Clinical Proteomics

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Computational proteomics to enhance personalized treatment of COVID-19 and Long COVID

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to significant global health burden, including both acute infections and persistent post-acute sequelae, also known as Long COVID (LC) in survivors. While clinical management has reduced case-fatality rates, a substantial proportion of patients develop LC, a heterogeneous syndrome with long-term symptoms. This complex continuum requires therapeutic strategies for both the acute and chronic phases. Plasma proteomics has emerged as a powerful tool in precision medicine, offering insights into systemic molecular changes and disease trajectories. Using targeted and untargeted proteomic analyses, researchers can identify disease-relevant pathways, perform cellular deconvolution to assess tissue-specific contributions, and pinpoint therapeutic targets for both acute infection and persistent symptoms. Combined with bioinformatics and machine learning, these proteomic insights support biomarker discovery and drug repurposing strategies.

Key Points

- This review examines how advanced protein analysis and artificial intelligence may enable personalized treatments for COVID-19 and Long COVID.
- By analyzing blood proteins, clinicians can identify patients at risk for severe disease and predict Long COVID development, moving beyond generic treatment approaches toward precision medicine tailored to individual molecular profiles.
- AI-driven computational approaches may support drug repurposing by prioritizing candidate compounds based on proteomic and network-based signatures, although rigorous experimental and clinical validation remains essential.

Keywords Computational proteomics, Personalized medicine, SARS-CoV-2, Long COVID, Bioinformatics

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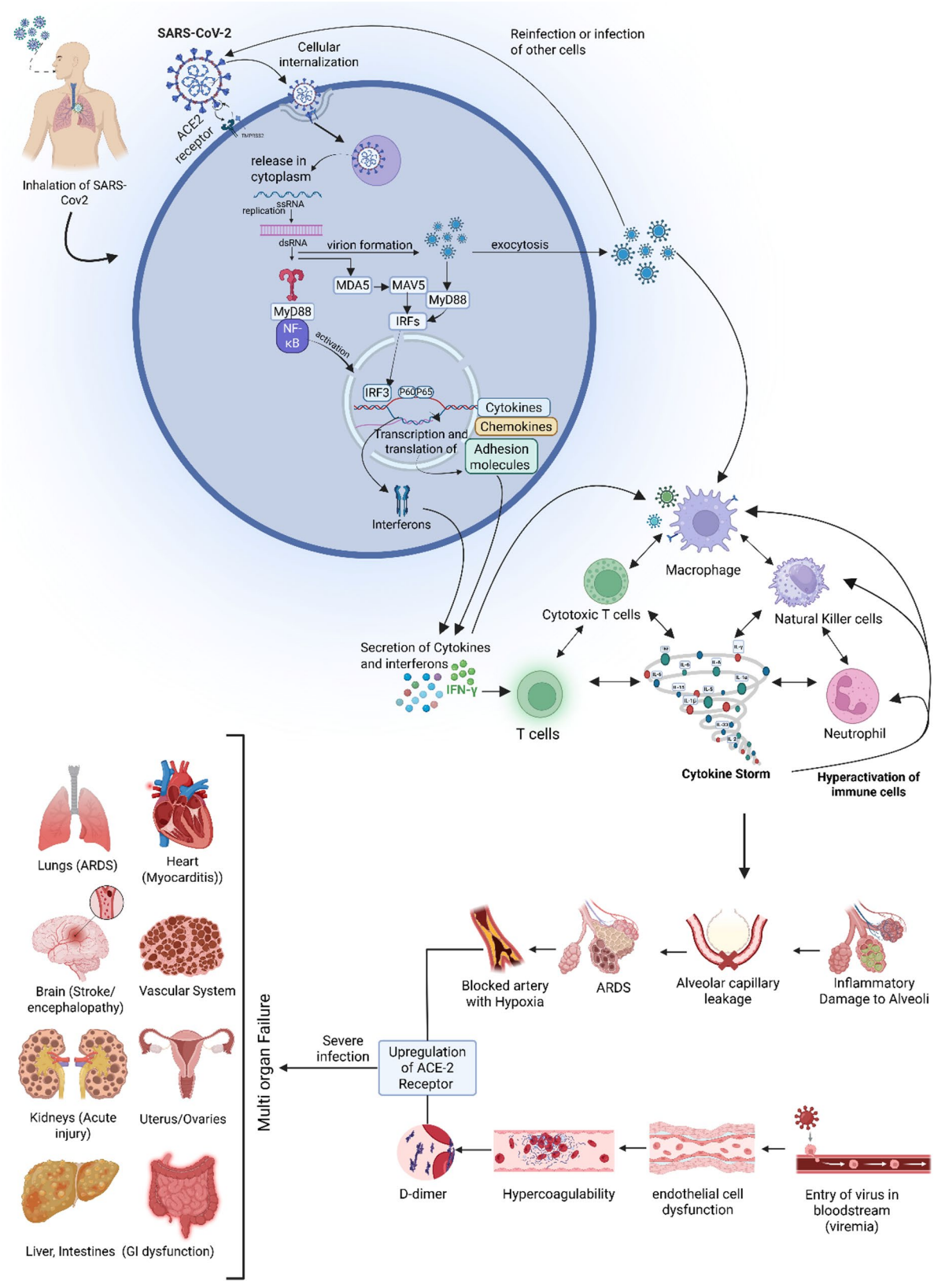

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Fig. 1 SARS-CoV-2 infection and pathogenesis followed by multi-organ failure. This schematic illustrates the multistage process of SARS-CoV-2 infection and its immunopathological consequences. Following inhalation, viral particles reach the respiratory epithelium where spike (S) protein binds to angiotensin-converting enzyme 2 (ACE2) receptors. In tissues with low ACE2 expression, neuropilin-1 (NRP1) serves as a co-receptor facilitating viral entry. Host proteases including TMPRSS2 and Furin cleave and activate spike protein, enabling membrane fusion or endocytosis and subsequent viral RNA release into the cytoplasm. Viral RNA is replicated and translated by RNA-dependent RNA polymerase (RdRp), producing new virions released via exocytosis. The innate immune response initiates when pattern recognition receptors (PRRs) including MDA5, RIG-I, and TLRs detect viral RNA, activating transcription factors (IRF3, IRF7, NF-κB) that drive type I interferon (IFN-α, IFN-β) and pro-inflammatory cytokine (IL-6, TNF-α, IL-1β) production. These cytokines recruit immune effector cells including macrophages, neutrophils, NK cells, and cytotoxic T lymphocytes for antiviral defense. In some individuals, dysregulated immune responses result in cytokine storms characterized by excessive inflammatory mediator secretion (IL-6, GM-CSF, IFN-γ), leading to systemic inflammation resembling secondary haemophagocytic lymphohistiocytosis (sHLH) or macrophage activation syndrome (MAS). In severe cases, uncontrolled inflammation damages the alveolar-capillary barrier, causing hyaline membrane formation, pulmonary oedema, and impaired gas exchange characteristic of ARDS. Viral dissemination to distant organs infects endothelial cells, inducing widespread vascular inflammation and dysfunction. This endothelial injury, combined with pro-inflammatory and prothrombotic states, contributes to thromboembolic events and multi-organ complications including myocarditis, acute kidney injury, hepatic dysfunction, and neurological manifestations

Introduction

COVID-19, caused by SARS-CoV-2, has emerged as a global health emergency, with over 779 million confirmed cases reported by the World Health Organization (WHO) as of February 2026 [1]. Initially regarded primarily as a respiratory illness that could lead to viral pneumonia, COVID-19 is now recognized as a multifaceted systemic disorder. It frequently necessitates intensive care unit (ICU) admission and can result in multi-organ failure (Fig. 1). The disease has been associated with high morbidity and mortality rates, particularly among ICU patients.

The current clinical understanding of COVID-19 can be classified into four distinct categories: asymptomatic, mild, severe, and long-term COVID-19 (also known as Long COVID, LC) (Fig. 2). LC, also known as post-acute sequelae of SARS-CoV-2 infection (PASC) or long-haul syndrome, is a prolonged phase of illness that significantly affects patients' health and quality of life. Many individuals with LC experience persistent symptoms, including neurocognitive, cardiovascular, and immunological dysfunction. Notably, traditional clinical parameters often fail to capture the variations in host immune responses, viral load, and molecular disparities that underlie these persistent symptoms [2].

Current treatment protocols for COVID-19 focus primarily on disease severity. Standard interventions for hospitalized patients include antiviral agents such as remdesivir, corticosteroids such as dexamethasone, anticoagulants such as heparin, and monoclonal antibody (mAb)-based therapies including tocilizumab and baricitinib. However, comprehensive guidelines for individualized pharmacological interventions are lacking [3]. Given the heterogeneous clinical manifestations of COVID-19, personalized treatment approaches are critical for optimizing patient outcomes.

SARS-CoV-2 variation is influenced by factors such as the viral strain, patient medical history, and the timing of infection, highlighting the impact of viral evolution on host immune responses. Consequently, personalized treatment strategies that incorporate proteomic and immune profiling, along with patient case history and viral strain variations, are essential for optimizing patient outcomes. Plasma proteomics, a high-throughput, minimally-invasive technique for profiling circulating proteins, offers valuable insights into host-pathogen interactions and disease progression. When integrated with bioinformatics (BI) and machine learning (ML) tools, proteomic data can reveal biologically relevant patterns, identify prognostic and predictive biomarkers, and guide the development of personalized therapeutic strategies [4, 5].

The central objective of this review is to examine how proteomics-driven insights can bridge disease biology with clinical biomarker development and therapeutic translation in COVID-19 and its post-acute sequelae. We also offer a comprehensive approach to integrating proteomics, analytics, and pharmacological methodologies into clinical workflows, with a focus on molecular stratification and personalized therapeutics. This article presents a narrative review of current evidence integrating proteomics technologies, clinical biomarker discovery, and translational applications, including machine learning and drug repurposing, in acute COVID-19 and LC.

Disease biology and clinical proteomic signatures in COVID-19

Acute COVID-19: immune dysregulation and proteomic signatures

SARS-CoV-2 infection

Acute COVID-19 is characterized by extensive viral spread and robust immune signaling cascades initiated by the entry of SARS-CoV-2 into host cells. SARS-CoV-2 enters host cells through the ACE2 receptor and the transmembrane protease serine 2 (TMPRSS2), facilitating viral entry and infection [6]. The virus then spreads systemically, infecting multiple organs, including the lungs, cardiovascular system, gastrointestinal tract, and central nervous system (CNS), resulting in tissue-specific tropism and systemic dissemination that contribute to the diverse clinical manifestations of the disease [7, 8]. Upon infection, the immune response is activated,

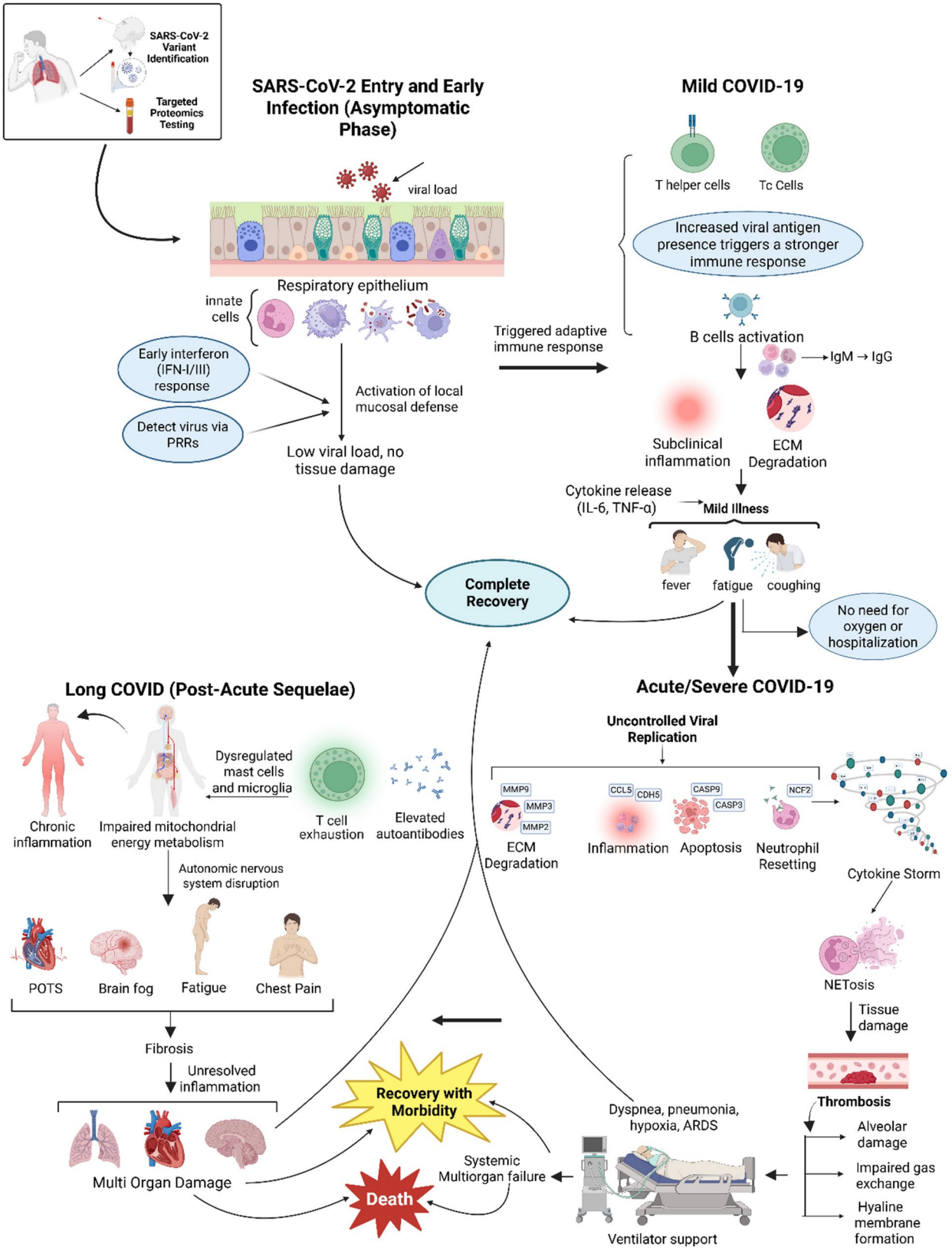

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Fig. 2 Cellular and clinical trajectory of SARS-CoV-2 infection from asymptomatic phase to long COVID. This schematic depicts the dynamic progression of SARS-CoV-2 infection across distinct clinical stages from asymptomatic infection through mild and acute/severe disease to potential long COVID development. Initial viral entry occurs via ACE2 receptors, facilitated by TMPRSS2, leading to early replication in nasal and respiratory epithelium. During the asymptomatic phase, robust type I and III interferon responses may limit viral spread, resulting in minimal tissue damage without clinical symptoms. In mild COVID-19, viral replication intensifies in upper airways, triggering adaptive immune responses (T and B cells) with localized inflammation and systemic symptoms including fever, fatigue, and cough. Disease progression to acute/severe COVID-19 is characterized by uncontrolled viral replication, hyperinflammatory responses (cytokine storm), endothelial dysfunction, and immunothrombosis, potentially leading to ARDS, multi-organ failure, and mortality. In some survivors, persistent viral reservoirs, immune dysregulation, mitochondrial dysfunction, and autonomic imbalance contribute to long COVID, a chronic condition affecting multiple organ systems including cardiovascular, respiratory, and neurological functions. Clinical outcomes range from complete recovery to recovery with morbidity or death

triggering early inflammatory reactions and the secretion of cytokines and chemokines, which are essential for limiting viral spread and coordinating adaptive immunity (Fig. 2) [9].

SARS-CoV-2 variants and immune response

COVID-19 severity is determined by the specific SARS-CoV-2 variant involved and the host's immune background. COVID-19 pathophysiology and patient outcomes are significantly influenced by SARS-CoV-2 variants of concern (VOCs), patient cohort characteristics, and the timing of sample collection. Critically ill patients exhibit adaptive immune responses that vary considerably across different VOCs [10–12]. These variations are reflected in the plasma proteome over time, with distinct host immune responses observed throughout the pandemic [13]. For example, Wave-1 patients infected with the wild-type strain developed neutralizing antibodies against all variants. In contrast, Wave-3 patients, who were primarily infected with the alpha variant, mounted robust antibody responses against the wild-type, alpha, beta, and delta variants. However, these responses were significantly lower against the beta and gamma VOCs [12–14]. Despite these immune responses, viral mutations enable the virus to partially evade neutralizing antibodies. Additionally, patients with comorbidities such as cancer or chronic obstructive pulmonary disease demonstrate reduced antibody production [13]. Regardless of VOC, a variable degree of dysregulated cytokine release leads to a hyperinflammatory condition known as a cytokine storm, a critical factor in the severity of COVID-19. This excessive immune response can cause acute respiratory distress syndrome (ARDS), thrombo-inflammation, and multi-organ dysfunction [15].

Clinical spectrum and immune features of COVID-19

COVID-19 presents a complex clinical spectrum ranging from asymptomatic infection to severe multi-organ failure, characterized by distinct immune dysregulation patterns. The disease features an early robust innate immune response with type 1 IFN activation and rapid SARS-CoV-2-specific T-cell induction [16]. Key inflammatory mediators, including TNF, IL-18, and granzyme B, are strongly associated with persistent proinflammatory states [17], while predictive markers at emergency department admission include IL-6, MCP-3, and TRAIL-R2 [18]. Elevated TNF-α and soluble TNFR1 levels indicate excessive inflammation and are associated with poor outcomes [19–22]. This hyperinflammatory response, termed the "cytokine storm," drives immune dysregulation and may lead to multi-organ failure.

COVID-19 patients also display unique immune profiles. Single-cell immune profiling revealed that asymptomatic patients exhibit increased $CD56^{bright}$ $CD16^{-}$ natural killer (NK) cells and upregulated IFN-γ in effector CD4 + and CD8 + T cells. These patients demonstrate robust TCR clonal expansion in effector CD4 + T cells, but limited BCR clonal expansion compared with moderate cases [23]. Elevated serum levels of MMP-10, IL-17 C, CXCL5, CCL23, FGF-19, FGF-21, and FGF-23 in asymptomatic individuals suggest that enhanced tissue repair mechanisms may regulate symptom development [24]. The transition from asymptomatic to symptomatic disease involves TIM-3 and PD-1 overexpression in CD4 + T cells [25]. Symptomatic COVID-19 patients maintain preserved T-cell function, balanced innate responses, effective interferon signaling, and classical monocyte predominance, with Th1 cells and their cytokines (IL-2, IFN-γ) activating macrophages, CTLs, and NK cells [26].

Severe COVID-19 is characterized by lymphopenia, a reduction in the number of NK cells and T cells, increased T cell activation, and elevated levels of inhibitory molecules. CD8 + T cells exhibit increased levels of cytotoxic molecules, with aberrant activation contributing to viral pathogenesis [27]. Targeted proteomics using proximity extension assays integrated with ML has identified key predictive markers associated with mortality, including CLM-1 and IL12RB1 [28]. Additional disease severity markers include IL-6, CKAP4, Gal-9, IL1RA, LILB4, and PDL1 [28, 29]. Protein stability markers such as IGF-1 and IL-6 measured during the first 10 days of intensive care unit (ICU) care indicate chronic inflammation and poor recovery prospects [30–33].

Intensive care unit (ICU) patients exhibit evolving immune profiles characterized by both persistent inflammation and immunosuppression. Elevated RAGE levels in ICU patients requiring invasive ventilation indicate

early alveolar injury [34]. Both RAGE and angiopoietin-2 (ANG-2) are associated with endothelial injury and progressive vascular damage affecting the lungs and kidneys. CNS-enriched protein profiling reveals distinct neurological damage signatures [35]. IL-6 and Gal-9 are implicated in respiratory, renal, and neurological manifestations, indicating multi-organ inflammatory effects [20, 28, 35].

Plasma analysis revealed an immunosuppressive state between days 3 and 7 of infection, coinciding with extensive organ damage [36]. This immune-deficiency shift involves reduced antigen presentation, increased neutrophil and M1 macrophage activity, and disrupted fibroblast function, contributing to impaired immune homeostasis and greater susceptibility to secondary infection.

High-dimensional flow cytometry and single-cell RNA sequencing of PBMCs revealed loss of non-classical $CD14^{low}$ $CD16^{high}$ monocytes, accumulation of HLA-DR^{low} monocytes, and significant calprotectin release in severe cases, which was correlated with myeloid dysfunction [37, 38]. The accumulation of immature neutrophils ($CD14^{low}$ $CD16^{high}$) in the blood and lungs suggests emergency myelopoiesis, whereas HLA-DR^{low} monocyte accumulation reflects impaired immune responses [39].

COVID-19 is associated with early elevations in both MCP-1 and MCP-3 [39]. Throughout disease progression, the levels of markers such as granzyme B and HSP70 remain consistently elevated in ICU patients, whereas the levels of IL-6 fluctuate. Persistent IL-6 elevation is associated with organ damage in severe cases. Early infection features increased levels of C-C and C-X-C family cytokines and monocyte chemoattractant proteins. The persistently high admission levels of MCP-1, MCP-3, Gal-9, LAMP3, GZMB, and LAG3 correlate with poor prognosis and mortality. Specific organ failure markers include IL-18, IL-15, and Gal-9 for respiratory failure, and CD28 and VEGF for renal failure [39].

Longitudinal ICU plasma profiling revealed a sustained increase in TNF, GZMB, HSP70, and IL-18, whereas IP-10 demonstrated transient increases on days 2–3, and elastase-2 progressively increased from days 2–7. HSP70 levels are specifically correlated with mortality [17]. In end-stage renal disease (ESRD) patients, longitudinal studies have revealed that inflammatory markers (IL-6), monocyte recruitment (CCL2), neutrophil activation (proteinase 3), and epithelial injury (KRT19) contribute to disease progression [40]. Plasma LRRC15 levels negatively correlate with ESRD severity, providing greater prognostic value than PBMC transcriptomics [41]. Deconvolution of plasma proteomic data through scRNA-seq reveals epithelial-myeloid-T cell interactions critical for mediating organ damage in severe COVID-19 [37].

Phenotyping COVID-19

Traditional clinical phenotyping methods fail to capture the biological complexity and heterogeneity of COVID-19 [42]. Despite common symptoms such as fever, cough, or respiratory distress, patients exhibit vastly different trajectories from asymptomatic infection to fulminant multi-organ failure. Symptom-based classification systems inadequately account for the underlying molecular mechanisms driving disease severity, immune dysregulation, and organ-specific pathology, necessitating advanced biology-based frameworks for improved risk stratification, therapeutic targeting, and prognostication.

COVID-19 manifests in four distinct clinical forms, each with five temporal analytic patterns that differentiate complications, such as coinfection and the inflammatory conditions, with the following combinations: high CRP and low ferritin, high CRP and high ferritin, low CRP and high ferritin, as well as other thrombotic complications [43]. IL-6 plays a central role in ARDS initiation. Macrophage activation-like syndrome (MALS) and complex immune dysregulation (CID) characterize severe COVID-19, enabling the development of personalized immunotherapies. Anakinra (an IL-1R inhibitor) is used to treat MALS or CID patients with elevated aminotransferases, whereas tocilizumab (an IL-6R inhibitor) is used to treat CID patients with normal aminotransferases [44, 45].

Predicting COVID-19-specific signaling pathways requires understanding pathway crosstalk between different disease etiologies and identifying targets related to comorbid conditions. In diabetic COVID-19 patients, TNFα and heterozygous insulin receptor (INSR) are key therapeutic targets. COVID-19 patients with cancer exhibit prominent pathways involving IL-6, CXCL8, EGFR, FOS, PIK3R1, and NFKB1. Hypertension and COVID-19 share the renin-angiotensin and peptide-hormone metabolism pathways [46, 47].

Multi-omics BI analyses revealed significant pathway overlaps between COVID-19 and comorbidities, including the interleukin, TLR, TNF-α, renin-angiotensin, Fc epsilon RI, insulin signaling, PI3K/AKT, and MAPK signaling pathways [48]. These insights suggest therapeutic opportunities for drug repurposing and personalized treatment strategies.

Long COVID (LC): persistent immune, pulmonary, and neurological signatures

LC is a progressive, multifaceted syndrome characterized by persistent symptoms lasting weeks to months following acute COVID-19 recovery [49], with serious implications for patients' quality of life. The timeline and stages of clinical progression from COVID-19 to LC are illustrated in Fig. 2. Patients present with diverse ongoing

symptoms, including severe fatigue, dyspnea, chest pain, cognitive impairments ("brain fog"), neuropsychiatric disorders, and cardiovascular and respiratory dysfunction [50]. These symptoms occur in both previously hospitalized and non-hospitalized individuals and often persist without detectable viral replication, suggesting that LC represents a post-infectious pathophysiological condition rather than prolonged viral shedding [51].

Immune dysregulation and persistent inflammation

LC is characterized by marked immune dysregulation and sustained inflammation. Patients exhibit an increased frequency of CD4 + T cells migrating to inflamed tissues, whereas SARS-CoV-2-specific CD8 + T cells exhibit exhaustion with elevated levels of virus-specific antibodies. Miscoordination between SARS-CoV-2-specific T and B-cell responses leads to improper cellular-humoral adaptive immune crosstalk, resulting in immune dysregulation, inflammation, and prolonged clinical symptoms [52, 53].

Persistent inflammation drives LC progression through multiple pathways [54]. CXCL10 is significantly upregulated in LC patients, distinguishing them from asymptomatic and acute COVID-19 patients [55]. Key inflammatory pathways involving TNF-α and TGFβ are upregulated [56], while type II IFN and NFκB signaling pathways are linked to prolonged neutrophil activation [57]. Chronic low-grade inflammation, which is characterized by elevated cytokine levels and sustained immune activation, impairs tissue repair and disrupts homeostasis [58].

Cellular immune alterations

LC involves major immune cell phenotype alterations (Fig. 2). Natural killer (NK) cells predominantly remain in resting states, in contrast to activated phenotypes during acute COVID-19, suggesting that immune exhaustion or dysregulation potentially contributes to persistent viral activity or secondary infections [59]. Neutrophil extracellular trap (NET) formation indicates shifted immune dynamics supporting ongoing inflammation and vascular disturbances [60, 61].

T cell exhaustion is characterized by PD-1 and TIM-3 expression, with reduced memory T-cell pools and impaired cytokine responses, indicating compromised immune surveillance and failure to eliminate viral antigens [36, 61]. This compromises immune surveillance, exacerbates chronic inflammation, and potentially allows viral antigen persistence at immunologically privileged sites, perpetuating immune activation and symptom persistence.

Thromboinflammation, endothelial injury, and complement activation

Endothelial damage contributes significantly to LC pathology through direct viral effects, immune-mediated endothelial damage, or microvascular thrombosis during early infection. Endothelial injury contributes to cardiopulmonary and neurological morbidities [36]. Elevated ANG-1 and VEGF-A levels underscore the central role of vascular changes [62, 63]. High VEGF-A levels are associated with impaired pulmonary diffusion capacity and persistent CT abnormalities [64], suggesting that vascular injury mediates some pulmonary and cardiovascular dysfunction. TGF-β1 signaling, potentially linked to suppression of EP300 protein, suggests vascular inflammation [36]. Combined with HIF-1 signaling, these pathways indicate a vasculo-proliferative process initiated by COVID-19 infection that persists into the post-acute phase, contributing to chronic vascular and organ damage [36].

Early proteomic studies have identified key biomarkers and pathways crucial for understanding the mechanisms underlying LC [36, 65]. PD-1 and TIM-3 on T-cell subsets indicate functional exhaustion [25]. Additionally, reduced memory T-cell pools and impaired cytokine responses suggest ongoing immune dysregulation [66]. Compromised immune surveillance can exacerbate chronic inflammation and potentially allow viral antigens to persist in immunologically privileged sites, thereby perpetuating a cycle of immune activation and symptom persistence.

Clinical presentation and symptom clusters associated with LC

Molecular disturbances mediate disease pathogenesis and manifest in diverse clinical presentations. LC patients exhibit dysregulated adaptive immune responses with increased numbers of CD4 + T cells primed to migrate into inflamed tissues, coupled with exhausted SARS-CoV-2-specific CD8 + T cells [53]. This miscoordination between T and B-cell responses leads to prolonged immune activation, contributing to the inability to resolve infection. Elevated antiviral antibodies suggest persistent but poorly coordinated immune engagement, preventing effective pathogen clearance [53].

Specific cytokines strongly correlate with clinical symptoms in patients with LC. SRPK2 and ITGA6 are associated with severe fatigue [67]. Elevated myeloid inflammation and complement activation markers, including IL-1R2, MATN2, and C1QA, are correlated with fatigue, mood disturbances, and cardiorespiratory symptoms [66, 68]. MATN2, CSF3, and C1QA are linked to gastrointestinal symptoms, while C1QA is correlated with cognitive impairment [66, 68]. Given the wide range and multifactorial pathology of LC, multitargeted

therapeutic approaches and personalized treatment strategies are essential for developing strategies to alleviate patient symptoms.

Supplementary Table 1 provides an overview of key proteins involved in COVID-19 and LC pathogenesis, detailing their biological functions, clinical significance, and associated immune or inflammatory pathways. The table highlights how protein dysregulation contributes to disease severity, immune dysfunction, and long-term complications, offering insights into potential biomarkers and therapeutic targets across different phases of SARS-CoV-2 infection.

Phenotyping of long COVID (LC)

LC presents with heterogeneous, multisystem clinical symptoms. Large-scale ML studies have classified LCs into clinically meaningful subphenotypes to characterize this complexity [69]. Electronic health record data analyses have also augmented LC classification into clinically meaningful subphenotypes [70]. These subphenotypes are supported by targeted blood proteomic analyses. Proteins map to diverse organ systems and cell types, including leukocytes, platelets, and endothelial cells, reflecting the multi-organ involvement observed in clinical subtypes [65]. Analysis of more than 137 symptoms revealed four reproducible groups: cardiac and renal; respiratory, sleep, and anxiety; musculoskeletal and nervous system; and digestive and respiratory sequelae. These subphenotypes are supported by targeted proteomic studies [68]. Identifying distinct, robust, and reproducible subphenotypes may enhance the understanding of host-pathogen interactions and improve patient selection for clinical trials [71, 72].

The overall severity and prevalence of LC among different SARS-CoV-2 variants have been reported to be comparable. For example, Omicron sub-lineages and other SARS-CoV-2 lineages show distinctive persistence and severity of LC [73]. The history of other infections and vaccinations have a substantial effect on the proteomic profiles of LC. These also vary according to the patient demographics such as sex, age, and pre-existing comorbidities [74]. These factors represent critical confounders for interpreting proteomic findings across LC cohorts and may partly explain the limited reproducibility of reported biomarker panels.

Proteomics technologies and analytical platforms

Proteomic analyses have mapped ML-defined subtypes to molecular endotypes. The cardiac and renal subtypes are associated with elevated inflammatory and vascular injury markers, particularly IL-1R2, MATN2, and COLEC12. These biomarkers are linked to endothelial dysfunction, fibrosis, fatigue, and anxiety [68, 75]. The respiratory, sleep, and anxiety subtypes present proteomic signatures of cytokines and neuroimmune modulators, consistent with persistent pulmonary inflammation and autonomic dysregulation [76, 77]. The musculoskeletal and nervous system subtypes are characterized by proteins involved in nerve tissue repair and neuroinflammation, which are associated with myalgia, neuropathy, and cognitive impairment [78]. The digestive and respiratory subtypes are associated with altered nerve tissue repair (SPON-1 and NFASC), elevated in cognitive impairment, and SCG3 elevation, suggesting a brain-gut axis disturbance in the gastrointestinal tract [68].

These findings validate ML-derived subphenotypes and highlight how the integration of proteomics with computational analyses connects clinical presentation to molecular pathology, insights that are often overlooked by traditional statistical methods. By combining proteomic data with ML-based phenotyping, this approach improves diagnostic accuracy and facilitates the identification of therapeutic targets specific to each subtype. This integrated strategy may inform personalized medicine by providing insights that could shift the focus from symptom-based management to mechanism-driven interventions in LC.

Proteomic analytical platforms

Omics technologies have emerged as powerful tools for elucidating the molecular underpinnings of the disease in personalized medicine contexts. These technologies facilitate the identification of endotypes, which are biologically distinct subtypes within clinically homogeneous populations [79]. Each endotype presents unique molecular signatures reflecting variations in immune activation, inflammation, coagulation, and metabolic pathways [80]. Plasma proteomics represents a particularly promising approach, offering a minimally invasive and scalable platform that captures circulating protein signatures. It provides valuable insights into systemic physiological and pathological states, offering real-time snapshots of biological processes across tissues and organs [81]. These findings are especially relevant for COVID-19, where disease progression often involves multi-organ involvement and rapid immune and inflammatory status fluctuations [82].

Affinity-based proteomics platforms (Olink and SOMAscan)

Modern proteomics employs powerful analytical platforms, including the Olink proximity extension assay (PEA), SOMAscan aptamer technology, and mass spectrometry (MS), each offering unique strengths and limitations for human proteome analysis (Table 1). Olink PEA utilizes antibody-based technology to quantify proteins with high specificity through dual-antibody binding, enabling high reproducibility and profiling over

Table 1 Comparison of high-throughput proteomics techniques for pathway analysis

Platform	Principle/Technology	Sensitivity	Throughput	Advantages	Limitations	Application in COVID-19	Application in Long COVID (LC)	Reference
Mass spectrometry	Ionization-based mass analysis	High	Moderate	Unbiased, label-free, high specificity	High cost, complex data analysis	Used extensively to profile proteomic changes, detect viral peptides, and identify biomarkers of disease severity	Emerging use to profile proteomic signatures associated with persistent inflammation and organ damage	[201]
Olink PEA	DNA-tagged antibodies	Very high	High	High specificity, multiplexing, scalable panels	Requires specialized equipment	Quantifies multiple cytokines and inflammatory proteins; used to stratify patients by disease severity	Applied to detect immune dysregulation markers and persistent inflammatory proteins in LC patients	[53, 202]
SOMAscan	Aptamer-based protein binding	Very high	Very high	Wide dynamic range, broad analytic coverage	Requires clinical validation	Broad plasma proteomics to identify novel COVID-19 biomarkers; monitor disease progression	Used to explore wide-ranging protein alterations associated with LC symptom clusters	[203]
CyTOF (Mass cytometry)	Single-cell metal-tagged antibodies	High (cellular)	Medium	High-dimensional, cell-type resolution	Limited mainly to cell-surface proteins	Characterizes immune cell phenotypes, tracks immune exhaustion, and hyperactivation states	Profiles immune cell subsets and their activation/exhaustion in LC; aids understanding of immune dysfunction	[204]
Luminex	Bead-based multiplex immunoassay	High	High	Multiplexing capability, quantitative	Requires specialized instruments	Profiling multiple inflammatory markers and immune proteins simultaneously in COVID-19	Used for multimarker panels to study persistent immune activation in LC	[205]

5,400 proteins, which has been particularly useful in characterizing immunological and inflammatory profiles critical for understanding COVID-19 severity [5, 83–85]. This platform offers superior specificity and requires minimal sample input, making it well-suited for targeted biomarker studies. SOMAscan employs aptamers to bind proteins with high affinity, enabling simultaneous quantification of more than 7,000 proteins with femtomolar sensitivity. While scalable and well-suited for large-scale studies, it may face challenges with off-target effects and interpretation complexities regarding aptamer binding versus antibody interactions. SOMAscan excels in scalability but requires careful interpretation of binding specificity [86]. Mass spectrometry (MS) remains the gold standard for unbiased, high-resolution proteomics and is excellent for discovery-based research, post-translational modifications, and protein interactions. Innovations, including data-independent acquisition (DIA) and tandem mass tags (TMTs), have enhanced capabilities. However, MS requires more complex sample preparation and technical expertise, limiting its use in high-throughput applications [87].

Luminex platforms utilize bead-based multiplex immunoassay technology, which offers high sensitivity and throughput. Primary advantages include multiplexing capability and quantitative analysis, though specialized instruments are required. In the context of COVID-19, Luminex enables simultaneous profiling of multiple candidate inflammatory markers and immune proteins to investigate persistent immune activation in LC patients [88].

Table 1 summarizes the key proteomics and immune profiling platforms used in COVID-19 and LC research, highlighting the principles, sensitivity, throughput, advantages, and limitations of each method. These technologies range from unbiased mass spectrometry to targeted assays providing complementary insights into protein biomarkers and immune responses relevant to disease progression and long-term effects.

Multi-omics integration and systems-level analysis

Role of single-cell proteomics in immune profiling

While plasma proteomics provides valuable insights into systemic protein dynamics and identifies inflammation, coagulation, and organ impairment markers in COVID-19 patients, it lacks the cellular resolution necessary to uncover the upstream immunologic processes driving these changes. Single-cell proteomics, particularly mass cytometry or cytometry by time-of-flight (CyTOF), addresses this gap by enabling high-dimensional, quantitative protein profiling at the single-cell level [89]. This ability is essential in COVID-19, where immune dysregulation, including lymphopenia and cytokine storms, plays a central role in disease progression and LC [90].

CyTOF uses metal-conjugated antibodies measuring up to 40–50 protein targets per cell, enabling detailed phenotypic and functional characterization of immune cell populations. These findings reveal that immune cell subpopulations, such as hyperinflammatory monocytes and exhausted T cells, are correlated with poor clinical outcomes in patients with COVID-19 [91]. CyTOF facilitates temporal analysis of immune cell evolution across various disease stages, from acute infection to chronic postviral syndromes [92].

Integrative proteomic approaches in COVID-19

Plasma proteomics and CyTOF represent complementary techniques. While plasma proteomics captures immune response outputs such as cytokines, CyTOF can identify immune cell subsets responsible for these responses. High plasma levels of IL-6 or TNF-α can be traced to activated monocytes or T helper cells, as revealed by CyTOF. This combined approach enhances biomarker interpretability, aids patient stratification, and identifies upstream therapeutic targets. Plasma proteomics platforms such as Olink, combined with single-cell mass cytometry, have facilitated the profiling of patients with varying degrees of COVID-19 disease severity [90].

Integration of plasma proteomics with single-cell mass cytometry enables monitoring of pharmacodynamic effects at both the cellular and systemic levels, guides targeted therapy development, and supports rational combination therapy approaches.

Deciphering proteomics data with bioinformatics

The role of bioinformatics (BI) in proteomics

Robust computational and BI methods are essential for extracting clinically relevant insights from high-dimensional proteomics data. The clinical utility of quantitative proteomics depends on technology choice, experimental design, and research objectives, thereby necessitating tailored computational biology workflows [93]. Modern BI pipelines analyze large-scale proteomic datasets and facilitate integration with other omics platforms. BI platforms and databases including HUPO, HPPP, HPPA, and HEVPA, along with integrated omics for single-cell mapping, are utilized [81, 94]. Cellular deconvolution, which estimates cell type proportions in tissue samples, enhances the interpretability of high-throughput omics data by mitigating confounding effects from cellular heterogeneity [95]. However, further protein validation is needed to meet advanced technology standards [96].

Data preprocessing and normalization

Effective data preprocessing enhances signal detection and minimizes noise. Initial preprocessing includes data normalization to reduce batch effects and measurement variability. Noise correction minimizes the degree of

technical variability and enhances the detection of biological variation. Bias in omics data arises from experimental or technical factors during sample preparation and acquisition, with normalization techniques addressing specific bias types [97]. Normalization methods are selected on the basis of the data type. Multiplex affinity-based methods require simpler normalization than MS approaches do, as they measure protein levels through targeted antigen-antibody binding without complications from protein isoforms and posttranslational modifications. Additional normalization strategies include LIMMA's batch effect removal function, surrogate variable analysis (SVA), and probabilistic estimation of expression residuals (PEER) [98–101].

Differential protein expression analysis

Identifying differentially expressed proteins (DEPs) is a cornerstone of proteomics studies. The choice of the statistical test depends on the data distribution and study design. DEP analysis employs parametric tests (t-tests, ANOVA) or nonparametric alternatives (Mann-Whitney U and Kruskal-Wallis tests), depending on sample characteristics [102]. For complex experimental designs, LIMMA enables reliable differential expression analysis for multifactor experimental designs [100], whereas multiple testing correction via the Bonferroni or Benjamini-Hochberg methods controls false discovery rates (FDRs) in large-scale studies [103, 104].

Since plasma proteomes reflect contributions from diverse cell populations, computational deconvolution algorithms such as CIBERSORT estimate the abundances of immune cell subsets [105]. Tools such as Seurat support multimodal integration for enhanced cell-type identification.

Functional interpretation of proteomic data

Meaningful biological insights require three complementary analytical approaches. Enrichment analysis determines whether protein sets are significantly associated with specific biological pathways via databases such as KEGG, Reactome, and Gene Ontology through over-representation analysis (ORA, also termed pORA). Topology analysis examines protein positions within pathway networks, distinguishing central regulatory nodes from peripheral components and identifying putative "gatekeeper" proteins connecting distinct biological processes [106, 107]. Signal perturbation impact analysis (SPIA) represents advanced functional analysis, integrating expression changes with pathway topology to assess perturbation effects and identify disrupted pathways in disease states.

Network inference and system-level understanding

Proteomic data support interaction network construction, clarifying regulatory mechanisms underlying health and disease. Personalized medicine applications rely on network inference methods that combine statistical models with protein abundance data to clarify protein interactions and their effects on biological functions and diseases [108]. These approaches reveal interactions that drive vital biological processes, particularly signaling pathways and regulatory mechanisms.

Researchers have validated inferred networks using repositories such as KEGG [109], ENCODE [110], PathVisio [111], MetaCore™ [112], WikiPathways [113], Reactome [114], BioGrid [115], STRING [116], and iPathwayGuide™ [117]. However, inference methods often generate overly complex, correlation-based networks, complicating interpretation owing to high-dimensional proteomic data, necessitating sophisticated analytical techniques, particularly ML algorithms, for extracting meaningful insights [118].

Reference databases and functional annotation tools

The functional annotation of proteomic data depends heavily on well-curated resources. Publicly available databases provide detailed information on protein identity, function, and biological relevance. Functional analyses utilize public repositories including UniProt [119], Ensembl [120], AmiGO [121], EggNOG [116], and MetaCore™ [112], as well as various pathway databases. These are often accessed through commercial platforms such as Ingenuity Pathway Analysis (IPA), iPathwayGuide [117], Qlucore, etc.

For robust validation and discovery, high-confidence reference collections including HUPO, Human Protein Atlas, the Human Plasma Proteome Project, and the Human Extracellular Vesicle Protein Atlas are utilized. These resources provide comprehensive data on protein expression profiles, subcellular localization, and disease associations, enhancing the interpretability and reproducibility of the results.

Table 2 outlines the major molecular and cellular pathways disrupted during SARS-CoV-2 infection, along with the physiological changes associated with COVID-19 and LC. Each pathway is characterized by its biological role, dysregulation mechanisms, and relevance to clinical manifestations, including inflammation, thrombosis, fibrosis, and neurocognitive dysfunction. This table provides a comprehensive overview of disease mechanisms, serving as a reference for identifying therapeutic targets and understanding the complex pathophysiology of COVID-19 and its long-term consequences.

Table 2 Key molecular and cellular pathways affected in COVID-19 and LC

Pathway	Biological role/mechanism	Associated Therapeutic strategies (Evidence-Based)	Predominant phase	References
Apoptosis (caspase activation)	SARS-CoV-2 infection induces caspase activation leading to lymphocyte depletion and haematologic abnormalities. Dysregulated apoptosis contributes to immune dysfunction in severe disease.	Caspase inhibitors, including the pan-caspase inhibitor emricasan (under investigation) have been proposed to modulate excessive apoptosis in severe COVID-19.	Primarily Acute	[206]
Pyroptosis (Inflammasome-mediated lytic cell death)	Viral infection activates inflammasomes leading to Gasdermin D–mediated cell lysis, LDH release, and IL-1β production. Elevated LDH correlates with severity.	IL-1 pathway blockade (e.g., anakinra) and inflammasome-targeted approaches investigated in severe COVID-19.	Acute	[207]
Inflammasome-driven inflammation	IL-1β induces IL-6, TNF, IL-8 production; promotes neutrophil recruitment and neutrophil extracellular trap (NET) formation; contributes to hypercoagulability.	IL-1 inhibitors (anakinra), IL-6 receptor blockers (tocilizumab), and anti-TNF approaches studied in hospitalized patients.	Acute	[208]
Arachidonic acid/COX pathway	SARS-CoV-2 activates COX-mediated prostaglandin production (e.g., PGE2), amplifying inflammation.	NSAIDs and COX inhibitors used symptomatically; no definitive evidence for disease-modifying benefit.	Acute	[209]
Autophagy/mTOR signaling	SARS-CoV-2 infection is associated with increased mTOR signaling and impaired autophagic flux, potentially facilitating viral replication.	mTOR inhibitors (e.g., rapamycin – investigational) explored for antiviral modulation; no definitive clinical approval.	Acute (investigational relevance)	[210]
Cholesterol metabolism	SARS-CoV-2 alters lipid metabolism (e.g., SREBP-2 activation). Hypolipidemia correlates with severity.	Statins investigated; some observational data suggest reduced severity, but not definitive antiviral therapy.	Acute	[211]
Coagulation and endothelial dysfunction	Elevated D-dimer, fibrinogen, P-selectin, and VWF reflect thromboinflammation and endothelial injury; associated with ARDS and mortality.	Anticoagulation (heparin), antiplatelet agents, and tissue factor inhibition studied in hospitalized patients.	Acute (with persistence in some Long COVID cases)	[212]
Complement activation	Activation of classical, alternative, and terminal complement pathways contributes to thromboinflammation; persistent complement activation described in Long COVID.	Complement inhibitors (e.g., C5 inhibitors such as vilobelimab; C1 esterase inhibitors under investigation).	Both (persistent in Long COVID)	[213]
Neurological inflammatory pathways	Elevated neurodegeneration markers in CSF; proteomics reveals inflammatory dysregulation in meninges and brain tissue.	No approved targeted therapies; supportive and symptom-based management; anti-inflammatory strategies under study.	Long COVID	[214]
Dysregulated microRNAs (pulmonary dysfunction)	miR-9-5p and miR-486-5p correlate with reduced DLCO and pulmonary dysfunction; linked to inflammation and senescence pathways.	Currently biomarker relevance only; no validated miRNA-targeted therapies for COVID-19.	Long COVID (pulmonary sequelae)	[74]
GPCR signaling dysregulation	Viral modulation of GPCR signaling disrupts CFTR and ENaC-mediated fluid balance, contributing to pulmonary oedema.	No established GPCR-targeted therapy in COVID-19; mechanistic relevance only.	Acute	[215]
HIF-1 pathway	HIF-1α regulates hypoxia responses, angiogenesis, metabolic adaptation; implicated in silent hypoxia and vasculopathy.	No approved HIF-targeted therapies in COVID-19; pathway considered mechanistic contributor.	Both	[216]
Renin-angiotensin system (RAS) dysregulation	ACE2 downregulation leads to Ang II/AT1R overactivation, promoting vasoconstriction, fibrosis, and inflammation.	ACE inhibitors/ARBs continued safely; recombinant ACE2 and ACE2 decoys investigated experimentally.	Acute (with possible long-term vascular impact)	[217]
Glycolysis pathway	Increased glucose uptake and metabolic shift promote inflammation and ROS production.	Metabolic modulation under investigation; metformin studied in early COVID-19 (reduced Long COVID risk in trials).	Acute; prevention relevance for Long COVID	[218]
Interferon signaling inhibition	Viral proteins inhibit RIG-I–mediated IFN-β production, suppressing antiviral immunity.	Early interferon therapy studied; mixed results depending on timing.	Acute (early phase)	[219]
JAK–STAT pathway upregulation	Hyperactivation contributes to cytokine storm and thrombosis.	JAK inhibitors (e.g., baricitinib) approved for hospitalized COVID-19 patients.	Acute	[220]
Matrix metalloproteinases (MMPs)	Elevated MMPs contribute to tissue damage and inflammation; correlate with severity and mortality risk.	No approved MMP-targeted therapy; investigational interest only.	Acute (potential chronic relevance)	[221]
Mitochondrial metabolism	Viral proteins impair mitochondrial respiration and autophagic clearance.	No specific approved mitochondrial-targeted therapy.	Acute	[222]

Table 2 (continued)

Pathway	Biological role/mechanism	Associated Therapeutic strategies (Evidence-Based)	Predominant phase	References
TNF-α/TACE Signaling	TACE activates TNF-α; it contributes to inflammatory amplification.	Anti-TNF strategies investigated; not standard of care.	Acute	[223]
TNFα/NF-κB Signaling	NF-κB promotes cytokine production and pulmonary inflammation.	Anti-TNF and NF-κB modulation explored; not standard therapy.	Acute	[224]
Nuclear pore/antiviral restriction	ORF6 blocks nuclear translocation of IRF3 and STAT1/2, impairing antiviral signaling.	No direct therapeutic targeting currently established.	Acute	[225]
Nucleic acid metabolism (pyrimidine synthesis)	SARS-CoV-2 enhances de novo pyrimidine synthesis via carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase (CAD) activation to support replication.	DHODH inhibitors and nucleotide synthesis inhibitors under investigation.	Acute	[226]
Proteostasis disruption (ER stress/UPR)	Viral infection disrupts protein folding homeostasis, contributing to ER stress and cellular dysfunction.	No validated proteostasis-targeted therapies in COVID-19.	Acute (possible chronic cellular stress relevance)	[227]
Suppression of host protein translation (NSP1)	NSP1 blocks ribosomal mRNA entry and inhibits host antiviral protein synthesis.	No approved direct therapeutic intervention targeting this mechanism.	Acute	[228]

Challenges in proteomics

High-throughput quantitative proteomics faces significant challenges due to wide protein dynamic ranges influenced by age, genetics, environment, and health factors [122]. Translating plasma proteome findings into clinical applications encounters several obstacles, including orthogonal biomarker requirements, low-abundance protein masking by high-abundance proteins, false discoveries from high-dimensional data, and limited understanding of growth, development, and aging effects on proteomes. Targeted proteomics using affinity-based methods requires careful interpretation since protein abundance does not always correlate with function. LC-MS analysis can quantify specific peptides in targeted workflows [123, 124], enabling functional protein assessments [125].

Computational and translational applications

Machine learning for proteomic biomarker discovery and prediction

Overview of machine learning (ML) in proteomics

ML methods provide powerful approaches for inferring biological networks from proteomics data. Unlike traditional statistical techniques, these methods can uncover potentially complex relationships between proteins and molecules, identify novel interactions, and reveal hidden patterns in complex datasets. However, ML techniques generally reveal correlations rather than causations, indicating that experimental validation remains essential for confirming biological relevance.

Traditional machine learning (ML) approaches: supervised and unsupervised learning

Proteomics employs both supervised and unsupervised ML strategies. Supervised methods, such as decision trees and random forest ensembles, construct classifiers that predict predefined labels (e.g., disease vs. healthy) on the basis of labelled examples of protein abundance profiles. Unsupervised learning serves exploratory purposes, clustering patients based on protein expression patterns using techniques such as t-distributed stochastic neighbour embedding (t-SNE) [126] and uniform manifold approximation (UMAP) [127, 128]. Such techniques can also facilitate dimensionality reduction, which maps high-dimensional proteomics data to simpler representations for visualization and interpretation. While these methods improve tractability, they may obscure subtle yet biologically important features due to information loss.

Graph-theoretic network analysis

Graph-theoretic approaches enable network analysis by applying thresholds to correlation matrices, resulting in adjacency matrices that represent pairwise relationships among entities such as patient data (e.g., clinical observations) and biomarkers [129]. These matrices facilitate clustering and network topology analysis. Protein overrepresentation analysis can identify protein suites that indicate metabolic pathways, while correlations between proteins and clinical observables can establish edges in bipartite graphs that connect pathways with clinical outcomes [130]. This framework supports integrative biomarker discovery and enhances clinical interpretation [131].

Natural language processing for proteomic annotation

Natural Language Processing (NLP) augments proteomics by extracting biologically meaningful terms from unstructured text data. NLP techniques determine protein expression patterns through named-entity recognition (NER) pipelines configured for preprocessing, negation detection, and pretrained models [132–134]. These tools enable fine-grained mapping of proteins to specific organs, tissues, and cell types, helping annotate proteomic datasets with the biological context derived from the literature or electronic health records [65].

Large language models and multimodal integration

High-throughput omics technologies have dramatically expanded the volume and complexity of biological data, often outpacing our ability to extract mechanistic insights. Large language models (LLMs) have demonstrated how integrating massive, heterogeneous datasets into unified architectures can unlock powerful downstream applications. Extending this paradigm to biology, multimodal foundation models pretrained on diverse omics datasets, including genomics, epigenomics, transcriptomics, proteomics with post-translational modifications, metabolomics, and spatial profiling, may represent a major step forward. These models enable integrated cross-omic analysis, improve prediction of molecular functions and disease associations, and accelerate data-driven hypothesis generation. As the field matures, the convergence of LLMs and multimodal omics may fuel new advances in systems biology, precision medicine, and therapeutic discovery [135].

General-purpose large language models (LLMs) have been used for biomedical literature mining, clinical note extraction, and hypothesis generation by processing unstructured text alongside structured omics data. Although their potential for narrative synthesis and data integration is increasingly recognized, the systematic validation of LLM outputs within proteomics workflows remains limited [136]. These models support scientific workflows through natural-language interaction with large biomedical datasets and computational tools. In parallel, specialized biological foundation models such as ESM3, a frontier multimodal generative language model reasoning over protein sequence, structure, and function, demonstrate that language models trained at scale on evolutionary data can generate functional proteins distant from known sequences [137]. At the translational level, the MMPD-DTA model integrates graph and sequence modalities of targets, pockets, and drugs to capture both global and local target and drug information, and by leveraging diverse sources of bioinformatics information, multimodal deep learning models hold the potential for successful drug discovery [138]. Together, these advances illustrate a broader paradigm in which AI systems integrate heterogeneous biological signals to interpret molecular mechanisms and accelerate discovery.

Clinical applications

In COVID-19 research, ML models have been applied to plasma proteomic datasets to predict ICU admission, need for mechanical ventilation, mortality risk, and progression to LC [139]. Supervised learning algorithms such as support vector machines, random forests, and gradient boosting methods have been used to identify protein panels associated with severity, including inflammatory cytokines, complement components, and coagulation markers [5, 140]. These models facilitate patient stratification and risk prediction based on molecular signatures rather than solely on clinical parameters.

Table 3 summarizes the significant AI/ML models utilized to analyze proteomics data related to COVID-19 and LC. It delineates each model's specific type (e.g., SVM, random forest, and neural networks), primary applications (e.g., classification, feature selection, and prognosis), and advantages in managing complex, high-dimensional datasets. The table highlights how these models predict disease severity, categorize patients, and identify proteomic signatures associated with persistent symptoms. This overview demonstrates the collaboration between ML and proteomics in advancing personalized medicine.

Despite promising predictive performance in discovery cohorts, many ML-based proteomic models in COVID-19 are limited by modest sample sizes, cohort heterogeneity, and variability across analytical platforms [141]. Differences in sample collection timing, disease stage, and proteomic workflows can introduce batch effects and reduce generalizability. External validation across independent multicenter cohorts and transparent reporting of model performance metrics are essential prerequisites for clinical translation.

Drug repurposing informed by proteomic and network signatures

ML-driven drug repurposing leverages high-dimensional vector representations to systematically identify novel therapeutic applications for existing pharmaceuticals (Fig. 3). Diseases and drugs are encoded as numerical vectors capturing their molecular signatures. Diseases are represented by characteristic protein expression profiles, gene expression patterns, and perturbed biological pathways, while drugs are vectorized based on chemical structures, molecular targets, and observed biological effects [142].

Algorithms including similarity-based methods (cosine similarity, Euclidean distance), matrix factorization techniques (SVD, NMF), deep learning architectures

Table 3 Comparative analysis of classical and deep learning models for diagnostic and prognostic prediction of SARS-CoV-2 sequelae

Model	Type	Application	Strengths	Application in COVID-19	Application in long COVID (LC)	Reference
support vector machine (SVM)	Supervised	Patient classification	High accuracy; good with small to medium datasets	Classifies COVID-19 patients based on clinical, imaging, and lab data; predicts disease severity	Used to differentiate Long COVID phenotypes and predict risk factors based on symptom patterns and biomarkers	[229, 230]
Random Forest	Supervised	Feature selection	Robust to overfitting; handles nonlinear relationships	Identifies key predictors of COVID-19 severity and mortality; analyzes complex clinical and demographic features	Detects important features linked to Long COVID symptoms and risk factors; interpretable results for clinical use	[231]
MLP (Neural Net)	Supervised (Neural Network)	Prognostic modeling	Can model complex nonlinear interactions; scalable	Predicts ICU admission, mortality, and clinical outcomes based on patient data	Risk modeling for Long COVID outcomes, including fatigue, cognitive dysfunction, and respiratory symptoms	[232, 233]
CNN	Deep learning	Image/signal analysis	Excels at extracting spatial features from images and signals	Detects COVID-19 pneumonia on chest X-rays and CT scans; quantifies lung involvement	Monitors lung abnormalities and fibrosis progression in Long COVID patients using imaging modalities	[234, 235]
SHAP	Explainable AI	Model interpretation	Provides interpretable explanations for complex models	Interprets model predictions for COVID-19 risk factors and biomarker importance; increases clinical trust	Identifies key variables contributing to Long COVID symptoms; enhances transparency in risk prediction models	[236, 237]
LSTM	Deep learning (Recurrent NN)	Time series prediction	Model temporal dependencies in sequential data	Forecasts COVID-19 case trajectories and hospital resource needs based on temporal clinical data	Analyzes longitudinal symptom progression and physiological signals in Long COVID cohorts	[238]

(autoencoders, graph neural networks), and embedding methods (Node2Vec, biological Word2Vec) that operate on these vector representations to identify drugs with high similarity scores to target disease profiles [143–145]. The mathematical foundation relies on the principle that drugs and diseases with similar vector representations in high-dimensional space share biological mechanisms, enabling systematic discovery of repurposing opportunities through geometric proximity calculations [146, 147].

Multi-modal vector fusion integrates diverse data types, including proteomic, genomic, chemical, and clinical vectors. Advanced techniques such as attention mechanisms, transfer learning, and ensemble methods enhance prediction accuracy and enable knowledge transfer across disease domains [148, 149]. Graph neural networks have emerged as particularly powerful tools for drug repurposing, with methods like DREAMwalk extending guilt-by-association principles for multi-layer knowledge graph learning using semantic information-guided random walks [150]. Other approaches combine graph convolutional networks with attention mechanisms to capture complex relationships between drugs, targets, and diseases [151–153].

This vector-based approach transforms the traditionally serendipitous drug repurposing process into a systematic, scalable methodology that analyzes millions of drug-disease combinations to generate ranked candidate lists for experimental validation, significantly accelerating therapeutic discovery while leveraging established safety profiles of approved medications [154, 155].

COVID-19 drug repurposing strategies

Personalized medicine aims to deliver optimal drug selection, dosing, and timing for individual patients (Fig. 4) [156]. Given the slow pace of new drug development relative to rapidly evolving pandemics characterized by high transmissibility and mortality, drug repurposing offers a promising COVID-19 management strategy utilizing compounds with established safety profiles [157].

Tachyphylaxis, a rapid decrease in drug response following repeated administration, necessitates alternative therapeutic strategies. This phenomenon significantly impacts COVID-19 treatments, exemplified by inhaled nitric oxide (iNO) for pulmonary hypertension, where patients develop tachyphylaxis leading to decreased effectiveness. Advanced technologies including mass cytometry and mass spectrometry facilitate molecular identification and quantification crucial for drug discovery. AI/ML approaches may predict potential tachyphylaxis in drug candidates, supporting development of treatments with prolonged efficacy.

Drug repurposing employs data-driven approaches integrating proteomic disease signatures, similarity analyses, network analyses, and comprehensive data mining. Numerous databases and computational tools support this approach, including e-Drug3D, DrugPredict, DrugBank, Promiscuous, Mantra2.0, PharmDB, DRAR-CPI,

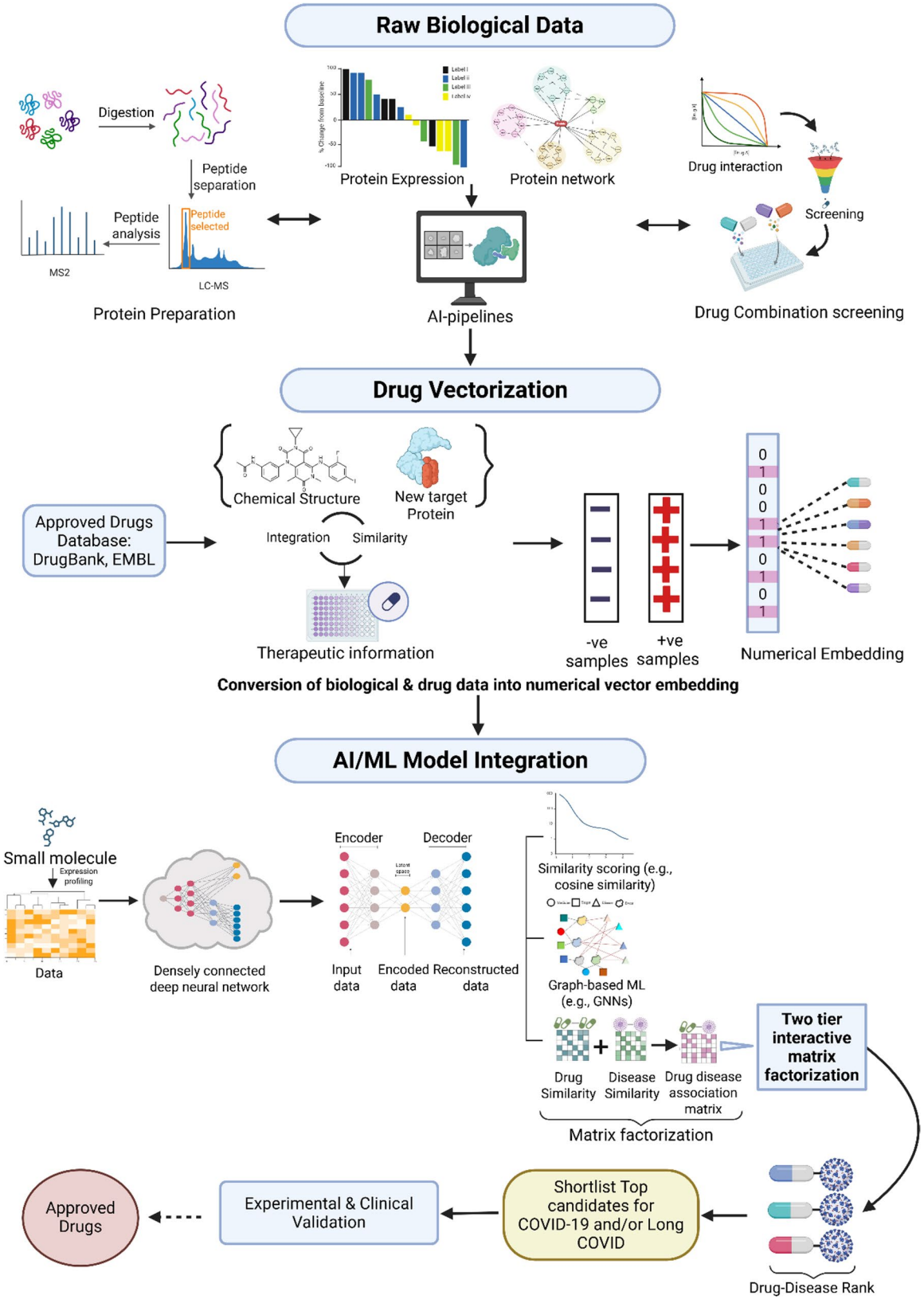

Fig. 3 (See legend on next page.)

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Fig. 3 Workflow for AI-Driven drug repurposing in COVID-19 and Long COVID.This computational framework outlines a multi-stage approach for drug repurposing, integrating biological data, cheminformatics, and artificial intelligence. The workflow begins with raw biological data including protein digestion, peptide properties (mass spectrometry), and protein expression profiles, processed through AI pipelines to construct protein interaction networks and identify drug-target relationships. Concurrently, drug vectorization utilizes databases (DrugBank, EMBL) incorporating chemical structures, therapeutic annotations, and protein similarity metrics. Both biological and pharmacological data are transformed into numerical embeddings and categorised into positive and negative samples. These embeddings are analyzed using AI/ML models including deep neural networks (encoder-decoder architectures), similarity scoring (cosine similarity), graph-based models (GCNs, GANs), and matrix factorization techniques. The pipeline culminates in experimental and clinical validation, identifying top candidate drugs for COVID-19 and long COVID treatment through systematic, data-driven repurposing strategies

repoDB, RepurposeDB, DeSigN, Cmap, and DPDR-CPI [158], enabling identification of pathogen and host-based targets through binding affinities and relevant parameters. The Excelra Consortium database provides commercial data on small molecules and biologics for identifying safe COVID-19 therapeutics.

Figures 3 and 4 illustrate an integrated computational framework for drug repurposing that combines proteomic data processing, drug vectorization, and AI/ML model integration. Raw biological and chemical data are embedded into numerical vectors and analyzed using neural networks and graph-based models to identify and rank potential therapeutic candidates for COVID-19 and LC. This end-to-end pipeline supports high-throughput, data-driven drug prioritization for experimental and clinical validation.

Current repurposing efforts target viral replication inhibition, viral entry prevention, cytokine release mitigation, and modulation of immune responses or endothelial dysfunction. Targeted proteomic methods have identified candidate therapeutic agents for repurposing [159]. ML and signal transduction modeling identified gefitinib and afatinib as repurposed drugs [160]. Combining temporal and cell-specific COVID-19 severity signatures with DRUG_BANK repository data revealed novel therapeutic targets, including FES kinase. Fostamatinib reduces organ damage by inhibiting TNFα, IL-8, and GM-CSF [161, 162].

FDA-approved drug candidates

Several FDA-approved drugs demonstrate repurposing potential. Selinexor and Ponatinib inhibit plasma proteins in severe COVID-19 patients [163, 164]. Selinexor, initially approved for multiple myeloma, selectively inhibits nuclear export via exportin-1, exhibits antiviral properties, protects against tissue damage, and downregulates pro-inflammatory cytokines while interacting with SERPIN family members A7 and D1 [163, 165, 166]. Ponatinib, a tyrosine kinase inhibitor for chronic myeloid leukaemia, also interacts with SERPIN A7 and D1 and may suppress cytokine storms associated with viral infections [167].

Novel therapeutic candidates

Additional therapeutic candidates include Andecaliximab, an MMP inhibitor for cancer therapy that mitigates inflammation and cytokine storms in severe COVID-19 [60]. Emricasan, a pan-caspase inhibitor for hepatic disease, addresses elevated caspase activity in COVID-19 plasma and reduces upregulated caspase-1 activity in CD4 + T cells [60, 168]. AI-ML approaches identified Verteporfin, Alatrofloxacin, Metergoline, Rescinnamine, Leuprolide, and Telotristat ethyl as spike protein-ACE receptor inhibitors preventing viral entry [169]. C5a, IL-6, TF, and PAI-1 represent potential druggable targets in clinical trials [170, 171].

Monoclonal antibodies and decoys

Computational design of ACE2 decoys that bind to spike protein prevents virus-ACE2 interaction, hindering SARS-CoV-2 cellular entry [172]. These decoys demonstrate efficacy against Omicron and Delta variants [173], while inhaled ACE2 analogues improve survival and minimize lung injury in mouse models [174]. Vilobelimab, a monoclonal antibody targeting the complement component C5a, improves survival and reduces inflammation and hypercoagulability in COVID-19 patients [175–177].

Polypharmacology and multi-targeted agents

Polypharmacology, targeting multiple pathways or proteins with a single drug, enhances the efficacy of COVID-19 treatments across diverse patient profiles. 2-deoxy-D-glucose (2-DG) demonstrates promise through glycolytic pathway effects, anti-inflammatory action, and viral protein interactions, while its azido analogue produces rapid oxidative stress and suppresses cytokine storms in critically ill patients [178]. Virtual screening identified covalent and non-covalent SARS-CoV-2 papain-like protease (PLpro) inhibitors with multitarget activities [179]. Methylene blue shows significant potential through polypharmacological action against SARS-CoV-2 as an inexpensive, widely available drug with minimal side effects [180].

Precision trials and clinical implementation

Host proteomic response profiling provides immense value for identifying therapeutic targets and developing personalized treatments [181]. Clinical trials are

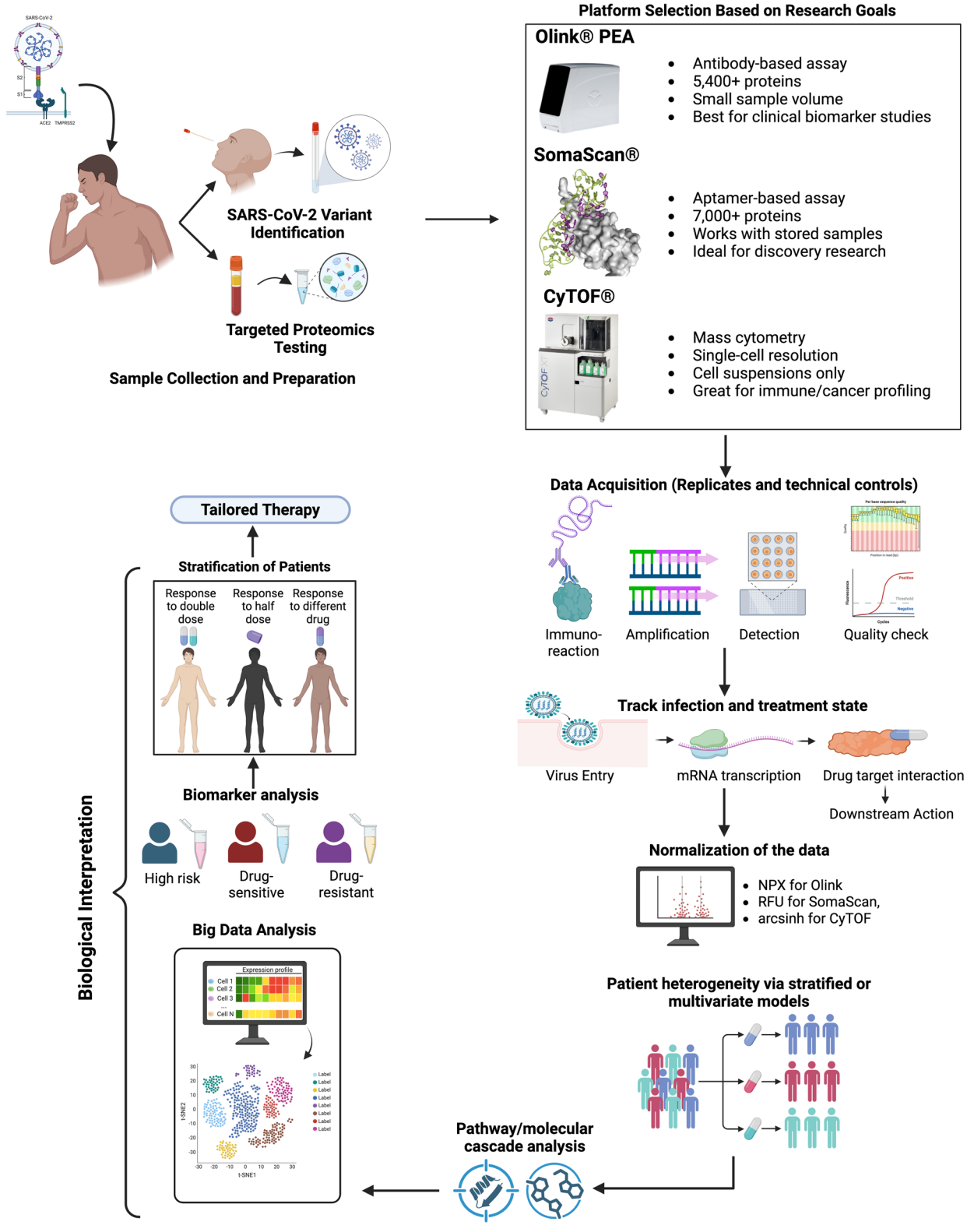

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Fig. 4 Precision medicine approaches to COVID-19 using multi-omics and pharmacogenomics.SARS-CoV-2 infection initiates through spike protein binding to ACE2 receptors with TMPRSS2 priming, promoting viral entry. Intracellular replication triggers transcriptional and translational cascades regulating host signalling pathways and drug target interactions. Inter-individual host response variability, driven by genetic and molecular heterogeneity, is captured through multi-omics profiling including genomics (ACE2 polymorphisms), transcriptomics (transcriptional reprogramming), and proteomics (protein abundance, post-translational modifications, signalling pathway changes). These molecular signatures guide pharmacogenomic testing to predict therapeutic response profiles including differential drug efficacy, dose sensitivity, and resistance patterns. Combined with biomarker-based stratification and high-dimensional data analysis, this approach enables classification into risk categories and drug response subtypes, ultimately directing rational design of individualized therapeutic regimens for precision COVID-19 treatment

underway to explore repurposed antiretrovirals, anti-inflammatories, glucocorticoids, non-steroidal anti-oestrogens, macrolide antibiotics, and biguanide anti-hyperglycaemic agents for COVID-19. Drug repurposing appeals through existing knowledge of structural optimization, pharmacokinetics, toxicological profiles, clinical efficacy, and safety data, enabling rapid advancement to Phase 2/3 trials [182].

Combining advanced proteomic analyses with repurposing strategies enhances precision and success in personalized medicine, though rigorous clinical evaluation remains crucial to ensuring the efficacy and safety of COVID-19 treatments.

Long COVID drug repurposing

LC is a multi-system disorder manifesting cardiovascular, respiratory, neuropsychiatric, and haematologic symptoms, individually or in combination. Therapeutic strategies require tailored, interprofessional approaches addressing both clinical and psychological aspects [183]. This chronic, heterogeneous pathophysiology differs fundamentally from that of acute viral infection, for which safety data were compiled [184]. Medications deemed safe for short-term acute illness (1–2 weeks) may not retain the same safety profile or efficacy when administered long-term for chronic, multi-systemic LC mechanisms.

Therapeutic targets for LC

Drug repurposing for LC targets various viral and host pathways, reflecting disease complexity. Therapies targeting spike proteins, 3CLpro, PLpro, Mpro, and RdRp can effectively combat SARS-CoV-2 [185]. Promising repurposing targets include entry sites, coating, proteolysis, RdRp enzyme, and ribonucleocapsid assembly [186].

LC is characterized by viral persistence and significant host dysregulation, including oxidative stress, chronic inflammation, calcium stress, and autoimmunity [187]. Simply targeting viral replication may be insufficient to address the full spectrum of symptoms. Multiple targets could demonstrate greater effectiveness and significantly decrease the likelihood of viral resistance, indicating that combination therapy or multiple targets should be prioritized [188].

A vital shift occurs from seeking a single "magic bullet" to developing synergistic combinations addressing viral factors and complex host-mediated pathologies contributing to LC. Antivirals are indicated for patients with viral persistence. Anti-inflammatories may be more effective if immune dysregulation or organ damage occurs after viral clearance. LC's complex pathophysiology suggests that universal strategies are unlikely to succeed, necessitating personalized drug repurposing approaches. This complexity makes identifying drug mechanisms of action challenging, requiring a deeper understanding of individual biology for effective intervention.

Promising repurposed drugs for LC

Clinical investigations highlight varying antiviral effectiveness for acute and established LC. Paxlovid and Molnupiravir effectively mitigate severe outcomes or prevent LC when administered during the acute infection stages [189], suggesting their antiviral properties benefit early disease progression.

WEHI-P8, an innovative Papain-like Protease (PLpro) inhibitor, shows promising preclinical findings. While most existing COVID-19 antiviral treatments, such as Paxlovid, primarily target the virus's main protease (Mpro), PLpro represents an underutilized pharmacological target. WEHI-P8 preclinical results are considered groundbreaking, significantly reducing acute and LC symptoms in preclinical models, including lung pathology and brain dysfunction [190].

Preliminary analyses indicate that another SARS-CoV-2 antiviral, Ensitrelvir, reduces the risk of LC. Additionally, the diabetes drug metformin, started within 7 days of infection, lowered LC risk by over 40% in a randomized controlled trial [191].

These findings illustrate the potential of systematic drug repurposing directed by proteomic and clinical data. Of note, The Long COVID (LC)–REVITALIZE trial (NCT06928272) is the first multi-continent, omics-informed, computational drug-repurposing trial in LC [192]. Using AI-assisted proteomic analysis of >5,400 plasma proteins from 1,028 participants, investigators identified dysregulated biological pathways and identified upadacitinib and pirfenidone as candidate therapies. The resulting Phase III, double-blind, placebo-controlled adaptive platform trial exemplifies how large-scale omics discovery can be translated into omics-informed precision therapeutic trials.

Table 4 presents a curated list of drugs repurposed or proposed for repurposing in COVID-19 and LC treatment. For each drug, the table includes its original clinical use, targeted differentially expressed proteins (DEPs), the mechanism of action in the context of SARS-CoV-2 infection, and its current clinical trial status. The table notes LC relevance, particularly for agents with anti-inflammatory, antiviral, or endothelial-protective properties, supporting the manuscript's discussion on leveraging proteomic insights for rapid therapeutic deployment.

Table 5 provides a structured overview of therapeutic strategies evaluated for both acute COVID-19 and LC. It includes repurposed drugs, corresponding clinical trial identifiers, primary endpoints, trial phases, and available outcomes. The table shows disease stages (mild, severe, post-acute) and highlights the evolving pharmacological landscape, including completed, ongoing, and terminated trials. This provides insight into the translational pipeline from drug discovery to clinical application, highlighting the importance of evidence-based repurposing and personalized treatment approaches.

Despite the promise of computational and mechanistic drug repurposing, clinical validation has not been achieved. In the ORCHID trial (NCT04332991), treatment with hydroxychloroquine did not show any significant improvement in the clinical status among the adult hospitalized COVID-19 patients [193]. Similarly, ivermectin did not have any significant improvement with respect to the symptom resolution [194]. Tocilizumab was also found insufficiently effective in the prevention of intubation and/or death in moderately severe ICU patients [195]. The WHO Solidarity trial, which enrolled more than 11,000 patients across 30 countries, demonstrated that none of four repurposed antivirals (lopinavir, hydroxychloroquine, remdesivir, or interferon regimens) had a significant effect on outcomes in hospitalized COVID-19 patients. There was no indication of improvement in the length of stay, ventilation initiation, and mortality rate [196].

Table 4 Drugs repurposed or proposed for COVID-19 and long COVID (LC) treatment

Drug	Original use	Proteomic target/ implicated pathway	COVID-19 application	COVID-19 clinical status	LC application	LC Clinical status	References
Tocilizumab	Rheumatoid arthritis, cytokine storm	IL-6 receptor (IL-6R)	Repurposed: Mitigates cytokine storm and ARDS	Approved/EUA; WHO-recommended for severe COVID-19	Not applicable	Not applicable	[239]
Baricitinib	Rheumatoid arthritis	JAK1/2, AAK1	Repurposed: Immunomodulation; inhibits viral entry and cytokine storm	Approved; FDA-authorized for hospitalized patients	Proposed for LC (Inflammation modulation)	Not applicable	[240]
Dexamethasone	Anti-inflammatory, corticosteroid	Multiple cytokines	Repurposed: Reduces inflammation in ARDS	Standard of care; demonstrated mortality reduction in severe cases	Not applicable	Not applicable	[241, 242]
Atorvastatin	Lipid-lowering (hyperlipidemia)	IL-1β, TNF-α	Repurposed: Anti-inflammatory; endothelial protection	Observational support; not standard of care	Not applicable	Not applicable	[243, 244]
Remdesivir	Antiviral (for Ebola, Hepatitis C)	Viral RNA-dependent RNA polymerase	Repurposed: Inhibits viral replication	FDA-approved for hospitalized COVID-19 patients	Not applicable	Not applicable	[245]
Fluvoxamine	Obsessive-compulsive disorder (OCD)	Sigma-1 receptor	Repurposed: Reduces inflammation; prevents clinical deterioration	Promising results in early trials; further studies ongoing	Not applicable	Not applicable	[246]
Fenofibrate	Hyperlipidemia	ACE2 modulation	Repurposed: Potentially reduces viral entry by affecting ACE2 modulation	Preliminary studies suggest benefit; clinical trials ongoing	Not applicable	Not applicable	[247]
Hydroxychloroquine	Antimalarial	Autophagy pathways	Repurposed: Early use in COVID-19; largely discredited	Clinical trials mostly discontinued due to inefficacy	Not applied to LC	Not applicable	[248, 249]

Table 5 Overview of therapeutic strategies for COVID-19 and long COVID (LC) treatment

Mild or Moderate COVID-19			
Trial ID	**Drug(s)**	**Status**	**References**
NCT04332991	Hydroxychloroquine	Completed (Phase 3)	[250]
NCT04349241	Favipiravir	Completed (Phase 3)	[251]
NCT04346628	Favipiravir	Completed (Phase 2)	[252]
NCT04390022	Ivermectin	Completed (Phase 2)	[253]
NCT04357782	L-ascorbic acid	Completed (Phases 1 and 2)	[254]
NCT04461353	Aerosolized Hydroxychloroquine Sulfate	Completed (Phase 1)	[255]
Severe or Hospitalized COVID-19 (Acute Infection)			
Trial ID	**Drug(s)**	**Status**	**References**
NCT04292899	Remdesivir	Completed (Phase 3). Approved for clinical use.	[256]
NCT04280705	Remdesivir	Completed (Phase 3)	[257]
NCT04356937	Tocilizumab	Completed (Phase 3)	[258]
NCT04328480	Colchicine	Completed (Phase 3)	[259]
NCT04315948	DisCoVeRy randomized controlled trial (remdesivir, lopinavir/ritonavir, interferon beta-1 A, hydroxychloroquine, AZD7442	Completed (Phase 3)	[260]
NCT04530136	Ruconest	Completed (Phase 2)	[261]
NCT04487886	Duvelisib	Completed (Phase 2)	[262]
NCT04425538	Infliximab	Completed (Phase 2)	[263]
NCT04391179	Dipyridamole	Completed (Phase 2)	[264]
NCT05082714	Baricitinib	Completed (Phase: Not applicable)	[265]
Long COVID			
Trial ID	**Drug(s)**	**Status**	**References**
NCT06928272	Upadacitinib, Pirfenidone	Recruiting (Phase 3)	[192]
NCT04678830	Leronlimab	Completed (Phase 2)	[266]

These results underscore that drug repurposing carries a high attrition rate, and that only the preclinical or proteomic basis does not reliably predict clinical efficacy. Acknowledging both successes and failures, Table 5 presents a curated list of drugs repurposed or proposed for repurposing in COVID-19 and LC treatment.

While these findings illustrate the potential of systematic drug repurposing informed by proteomic and clinical data, they must be interpreted alongside a substantial body of trial evidence demonstrating that early promise does not reliably translate to clinical benefit.

Personalized medicine and clinical translation

Personalized medicine represents a paradigm shift from reactive, one-size-fits-all healthcare to predictive, precision-based therapeutic strategies. This approach emphasizes biomarker identification for disease prevention and treatment response prediction while facilitating targeted preventive interventions.

Recent advances in proteomic technologies have enabled high-dimensional dataset generation, improved diagnostic accuracy, and facilitated informed therapeutic decision-making. Plasma proteomics identifies key biomarkers to predict COVID-19 severity and inform targeted interventions, while single-cell proteomics reveals cellular immune responses for precise therapeutic targeting. ML models benefit significantly from proteomic data, enabling predictions of patient outcomes and therapeutic responses. Critical factors, including analytical methodology selection, ensemble learning approaches, and integrated multi-omics strategies, are essential for establishing robust personalized medicine frameworks.

Clinical applications in COVID-19: therapies and trials

Personalized medicine customizes therapies to individual biomarker profiles, enhancing efficacy while reducing adverse effects. Drug repurposing accelerates treatment development by utilizing proteomic insights to address urgent clinical needs. For example, COVID-19 patients experiencing hyperimmune reactions during acute infection may benefit more from anti-inflammatory drugs than from antivirals, with tocilizumab targeting IL-6 receptors improving disease symptoms. However, large-scale personalized medicine applications remain insufficient in healthcare, highlighting the need for extensive research and integration strategies into routine clinical practice [197].

Despite promising personalized approaches, scalability remains challenging. High costs and validation complexities hinder widespread personalized therapy adoption, requiring government funding and global collaboration to overcome barriers and ensure equitable access while minimizing drug resistance through targeted interventions [198].

From population health to personalized prediction

Clinical integration of omics platforms supports the development of preventive strategies tailored to individual profiles, including improved outbreak detection, monitoring of transmission patterns, and patient

stratification on the basis of risk. Clinical considerations emphasize cautious trial approaches due to toxicity risks and population heterogeneity involving age, sex, race, and polymorphisms in key signaling molecules. Biomarker-based personalized therapy can mitigate adverse effects [199].

Precision therapeutic approaches, partially implemented in COVID-19 management, clarify individual susceptibility to infection and explain the variability in clinical course, prognosis, and treatment response. The broad clinical spectrum of COVID-19, ranging from asymptomatic to severe cases, underscores the need for tailored patient care, enabling healthcare providers to better predict outcomes and optimize treatments [200].

Advances in biomedical knowledge and technologies have reduced the costs of high-throughput methods, including next-generation sequencing (NGS) and targeted genomics, positioning omics as a key approach for deciphering molecular disease patterns and supporting the clinical application of precision medicine.

COVID-19 personalized medicine operates through multilayered approaches. Proteomics and computational research projects have developed novel methods, including immunohistochemistry, plasma proteomics, and DNA profiling, facilitating personalized diagnostics based on individual genetic makeup and environmental factors. Examining COVID-19 tissue-specific immune system dysfunction identifies novel markers differentiating disease stages or treatment responses (Fig. 4).

Analytical limitations, reproducibility, and platform suitability

While mass spectrometry (MS), Olink proximity extension assays, and SOMAscan aptamer-based platforms have substantially advanced COVID-19 proteomics, each technology presents distinct analytical constraints that must be considered when interpreting results and translating findings into clinical applications.

Mass spectrometry (MS) provides unbiased, discovery-driven proteome profiling with high specificity and broad dynamic range. It is particularly suited for hypothesis generation and pathway discovery. However, plasma proteomics by MS is sensitive to pre-analytical variability, including sample handling time, freeze–thaw cycles, haemolysis, and storage conditions. Data-dependent acquisition (DDA) workflows may introduce missing values, while instrument drift, column aging, and ion suppression effects can contribute to batch variability. Rigorous normalization and quality control procedures are therefore essential.

Olink proximity extension assays offer high sensitivity, minimal sample volume requirements, and strong reproducibility within predefined protein panels. However, Olink provides relative quantification (NPX units) rather than absolute concentration, and analysis is restricted to targeted protein panels. Cross-panel comparisons and inter-study harmonization may require additional normalization strategies, particularly in multicenter investigations.

SOMAscan enables high-dimensional profiling of thousands of proteins simultaneously and is particularly advantageous for large-scale screening. Nevertheless, aptamer-based detection may be affected by cross-reactivity and matrix effects, and orthogonal validation (e.g., ELISA or MS confirmation) is recommended for key findings. Batch correction and calibration controls are critical for ensuring reproducibility across cohorts.

Across platforms, inter-study reproducibility remains a challenge due to heterogeneity in patient populations, disease stage at sampling, analytical workflows, and statistical pipelines. Multiple hypothesis testing, missing data imputation, and small cohort sizes can introduce bias if not properly controlled. Furthermore, proteomic signatures identified in discovery cohorts frequently lack independent external validation.

In terms of translational suitability, untargeted MS is most appropriate for discovery-phase investigations, whereas Olink panels are particularly suited for focused biomarker validation and longitudinal monitoring. SOMAscan occupies an intermediate role as a high-dimensional screening platform but requires confirmatory validation prior to clinical application.

Standardization of pre-analytical workflows, cross-platform harmonization, multi-center replication, and integration with orthogonal assays will be essential to advance COVID-19 proteomics from exploratory studies to clinically actionable biomarker implementation.

Conclusions

The COVID-19 pandemic has caused unprecedented loss of life, economic disruption, and widespread physical and mental distress. While vaccines provide protection, effective universal therapies remain elusive, with current treatments yielding inconsistent results and varying adverse effects. These discrepancies reflect individual differences, including age, sex, comorbidities, and biological factors. Treatment variability stems significantly from genetic and proteomic diversity within human populations, as variations in genes and proteins involved in drug metabolism influence therapeutic outcomes, underscoring the critical need for personalized COVID-19 care approaches.

Computational proteomics has emerged as a transformative approach for enhancing personalized COVID-19 treatment through sophisticated BI workflows. From initial data preprocessing and normalization to advanced ML applications, these methods enable the extraction of clinically relevant insights from high-dimensional

proteomic datasets. Differential expression analysis, functional pathway enrichment, and network inference techniques reveal disease mechanisms and therapeutic targets, whereas deconvolution algorithms elucidate cell-type-specific signatures within complex plasma proteomes. Integration of traditional statistical methods with cutting-edge artificial intelligence, including large language models, enables comprehensive analysis of protein interactions and identification of novel biomarkers for precision medicine applications.

Drug repurposing strategies, accelerated through proteomic insights and computational modeling, offer rapid therapeutic solutions by identifying existing compounds with established safety profiles for COVID-19 treatment. Notable successes include tocilizumab for hyperimmune responses, various tyrosine kinase inhibitors, and polypharmacological agents that target multiple pathways simultaneously. Advanced techniques, including proximity extension assays and aptamer-based technologies, enhance the precision of biomarker discovery, while comprehensive databases provide essential multi-omics resources for translational research.

Integration of proteomics with advanced analytics could lead to enhanced, tailored COVID-19 interventions through the identification of protein signatures linked to disease progression. This approach enables clinicians to predict patient outcomes more accurately, select optimal therapies, improve treatment efficacy, and minimize adverse effects. However, clinical implementation requires thorough validation and careful interpretation, as the complex interplay of genetic, proteomic, metabolomic, and environmental factors necessitates multidisciplinary approaches for research and clinical application.

As the scientific community continues to address COVID-19 challenges, advancing personalized medicine approaches that leverage proteomic insights represents a crucial frontier for improving patient care and outcomes during this ongoing global health crisis. The convergence of computational biology, advanced analytics, and clinical application positions proteomics as an essential tool for developing precision therapeutic strategies that account for individual patient variability and optimize treatment outcomes. Proteomics may play an important role in this transition, enabling the development of precision therapies tailored to both the virus and the patient in the context of personalized medicine for infectious diseases.

Supplementary Information

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Supplementary Material 1.

Author contributions

DDF conceived the review. DS, LRVN, DT, and DDF wrote the initial copy. DS created all figures. All authors revised the manuscript and consent to publication.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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