualization, Writing–original draft, Writing–review & editing.

M.W., Z.W. (Zijun), J.Z., Z.W. (Zijing), Q.S., J.L., W.C., X.G.: Data curation, Investigation, Writing–review & editing.

Y.C., B.C., J.E.: Conceptualization, Methodology, Writing–review & editing, Supervision.

Y.C., B.C., and J.E. accessed and verified the underlying data. All authors were responsible for the decision to submit the manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request. The data will be made available to researchers for purposes of reproducing the results or conducting secondary analyses. Requests for data access should be directed to the corresponding authors (chevidence@lzu.edu.cn). There are no restrictions on the use of the data, but proper attribution and citation of the original study are required.

Declaration of interests

None.

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BW utilized ChatGPT-4o (version GPT-4o-2024-05-13) to polish some sentences in the manuscript on May 11, 2024. The content generated by the GAI tool was verified by YC and corrected when necessary. All authors were aware of the involvement of ChatGPT in writing and reviewed and verified the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103705.

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