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REVIEW ON IMMUNOPATHOPHYSIOLOGY AND INFLAMMATORY BIOMARKERS IN SEVERE COVID-19. FROM MECHANISMS TO CLINICAL APPLICATIONS

Lidia PLĂCINTĂ, ORCHID: 0000-0001-9969-867X[1],
Adrian BELÎI, ORCHID: 0000-0002-4128-1318[2],
Diana GUȚANU, ORCHID: 0000-0003-1853-6420[3]

[1]Department of Infectious, Tropical Diseases and Medical Parasitology, IP USMF „N. Testemițanu”, Chisinau, Republic of Moldova
[2]„Valeriu Ghereg” Anaesthesiology and Resuscitation Department No. 1, IP USMF „N. Testemițanu”, Chisinau, Republic of Moldova
[3]„Toma Ciorbă” Clinical Hospital of Infectious Diseases, Chisinau, Republic of Moldova
e-mail: *lidia.placinta@usmf.md, 079269023*

Summary.

Introduction. Severe COVID-19 cases are characterized by a complex interaction involving viral-induced cellular damage, immune system imbalances, endothelial impairment, and inflammation-driven blood clotting. This article provides a comprehensive overview of the key pathophysiological mechanisms, it underscores the critical importance of inflammatory biomarkers in the diagnostic process, prognostic stratification, and therapeutic guidance. Understanding the relationship between these mechanisms and specific biomarkers facilitates a more personalized approach to managing critically ill patients with COVID-19.

Aim og the article. The aim of this article is to provide a comprehensive and up-to-date review of the immune-related pathophysiological mechanisms underlying severe forms of COVID-19, with a particular focus on the diagnostic, prognostic, and therapeutic relevance of inflammatory biomarkers. By integrating recent clinical and molecular evidence, the paper seeks to highlight how these biomarkers can support early risk stratification and guide personalized therapeutic strategies, ultimately contributing to improved outcomes in critically ill patients.

Material and Methods. The review was carried out through a systematic and extensive search of the specialized literature published between January 2020 and May 2025, using relevant databases (PubMed, Scopus, Web of Science, Google Scholar). Search terms such as: “severe COVID-19”, “inflammatory biomarkers”, “cytokine storm”, “immune dysregulation”, “CRP”, “IL-6”, “TNF-α”, “ferritin”, “D-dimer”, “RAAS”, “ARDS”, “NETs”, “endothelial dysfunction” were included. The included studies were selected based on the criteria of quality, thematic relevance, methodological validity and clinical applicability. Non-scientific articles, pediatric cases, commentaries and papers published in languages other than English were excluded. The selected articles were grouped by major themes: pathogenesis, biomarker classification, clinical utility and prognostic value.

Results. The results of the analysis highlight that the severity of COVID-19 is determined by a complex interaction between endothelial dysfunction, excessive immune activation, RAAS imbalance and hypercoagulability. These mechanisms lead to systemic inflammation, immunothrombosis and multisystemic damage, especially pulmonary, renal, cardiac and neurological. The identified biomarkers – such as IL-6, CRP, D-dimer, TNF-α, ferritin and CXCL10 – reflect these processes and allow a dynamic assessment of the severity of the disease. Clinical studies have demonstrated that increased levels of these markers correlate with high mortality and variable therapeutic response. The use of biomarkers in guiding immunotherapy has shown significant benefits in prognosis and individualization of treatment.

Keywords: severe COVID-19, inflammatory biomarkers, chemokine, ARDS, immune dysregulation, tocilizumab.

Rezumat. Reviu asupra imunopatofizologiei și biomarkerilor inflamatori în formele severe de COVID-19. De la mecanisme la aplicații clinice.

Introducere. Formele severe de COVID-19 se caracterizează printr-o interacțiune complexă ce implică deteriorarea celulară indusă de acțiunea virusului, dezechilibre ale sistemului imunitar, afectarea endoteliului vascular și coagularea sanguină determinată de inflamație. Acest articol oferă o prezentare comprehensivă a principalelor mecanisme fiziopatologice, evidențiind importanța crucială a biomarkerilor inflamatori în procesul de diagnostic, stratificarea prognosticului și ghidarea terapeutică. Înțelegerea relației dintre aceste mecanisme și biomarkerii specifici permite o abordare mai personalizată în managementul pacienților cu COVID-19 în forme critice.

Scopul articolului. Scopul acestui articol este de a realiza o sinteză amplă și actualizată a mecanisme de imunopatogeneză implicate în formele severe de COVID-19, punând accent pe identificarea și aplicabilitatea clinică a

biomarkerilor inflamatori. Articolul urmărește să evidențieze modul în care acești biomarkeri pot fi utilizați în diagnostic, prognostic și ghidarea terapiei personalizate, contribuind astfel la optimizarea tratamentului pacienților critici și la reducerea mortalității asociate cu infecția SARS-CoV-2.

Materiale și metode. Acest reviu a fost realizat prin căutarea sistematică și amplă a literaturii de specialitate publicată în perioada ianuarie 2020 și mai 2025, utilizând baze de date relevante (PubMed, Scopus, Web of Science, Google Scholar). Au fost incluși termeni de căutare precum: "COVID-19 sever", "biomarkeri inflamatori", "furtuna citokinică", "disfuncție imună", "CRP", "IL-6", "TNF-α", "feritina", "D-dimer", "RAAS", "ARDS", "NETs", "disfuncția endotelială". Studiile incluse au fost selectate pe baza criteriilor de calitate, relevanță tematică, validitate metodologică și aplicabilitate clinică. Au fost excluse articolele non-științifice, cazurile pediatrice, comentariile și lucrările publicate în alte limbi decât engleza. Articolele selectate au fost grupate pe teme majore: patogenia, clasificarea biomarkerilor, utilitatea clinică și valoarea prognostică.

Rezultate. Rezultatele analizei evidențiază faptul că severitatea COVID-19 este determinată de o interacțiune complexă între disfuncția endotelială, activarea imună excesivă, dezechilibrul RAAS și hipercoagulabilitate. Aceste mecanisme conduc la inflamație sistemică, imunotromboză și afectare multisistemică, în special pulmonară, renală, cardiacă și neurologică. Biomarkerii identificați – precum IL-6, CRP, D-dimer, TNF-α, feritina și CXCL10 – reflectă aceste procese și permit o evaluare dinamică a severității bolii. Studiile clinice au demonstrat că nivelurile crescute ale acestor markeri se corelează cu mortalitatea ridicată și răspunsul terapeutic variabil. Utilizarea biomarkerilor în ghidarea imunoterapiei a demonstrat beneficii semnificative în prognostic și individualizarea tratamentului.

Cuvinte cheie: forme severe de COVID-19, biomarkeri inflamatori, chemokine, ARDS, disfuncție imună, tocilizumab.

Резюме. Обзор иммунопатофизиологии и воспалительных биомаркеров при тяжелых формах COVID-19. От механизмов к клиническим применениям.

Введение. Тяжелые формы COVID-19 характеризуются сложным взаимодействием, включающим вирус-индуцированное клеточное повреждение, дисбаланс иммунной системы, эндотелиальные нарушения и воспалительно-обусловленное тромбообразование. Данная статья представляет всесторонний обзор ключевых патофизиологических механизмов, подчеркивая критическую важность воспалительных биомаркеров в диагностическом процессе, прогностической стратификации и терапевтическом руководстве. Понимание взаимосвязи между этими механизмами и специфическими биомаркерами способствует более персонализированному подходу к ведению критически больных пациентов с COVID-19.

Цель статьи. Цель настоящей работы — всесторонний анализ иммунопатологических процессов, лежащих в основе тяжёлых форм COVID-19, с акцентом на клиническую значимость воспалительных биомаркеров. На основе синтеза современных научных данных статья рассматривает, каким образом использование биомаркеров может способствовать индивидуализации терапии и улучшению прогноза у пациентов в критическом состоянии.

Материалы и методы. Обзор был проведен посредством систематического и обширного поиска специализированной литературы, опубликованной между январем 2020 и маем 2025 года, с использованием соответствующих баз данных (PubMed, Scopus, Web of Science, Google Scholar). Были включены поисковые термины, такие как: « тяжелые формы COVID-19», «воспалительные биомаркеры», «цитокиновый шторм», «иммунная дисрегуляция», «CRP», «IL-6», «TNF-α», «ферритин», «D-димер», «РААС», «ОРДС», «НЭТ», «эндотелиальная дисфункция». Включенные исследования отбирались на основе критериев качества, тематической релевантности, методологической валидности и клинической применимости. Были исключены ненаучные статьи, педиатрические случаи, комментарии и работы, опубликованные на языках, отличных от английского. Отобранные статьи группировались по основным темам: патогенез, классификация биомаркеров, клиническая полезность и прогностическая ценность.

Результаты. Результаты анализа подчеркивают, что тяжесть COVID-19 определяется сложным взаимодействием между эндотелиальной дисфункцией, избыточной иммунной активацией, дисбалансом РААС и гиперкоагуляцией. Эти механизмы приводят к системному воспалению, иммунотромбозу и мультисистемному повреждению, особенно легочному, почечному, сердечному и неврологическому. Идентифицированные биомаркеры – такие как IL-6, CRP, D-димер, TNF-α, ферритин и CXCL10 – отражают эти процессы и позволяют динамическую оценку тяжести заболевания. Клинические исследования продемонстрировали, что повышенные уровни этих маркеров коррелируют с высокой смертностью и вариабельным терапевтическим ответом. Использование биомаркеров для руководства иммунотерапией показало значительные преимущества в прогнозировании и индивидуализации лечения.

Ключевые слова: тяжелые формы COVID-19, воспалительные биомаркеры, хемокины, ОРДС, иммунная дисрегуляция, тоцилизумаб.

Introduction.

Since its onset in late 2019, the SARS-CoV-2 virus has caused a spectrum of clinical manifestations, from mild respiratory illnesses to severe systemic syndromes requiring intensive care. The severity of COVID-19 is determined not solely by viral strain viral or viral load, but by the host's exaggerated immune response, coagulopathic state, and organ-specific vulnerabilities. The identification and application of pertinent inflammatory biomarkers have become crucial in guiding clinical decision-making and advancing research.

Aim og the article.

The aim of this article is to provide a comprehensive and up-to-date review of the immune-related pathophysiological mechanisms underlying severe forms of COVID-19, with a particular focus on the diagnostic, prognostic, and therapeutic relevance of inflammatory biomarkers. By integrating recent clinical and molecular evidence, the paper seeks to highlight how these biomarkers can support early risk stratification and guide personalized therapeutic strategies, ultimately contributing to improved outcomes in critically ill patients.

Methodology.

To achieve the established objective, an initial search of specialized scientific publications was performed, using Google Search and databases such as PubMed, Hinari (Health Internet Work Access to Research Initiative), SpringerLink, the National Center for Biotechnology Information and Medline. Search terms such as: "severe COVID-19", "inflammatory biomarkers", "cytokine storm", "immune dysregulation", "CRP", "IL-6", "TNF-α", "ferritin", "D-dimer", "RAAS", "ARDS", "NETs", "endothelial dysfunction" were included. For advanced source selection, the following filters were applied: full-text articles in English, published between 2020 and 2025, original research articles, editorials, narrative reviews, systematic reviews and meta-analyses, which contained only information on severe COVID-19. To minimize the risk of systematic errors (bias) in the study, we performed in-depth database searches for updated information from relevant publications that matched the study purpose, evaluating only studies that met the validity criteria and applying reliable article exclusion criteria. Publications and articles that did not align with the study purpose, as well as those that were not accessible in full format, were excluded from the list of publications generated by the search engine. Following information processing through Google Search and databases such as PubMed, Hinari, SpringerLink, the National Center for Biotechnology Information, and Medline, 287 articles addressing the pathophysiology of COVID-19, the role of biomarkers in COVID-19, were identified based on the search criteria. After a detailed review of the titles and abstracts, conclusions - 93 articles were initially considered as potentially relevant for this synthesis. Following a comprehensive review, 66 publications were ultimately selected as relevant to the established objective and were included in the final bibliography, representing the materials considered significant for the purpose of this synthesis article. Publications that did not address the topic, even if initially selected by the search program, and articles inaccessible in full format, either through the HINARI database or in the scientific medical library of the "Nicolae Testemițanu" State University of Medicine and Pharmacy, were subsequently excluded from the final list.

Results.

I. Molecular and genomic mechanisms in the pathogenesis of SARS-CoV-2

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. The SARS-CoV-2 virus consists of a positive-sense single-stranded RNA (+ssRNA) with an average length of approximately 30,000 nucleotides and a 5′-head and 3′-poly-A tail structure. The viral genome encodes approximately 9,860 amino acids and contains several open reading frames (ORFs), notably ORF1a and ORF1b, which encode replication enzymes [1]. Structural proteins of SARS-CoV-2 include the envelope protein (E), spike protein (S), nucleocapsid protein (N), and membrane protein (M) [2]. Together with a lipid bilayer derived from the host cell membrane, these proteins form an enveloped virion that can transport the viral genomic RNA into new cells. The SARS-CoV-2 genome has a guanine and cytosine (G+C) content of between 32% and 43%, a parameter that influences its genetic stability [3]. This composition is closely linked to an evolutionary strategy characteristic of coronaviruses – the suppression of CpG motifs – designed to avoid recognition by the antiviral protein ZAP, which degrades viral RNAs rich in CpG sequences. However, in the SARS-CoV-2 genome, the ORF encoding the E protein retains a relatively high content of CpG motifs, which makes it vulnerable to ZAP activity, suggesting a possible weak point in the virus's immune evasion strategy [1].

Pathophysiology of Severe COVID-19

Severe cases of COVID-19 result from a convergence of intricate interactions involving SARS-CoV-2 and the host's immune response, ultimately leading to multisystem dysfunction [2].

The fundamental pathophysiological mechanisms underlying disease severity include endothelial dysfunction, dysregulated immune activation, thromboinflammation, and disturbances in the renin–angiotensin–aldosterone system (RAAS) [3].

Viral Entry and RAAS Dysregulation

SARS-CoV-2 infection is usually transmitted by inhalation of viral particles or contact with contaminated surfaces. The virus enters epithelial cells of the upper and lower respiratory tract through the interaction of the spike protein (S) with the ACE2 receptor expressed on the surface of host cells [6]. Type 1 (involved in gas exchange) and type 2 (surfactant-producing) pneumocytes are the main target cells [7]. Binding of the spike to ACE2 is followed by its proteolytic cleavage by TMPRSS2, which allows fusion of the viral and cellular membranes and initiation of replication [8].

After entry, the viral genome is used for the synthesis of negative-strand RNA and subgenomic RNAs, which are required for the synthesis of structural proteins. The newly formed virions are assembled in the endoplasmic reticulum and Golgi, and are released by exocytosis. A single cell can produce thousands of virions, which spread locally and systemically [3].

Systemic dissemination allows infection of ACE2-expressing organs, such as the kidney, heart, liver, intestine, and central nervous system. Because ACE2 is a component of the renin–angiotensin–aldosterone system (RAAS), viral binding results in reduced expression and function [7,9]. Physiologically, ACE2 degrades angiotensin II (Ang II)—a vasoconstrictor, proinflammatory, and profibrotic mediator—to angiotensin 1–7, which has protective effects. Inhibition of ACE2 leads to the accumulation of Ang II, favoring activation of AT1 receptors and contributing to endothelial injury, coagulopathy, and systemic inflammation [5].

The RAAS is activated by the secretion of renin by the renal juxtaglomerular apparatus under conditions of hypoperfusion. Renin converts hepatic angiotensinogen to angiotensin I (Ang I), which is then converted to Ang II by the action of angiotensin-converting enzyme (ACE), predominantly in the lungs [10]. Ang II acts on AT1R receptors, causing vasoconstriction, sodium retention, and aldosterone secretion. The RAAS imbalance observed in severe COVID-19 contributes to altered tissue perfusion and ventilation/perfusion mismatch [9].

Systemic Inflammation and Cytokine Storm

In addition to direct targeting of the ACE2 receptor by SARS-CoV-2, other mechanisms contribute to the imbalance of the renin-angiotensin system (RAAS). One of these is the activation of the metallopeptidase ADAM17, also known as TACE (TNF-α converting enzyme), which cleaves the inactive form of TNF-α into a soluble and active form, enhancing systemic inflammation [11]. Activation of the AT1R receptor by angiotensin II indirectly stimulates ADAM17, generating a vicious inflammatory cycle in severe COVID-19 [7].

An important modulatory role is played by vitamin D, which suppresses renin gene expression and can support RAAS inhibition, especially when combined with AT1 receptor blockers or ACE inhibitors [12]. Low vitamin D levels have been associated with increased risk of ARDS [13], increased mortality in patients with community-acquired pneumonia [14], as well as severe COVID-19, although current evidence is largely indirect [15].

Regarding viral entry, in addition to ACE2 and TMPRSS2, other coreceptors such as neuropilin-1 and proteases such as cathepsin L, TMPRSS11D and TMPRSS13 have been identified, but their pathogenic role remains incompletely elucidated [16].

Toll-like receptors (TLRs), in particular TLR3, TLR4 and TLR7, play a dual role in COVID-19, they contribute to antiviral defense, but also to the development of immunopathology in severe forms, including cytokine storm [17,18]. In the context of bacterial coinfections, TLR activation influences the efficiency of the immune response and requires appropriate antibiotic therapy.

After viral entry, the SARS-CoV-2 genome (+ssRNA) rapidly initiates the synthesis of viral proteins, including those involved in replication, which induce the formation of double-membrane vesicles (DMVs) in the endoplasmic reticulum, where protected RNA transcription occurs (7). The main viral recognition pathway is through the cytoplasmic receptor MDA5, which detects double-stranded RNA (dsRNA) and activates the synthesis of type I and III interferons [19]. Interferons induce the expression of interferon-stimulated genes (ISGs), with direct antiviral effects and immune cell recruitment [20].

In parallel, the massive release of proinflammatory cytokines – IL-6, IL-1β, IFN-γ, TNF – contributes to systemic inflammation and organ damage [21]. Chemokines such as CXCL10, CXCL9, MCP-1, and MIP-1α attract immune cells to inflammatory foci, enhancing tissue damage [22]. Elevated levels of IL-6 and other interleukins are associated with severe complications, including ARDS [23].

Genetic Susceptibility and Antiviral Defense Defects

In a subset of patients with severe COVID-19, neutralizing autoantibodies against type I interferons,

particularly IFN-α2 and IFN-ω, have been identified, compromising the antiviral response and favoring disease progression. These autoantibodies have been detected in approximately 10% of patients with severe forms, but were absent in asymptomatic or mild individuals [24, 25].

In addition to autoimmune mechanisms, innate genetic defects in interferon signaling pathways have been described, which increase susceptibility to critical forms. Genetic studies have revealed mutations in the JAK1 and TYK2 genes, involved in the transmission of signals for type I interferons and IL-6, both of which are associated with the severity of the infection [8, 26].

Comorbidities such as hypertension, heart failure, diabetes, chronic lung disease, and renal dysfunction increase the risk of respiratory complications and mortality in severe COVID-19 [27].

It has also been proposed that the higher mortality in men may be related to reduced ACE2 expression. The ACE2 gene, located on the X chromosome, may be compensated for in women by the second X chromosome, unlike men, who have only one functional copy. This difference may be exacerbated by the effects of aging on ACE2 expression [7].

Thromboinflammation and Immunothrombosis

In severe COVID-19, monocytes respond to SARS-CoV-2 infection by releasing tissue factor (TF) and activating the NLRP3 inflammasome, which stimulates the production of IL-1β and IL-18 [28]. The alveolar epithelium releases IL-6, which induces hepatic synthesis of procoagulant factors and endothelial TF expression.

Neutrophils contribute to immunothrombosis by forming neutrophil extracellular traps (NETs), which activate factor XII, bind to von Willebrand factor, and recruit platelets. NETs and complement fragments (C3a, C5a) activate platelets, and enzymes such as elastase and myeloperoxidase inhibit anticoagulant mechanisms, favoring coagulation [29].

Activated platelets release proinflammatory cytokines, platelet factor 4, HMGB1, and extracellular vesicles, amplifying the immune response and coagulation. In parallel, increased expression of plasminogen activator inhibitor reduces fibrinolysis, contributing to thrombosis [30].

Generalized immunothrombosis has been demonstrated by postmortem studies, which showed thrombotic microvascular lesions in the lungs and skin, accompanied by complement deposits (C5b-9, C4d, MASP2), without extensive inflammation or fibrosis [31]. These microvascular lesions contribute to respiratory failure, with paradoxically increased lung compliance and elevated dead space fraction, deviating from the typical profile of non-COVID ARDS.

Pulmonary Histopathology and Diffuse Alveolar Damage

Histological examinations in ARDS, including severe forms of COVID-19, consistently reveal diffuse alveolar damage (DAD) as the predominant pattern of lung involvement [16,32]. It progresses through three phases:

- Exudative – alveolar edema, epithelial lesions, hyaline membranes;
- Proliferative – alveolar regeneration with proliferation of type II pneumocytes;
- Fibrotic – collagen deposition, pulmonary fibrosis [33].

COVID-19 autopsies confirm the presence of LAD and its correlation with severe respiratory impairment [34]. In COVID-19 ARDS (CARDS), extensive endothelial damage and immunothrombosis are observed, with complement activation (C5b-9, C4d, MASP2) and pulmonary and cutaneous microthrombosis, in the absence of a widespread inflammatory infiltrate [31]. Radiologically, early forms may appear inconclusive, which delays recognition of severity and early intervention [35]. The pathogenesis of hypoxemia involves impaired pulmonary perfusion, characterized by ventilation/perfusion (V/Q) mismatch and intrapulmonary shunts, with impaired hypoxic vasoconstriction [9]. Hyperperfusion of hypoventilated areas and dysfunctional neovascularization contribute to hypoxemia [36]. Hyperinflammation is essential in disease progression. Activation of immune cells (monocytes, macrophages, T cells, NK cells, dendritic cells) generates a disproportionate secretion of cytokines (IL-1β, IL-2R, IL-6, IL-8, IL-17, TNF-α) and chemokines (CCL2, CCL5, CXCL10), leading to a cytokine storm [37–39]. This is directly correlated with clinical severity [28]. Dysregulation of signaling pathways, such as IL-6/JAK/STAT, TNF-α/NF-κB, TLR, BTK, and RAS, supports the amplification of this inflammatory reaction [26]. The deficient T cell response contributes to ineffective viral clearance and perpetuation of inflammation.

Multiorgan Involvement and ACE2 Distribution

Although COVID-19 was initially considered a respiratory disease, clinical data confirm its multisystemic nature, affecting the gastrointestinal, cardiovascular, renal, neurological, hepatic, endocrine, and integumentary systems [30]. Severe cases are frequently associated with a prothrombotic state and may progress to multiorgan failure. SARS-

CoV-2 infects various tissues through the ACE2 receptor:

● Cardiovascular: Hypercytokinemia reduces myocardial ACE2 expression, increasing angiotensin II and promoting hypertension, contractile dysfunction and myocardial ischemia, up to acute coronary syndrome [40].

● Neurological: COVID-19 can cause stroke, encephalopathy, Guillain-Barré syndrome or neuropsychiatric symptoms. The virus has been detected in the cerebral endothelium, but not in neurons, suggesting a systemic inflammatory mechanism [41, 42].

● Renal: Acute renal failure (ARF) is common and associated with increased mortality. SARS-CoV-2 directly infects proximal tubular cells and podocytes through ACE2 and TMPRSS2 [43, 44].

Hepatic: Lesions include steatosis, necrosis, lymphocytic infiltrate, and sinusoidal thrombosis. The causes are multifactorial: viral attack, hypoxia, drugs, inflammation, or coagulopathy. Patients with NAFLD are at increased risk of severe disease and prolonged viral shedding [45–47].

● Endocrine: SARS-CoV-2 may affect the adrenal axis, destabilize diabetes, or trigger acute endocrine crises [48].

● Cutaneous: Manifestations include viral rashes, vasculitis, hemorrhagic lesions, and HHV reactivation with the appearance of pityriasis rosea [45, 48].

Collectively, these mechanisms represent a dynamic and evolving interplay between the virus and host immunity, where an initially protective immune response becomes maladaptive. The dysregulation between proinflammatory and regulatory immune pathways, along with endothelial damage and RAAS disruption, exacerbates systemic injury. The ensuing pathophysiological state is characterized by hyperinflammation, increased vascular permeability, coagulopathy, and immunoparalysis, underscoring the need for timely and targeted therapeutic interventions.

I. Diagnostic and Prognostic Role of Inflammatory Biomarkers

Inflammatory biomarkers act as molecular reflections of the underlying pathogenic processes in COVID-19. They are critical for early risk assessment, therapeutic strategies, and monitoring clinical progression. Based on their functional characteristics, these biomarkers can be classified into several categories [2, 4, 5]:

Systemic Inflammatory Cytokines

● IL-6: Produced by macrophages, T cells, and endothelial cells, IL-6 levels correlate strongly with disease severity, ICU admission, and mortality.

● TNF-α: Increases endothelial permeability and intensifies cytokine cascades. Its elevation has been associated with respiratory insufficiency and multiorgan dysfunction.

● IL-1β: Activated through inflammasomes (NLRP3), it promotes vascular leakage and systemic inflammation.

Coagulation Biomarkers

● D-dimer: A fibrin degradation product elevated in hypercoagulable states, predicting thrombotic complications and mortality risk.

● Fibrinogen: Acute-phase reactant with diagnostic value in coagulation disorders and hepatic impairment; high levels are linked to poor prognosis in ICU patients.

Chemokines and Cell-Mediated Immunity Markers [6]

● CXCL10 (IP-10): Associated with viral load and immune dysregulation [7].

● CXCL8 (IL-8): A potent neutrophil chemoattractant, highly expressed in severe cases and correlating with ARDS development [8].

Adaptive Immunity Cytokines

● IL-10: Reflects compensatory immunosuppression after hyperinflammation. High levels are suggestive of immune exhaustion.

● IL-17: Stimulates neutrophilic inflammation, associated with lung tissue damage and pulmonary fibrosis.

Acute Phase and Tissue Damage Biomarkers

● CRP: Synthesized by hepatocytes under IL-6 influence, correlates with disease severity and the efficacy of therapeutic interventions.

● Ferritin: Indicator of macrophage activation and oxidative stress; high levels mark cytokine storm and poor outcome.

● LDH: Marker of tissue necrosis; elevated levels are particularly relevant in lung damage [9].

Emerging Biomarkers

● GM-CSF: Facilitates monocyte and macrophage activation, involved in hyperinflammation [10].

● sST2: Inhibits IL-33 signaling; elevated levels correlate with cardiac injury and systemic inflammation [11].

I. Clinical Integration and Evidence from Trials

Severe COVID-19 is associated with elevated levels of proinflammatory cytokines and chemokines, such as IL-6, IL-10, TNF, and IFN-γ, which are involved in the amplification of the systemic immune response. These molecules have been therapeutic targets in attempts to control the cytokine storm and limit tissue damage. Strategies investigated include

blocking IL-6 with monoclonal antibodies such as tocilizumab and sarilumab, inhibiting TNF with established anti-inflammatory agents (adalimumab, etanercept), and using JAK-STAT inhibitors such as ruxolitinib to counteract the effects of IFN-γ [49]. Modulation of IL-10, alone or in combination with PD-1 blockade, has also been proposed as a means of restoring T-cell function and reducing lung inflammation [57]. Recent studies highlight the critical role of inflammatory biomarkers in the prognosis and treatment of severe COVID-19.

In a study of 101 COVID-19 patients in the ICU, high baseline levels of IL-6 and CRP were associated with mortality, and persistence of inflammation and lymphopenia was predictive of poor outcome [58]. Similarly, an international study of 2149 patients identified nucleocapsid antigen, CRP, and IL-6 as predictors of severity, suggesting the importance of combined antiviral and immunomodulatory therapy [59].

The study by Takehiro Hasegawa et al. [60] analyzed the inflammatory endotype type 1 (T1). The researchers identified a subgroup (cluster IV) with the highest levels of T1 markers, in which the majority of patients developed severe forms. Elevated levels of IL-6 and CRP indicated marked systemic inflammation. The differences observed between the biomarkers VEGF and CCL17 suggest an interaction between T1 and T2 inflammatory responses. This inflammatory profile, characterized by elevated levels of cytokines such as CXCL9, IL-18, and CCL3, is associated with serious complications, including ARDS, renal injury, and pulmonary fibrosis. Monitoring T1 biomarkers may predict disease severity and guide treatment. Leronlimab administration to critically ill patients reduced IL-6/TNF-α levels, with clinical improvement and normalization of the CD4+/CD8+ ratio [61]. Another study showed that excessive complement activation (sC5b-9, C3a, Bb) is associated with disease progression and mortality, and low MBL was correlated with impaired antiviral response [62]. Complement thus contributes to a vicious cycle of inflammation, tissue damage, and immune dysfunction.

Early use of tocilizumab in patients with systemic inflammation was associated with decreased length of hospital stay and reduced risk of progression to ventilation or death, without increasing secondary infections [63, 64].

A controlled study conducted in the Republic of Moldova showed that a reduced dose of tocilizumab (200 mg) may be comparable to the standard dose in clinical improvement, supporting efficient use of resources and reducing the risk of adverse reactions. Dosage adjustment is recommended based on disease severity and patient profile [65].

In a pilot study, the combination of tocilizumab + pembrolizumab demonstrated promising results in the recovery of severely ill patients, with reduced length of hospital stay and possible immune restoration, although methodological limitations are acknowledged [66].

However, cytokine profiles vary between patients, highlighting the need for individualized assessment of IL-6, TNF-α, IFN-γ before initiating immunotherapy. Combining antiviral and immunomodulatory treatments may optimize clinical outcomes, but further studies are needed to validate safety, especially regarding the risk of chronic inflammation associated with strategies such as IL-10 modulation.

Conclusions.

1. Effective management of severe COVID-19 requires a comprehensive understanding of the complex pathophysiological processes underlying disease progression—specifically, dysregulated immune activation, endothelial dysfunction, immunothrombosis, and RAAS imbalance. These mechanisms act synergistically to generate the clinical manifestations observed in critical illness, ranging from acute respiratory distress syndrome (ARDS) to multiorgan failure.

2. Within this intricate biological context, inflammatory biomarkers serve as essential tools linking molecular pathology to clinical application. Their dynamic expression patterns reflect the ongoing immunological perturbations and tissue injury characteristic of severe SARS-CoV-2 infection. As such, these biomarkers not only facilitate early and accurate diagnosis, but also enable risk stratification, monitoring of therapeutic response, and prognostic assessment.

3. The integration of biomarker profiling into standard clinical protocols allows for personalized medicine approaches, aligning therapeutic strategies with the patient's inflammatory phenotype and disease trajectory. Biomarkers such as IL-6, CRP, D-dimer, and ferritin, among others, provide real-time insight into the host's immune status and the extent of systemic involvement.

4. The clinical relevance of these biomarkers is reinforced by their direct correlation with the pathophysiological determinants of disease severity, such as cytokine storm syndrome, endothelial injury, coagulopathy, and impaired interferon responses. Their function surpasses that of mere passive markers; they actively inform therapeutic decision-making, such as timing and selection of immunomodulatory agents, anticoagulants, or antiviral therapies.

5. Inflammatory biomarkers constitute a cornerstone of modern COVID-19 management. Their use, grounded in an in-depth comprehension of the disease's pathophysiology, enhances clinical accuracy, enables early intervention, and holds the potential to significantly improve outcomes in patients with severe forms of COVID-19. Ongoing investigation of novel biomarkers and their underlying mechanisms will enhance therapeutic strategies and facilitate the development of adaptive, evidence-based clinical management.

Discussion and Limitations.

The integration of inflammatory biomarkers into routine clinical algorithms for COVID-19 is a rapidly advancing field. Future directions should focus on the development of standardized biomarker panels that allow for early stratification of disease severity, prediction of therapeutic response, and evaluation of risk for long-term complications, including pulmonary fibrosis and cardiovascular sequelae.

Moreover, the characterization of distinct inflammatory endotypes via biomarker profiling and machine learning may facilitate the implementation of precision medicine strategies, tailoring immunomodulatory therapies to individual inflammatory patterns. As new therapeutic agents, such as complement inhibitors, IL-1 blockers, or checkpoint modulators, enter clinical use, real-time biomarker monitoring will be essential for timing interventions and minimizing adverse effects.

Furthermore, prospective studies should investigate the temporal dynamics of biomarker profiles, particularly in post-acute COVID-19 syndromes ("long COVID"), to elucidate chronic inflammatory mechanisms and guide rehabilitation strategies.

Finally, the integration of multi-omics data (transcriptomics, proteomics, metabolomics) combined with biomarker analyses may provide deeper insights into COVID-19 immunopathology and facilitate early identification of patients at risk for severe outcomes, across various viral variants and patient populations.

Despite the comprehensive synthesis provided in this narrative review, several limitations must be acknowledged.

First, the variability in study designs and patient cohorts within the reviewed literature presents potential bias in the comparative analysis of outcomes and biomarker significance. Many included studies differ in their definitions of "severe COVID-19," timing of biomarker measurements, and clinical endpoints. Second, a substantial portion of the evidence is derived from observational studies and retrospective analyses, which may be confounded by uncontrolled variables, such as prior comorbidities, treatment heterogeneity, and viral variants. Third, due to the rapid evolution of the pandemic, some emerging biomarkers and therapeutic strategies may not yet be fully validated in large-scale randomized controlled trials (RCTs), and their clinical utility remains provisional. Additionally, the exclusion of non-English articles may have limited the cultural and regional diversity of the evidence.

Author Contributions.

AB conceived and designed the review, coordinated the literature search strategy, synthesized key mechanistic insights, and drafted substantial sections of the manuscript. LP performed the systematic screening and critical appraisal of the inflammatory-biomarker literature, prepared the tables/figures, and contributed to drafting and refining the clinical applications section. Both authors critically reviewed the entire work, provided intellectual input throughout the writing process, and approved the final version of the manuscript, accepting full responsibility for its content.

Research Hypothesis

A comprehensive analysis of current scientific evidence will demonstrate that inflammatory biomarkers play a central role in the pathophysiological progression, risk stratification, and therapeutic guidance of severe COVID-19, and that their integration into clinical practice can enhance personalized medical interventions and improve patient outcomes.

The novelty added by the manuscript to the already published scientific literature

This review uniquely integrates immunopathogenic mechanisms with clinically relevant inflammatory biomarkers in severe COVID-19, highlighting emerging markers and their role in precision therapy. The paper provides a structured connection between molecular pathways and therapeutic decisions, bringing up-to-date insights that have not previously been synthesized in a unified clinical-immunological framework.

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