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REVIEW ARTICLE

Post COVID-19 Syndrome and Biological Markers: A New Enigma

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ABSTRACT

Since the onset of the COVID-19 pandemic, there has been a considerable rise in the number of individuals who have successfully recovered from COVID-19 infections. However, in certain cases, symptoms may persist for months or even years, potentially leading to disability. This phenomenon is commonly referred to as post-COVID-19 syndrome (PCS). PCS includes a diverse array of symptoms, such as fatigue, dyspnea, chest pain, arrhythmias, changes in bowel habits, appetite disturbances, olfactory/gustatory dysfunction, anxiety and depression. Various risk factors have been recognized as key contributors to the onset of post-COVID-19 syndrome. There is no single factor that can fully explain the occurrence of this condition; rather, multiple factors interact in its pathogenesis. As a result, PCS has emerged as a new challenge in diagnosis and treatment. Thus, there is a growing focus on studying the significance of various biomarkers in the areas of diagnosis, prognosis and ongoing monitoring. This review will focus on the pathogenesis, risk factors, clinical symptoms, and biological markers associated with the development of post-COVID-19 syndrome.

INTRODUCTION

SARS-CoV was the coronavirus responsible for the first major pandemic of the 21st century, originating in November 2002 at an animal market in Guangdong Province, China, and spreading to over 30 countries within eight months. A decade later, MERS-CoV, another coronavirus from the Middle East, infected over 2,000 people globally, with Saudi Arabia reporting the highest number of cases [1].

In late December 2019, an outbreak of atypical pneumonia cases was reported in Wuhan City, China [2]. On January 12, 2020, the World Health Organization (WHO) identified the virus as a novel coronavirus (2019-nCoV). By February 12, 2020, the disease was officially named coronavirus disease 2019 (COVID-19). The virus was later recognized as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) through phylogenetic analysis and established taxonomy [3].

COVID-19 spread rapidly across the globe, posing a worldwide threat. On March 11, 2020, the WHO declared COVID-19 a pandemic, joining the ranks of previous pandemics, including the 1918 Spanish flu (H1N1), 1957 Asian flu (H2N2), 1968 Hong Kong flu (H3N2), and 2009 H1N1 pandemic [4]. COVID-19 was a respiratory illness with varying severity: 80% of cases were mild to moderate, 15% were severe, and 5% were critical [5].

An additional concern with COVID-19 was the prevalence of long-term symptoms, known as post-COVID-19 symptoms (PC), experienced by many patients [6]. It is estimated that 10% to 35% of individuals who did not require hospitalization experienced post-COVID symptoms [7], with rates as high as 80% among hospitalized patients [8].

Definition of Post-COVID Syndrome

Post-COVID syndrome or long COVID described symptoms that persisted for over three weeks following a COVID-19 diagnosis [9].

Greenhalgh et al.[7] initially defined post COVID syndrome as an illness lasting more than three weeks after the onset of COVID-19 symptoms, and chronic COVID-19 as symptoms persisting beyond 12 weeks. His definition was later modified by Amenta et al.,[10] who stated that the post-acute period begins after a patient's discharge from inpatient acute care if they were hospitalized for more than three weeks following symptom onset.

Risk factors of Post-COVID Syndrome

Several factors have been linked to the development of post-COVID-19 conditions, including a mild anti-SARS-CoV-2 antibody response [11], illness severity [12], female sex [13], the presence of more than five symptoms in the first week of illness [14], as well as

advanced age and pre-existing comorbidities [15]. Other factors such as early dyspnea, prior psychiatric disorders, and lymphocyte count have also been identified as risk factors [16].

Classifications or categories of Post-COVID Syndrome

The University of Cincinnati Medical Center proposed criteria for categorizing long COVID, identifying five types based on symptom onset, duration, and initial symptoms. Type 1 patients had varying recovery times based on the severity of acute infection, organ complications, and underlying conditions. Type 2 was marked by symptoms lasting six weeks post-infection. Type 3 included a period of near-complete recovery followed by recurring symptoms lasting at least three months (Type 3A) or six months (Type 3B). Type 4 patients were asymptomatic at the time of the positive SARS-CoV-2 test but became symptomatic between one to three months (Type 4A) or more than three months later (Type 4B). Type 5 referred to patients who were asymptomatic or mildly symptomatic at diagnosis but died within 12 months [17].

Amenta et al.[10] from Baylor College of Medicine classified post-acute COVID-19 manifestations into three categories: (1) Persistent symptoms following recovery from acute infection; (2) Persistent organ dysfunction post-recovery; and (3) Emergence of new symptoms or syndromes following initial mild or asymptomatic infection.

Fernandez-de-Las Penas et al.[18] classified undiagnosed cases into four categories based on time: infection-related symptoms (up to 4-5 weeks), acute post-COVID symptoms (weeks 5-12), long post-COVID symptoms (weeks 12-24), and persistent post-COVID symptoms (more than 24 weeks).

Pathogenesis of Post-COVID Syndrome

Post-COVID syndrome results from a combination of viral and host factors interacting to form a common pathology. This approach connects SARS-CoV-2 infection to cellular damage, organ dysfunction, and the development of post-COVID syndrome [19].

Viral persistence and latent virus reactivation

Unlike DNA viruses, RNA viruses typically cause short-lived infections followed by recovery and immunity. However, some RNA viruses like Polio and Measles can persist in tissues after infection, potentially causing later complications [20]. Viral persistence might contribute to long-term COVID due to the relapsing and remitting symptoms observed in this condition [21].

The gut is a potential site of viral persistence, with evidence of SARS-CoV-2 nucleocapsid protein found in intestinal biopsies four months after infection, even in mild cases. While viral persistence could enhance the immune response, it may also trigger autoimmunity by mimicking host antigens [22].

Long-term COVID has also been associated with the reactivation of latent viruses, such as Epstein-Barr virus (EBV), which has been linked to fatigue, cough, and memory issues in long COVID patients [23].

Microbiome and microbial translocation

Viral persistence in the gut may alter the microbiota, leading to dysbiosis. Key immunomodulatory species, such as *Faecalibacterium prausnitzii* and *Eubacterium rectale*, were found to be reduced in individuals with post-COVID syndrome [24]. This dysbiosis may increase intestinal permeability. Studies have shown that individuals with prolonged COVID had higher levels of Beta-D-glucan, a fungal translocation marker, and Zonulin, which regulates intestinal permeability. These markers correlated with elevated inflammatory cytokines like IL-6, TNFa, and IP-10, and lower quality of life scores [25].

Endotheliopathy

Severe SARS-CoV-2 infection is associated with coagulopathy, elevated D-dimers, and increased thrombotic complications[26]. Even after recovery, COVID-19 patients may have persistent disruptions in coagulation pathways, with up to 25% of individuals showing elevated D-dimer levels four months post-infection [27]. Elevated levels of von Willebrand factor, indicating endothelial cell activation, may contribute to ongoing low-grade thrombus formation in the microvasculature, which could explain symptoms in long COVID patients [28].

Immune dysregulation

Prolonged T-cell activation is seen after the resolution of SARS-CoV-2 infection, with increased expression of exhaustion markers such as programmed cell death ligand 1 (PD-L1) and T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT) [29]. Moreover, declines in naïve B cells have been observed in convalescent long COVID patients. Furthermore, myeloid cells exhibit an activated phenotype and produce type I and III interferons, suggesting heightened innate immune activation [30].

Autoimmunity

While early neutralizing antibody responses were linked to survival during acute COVID-19, abnormal humoral responses may contribute to excessive immune activation in severe cases. Acute infection may trigger autoantibodies against nuclear components, type I interferons, and markers related to autoimmune diseases such as myositis and systemic sclerosis [31]. Neutralizing anti-interferon antibodies, produced during acute infection might promote viral persistence and contribute to long-term COVID [32]. Afucosylated anti-spike IgG may promote inflammation by attracting macrophages and natural killer cells [33].

Clinical manifestations of Post-COVID Syndrome

Post-COVID Syndrome (PCS) encompasses a wide array of conditions and symptoms. Fatigue was the most prevalent symptom, affecting 17-72% of critically ill COVID-19 patients[34]. Respiratory symptoms were common among PCS patients, including chest pain

(22%), dyspnea (10-40%), and exercise intolerance (10-40%). Dyspnea could worsen by up to 65% during ICU hospitalization [35].

Cardiac issues and endothelial dysfunction may result in arrhythmias, postural hypotension, and persistently high blood pressure, including hypertension [36]. Gastrointestinal symptoms, such as nausea, vomiting, diarrhea, changes in bowel habits, and appetite disturbances, could last for over two months after discharge in 30% of COVID-19 patients [37].

Neuropsychiatric disorders, including olfactory/gustatory dysfunction, affected 9-11% of patients and could persist for 6-8 months after mild COVID-19 [9]. Furthermore, anxiety (26%) and depression (40%) were experienced by patients within six months of acute COVID-19 onset [38].

Post-traumatic stress disorder (PTSD) was observed in up to 20.3% of recovered COVID-19 patients [39]. Additional neurological conditions reported in PCS patients included Guillain-Barré syndrome, ischemic stroke, cerebral vasculitis, transverse myelitis, and seizures [40]. Psychiatric complications such as aggression, cognitive impairment, reduced social activity, and obsessive-compulsive disorder were also common [41].

Biomarkers related to the pathogenesis of post COVID-19 syndrome

Biomarkers of systemic inflammation

Cytokines and chemokines

During the acute phase, individuals who later developed long COVID showed an elevation of IL-2, IL-6, IL-17, IFN-γ, CCL5/RANTES, and CCL3. In contrast, GM-CSF and CCL4 were found to be reduced during COVID-19 infection in patients who subsequently developed persistent symptoms [42].

Acute phase proteins (APPs)

Serum Amyloid A1 (SAA1) and SAA4 were found to be elevated in plasma microclots of post-COVID patients at three months [43]. Conversely, decreased levels of α-1-acid glycoprotein 1, an inflammation regulator, were detected in the microclots of patients at 7 months[44].

Endothelial or vascular biomarkers

Elevated levels of vascular endothelial growth factor (VEGF), a key regulator of angiogenesis, have been identified as potential biomarkers for COVID-19 progression [45].

Elevated endothelin-1, a vasoconstriction biomarker, and reduced angiopoietin-2 levels, a biomarker of vascular angiogenesis, were found in patients with long COVID and fatigue. Decreased angiopoietin-2 was especially noted in post-COVID patients, distinguishing it from myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)[46].

Complement proteins biomarkers

The complement system may play a role in vascular complications in post-COVID patients. Elevated levels of complement components C7, C6, and factor 1 were found in plasma microclots of patients at three months[43]. The complement complex C5b-9 also remained elevated even after the infection cleared, regardless of pathology severity [47].

Biomarkers of coagulation and fibrinolysis

Microclots in the plasma of long COVID patients were associated with altered levels of coagulation and fibrinolysis proteins. These include increased von Willebrand factor (vWF), platelet factor 4, fibrinogen chains, factor XIII, plasminogen, and antiplasmin (α2AP), as well as decreased plasma kallikrein [43, 44]. Elevated D-dimer levels also serve as a diagnostic marker for post-COVID patients, especially those with prolonged symptoms or organ abnormalities[48].

Hormonal biomarkers

Low cortisol levels were linked to dysosmia/dysgeusia. Additionally, low serum growth hormone and elevated serum FT4 were associated with general fatigue, while higher thyrotropin (TSH) and lower FT4/TSH ratios were observed in severe long COVID cases [49].

Metabolic biomarkers

Increased kynurenine-to-tryptophan (K/T) and quinolinic acid-to-tryptophan (Q/T) ratios, as well as elevated levels of S-sulfocysteine, were found in post-COVID patients[25]. Dysregulation of sphingolipid metabolism was linked to fatigue and muscle pain in these patients [50]. Additionally, the accumulation of free and carnitine-conjugated fatty acids was associated with erythrocyte dysfunction, which could impair oxygen delivery [51].

Various proteins as biomarkers

Trefoil factor 2 (TFF2), which is released with mucin from the mucosal epithelium, was detected at high concentrations in post-COVID patients, indicating persistent mucosal epithelial dysfunction. Elevated levels of lysosome-associated membrane glycoprotein 3 (LAMP3), follistatin (FST), and lung surfactant protein SCGB3A2 were also found in these patients [52].

Biomarkers of COVID 19 persistence

A histopathological study on 44 COVID-19 autopsy cases revealed that SARS-CoV-2 RNA was present in 84 different anatomical sites, detectable up to 230 days after infection. Despite viral RNA being undetectable in plasma in deceased cases, low viral loads were still present in various tissues [53].

Biomarkers of reactivation of latent viruses

Reactivation of herpesviruses like EBV and HHV-6 was observed in post-COVID patients. EBV viremia or increased anti-EBV antibody titers may serve as predictive biomarkers for long COVID, especially associated with fatigue, respiratory symptoms, and cognitive dysfunction [32, 54, 55].

Autoimmunity biomarkers

A range of autoantibodies were found in long COVID patients, including elevated antinuclear antibodies (ANAs) (such as anti-U1-snRNP and anti-SS-B/La), antineuronal antibodies, anti-IFN antibodies, and autoantibodies targeting ACE2, angiotensin II receptors, β2-adrenoreceptors, and muscarinic M2 receptors. ANA levels were associated with persistent fatigue and dyspnea, while antineuronal antibodies were linked to cognitive impairment [56, 57].

Biomarkers associated with post COVID-19 clinical manifestations

Biomarkers for fatigue

Fatigue symptoms in long COVID were associated with early EBV viremia, elevated antibody titers against EBV, increased anti-SARS-CoV-2 spike IgG two months post-infection, and the presence of ANAs. Other markers include higher levels of endothelin-1, agrin, and FT4, along with lower levels of angiopoietin-2, cortisol, and growth hormone [46, 50].

Biomarkers for neurological symptoms

Neurological symptoms were among the most common clinical manifestations of long COVID. Neurofilament light chain (NFL) and glial fibrillary acidic protein (GFAP) were structural proteins that helped maintain the stability of neuron axons and astrocytes. The presence of these neural peptides in circulation could serve as biomarkers indicative of neuronal degeneration and damage [58]. Long COVID patients with elevated serum levels of NFL and GFAP experienced more severe headaches and persistent neuropathic pain [59]. Low levels of the anti-inflammatory protein tumor necrosis factor (TNF)-related activation-induced cytokine (TRANCE), combined with elevated proinflammatory proteins TNF Receptor Superfamily Member 9 (TNFRSF9) and IFN-γ, were effective single protein predictors in cerebrospinal fluid (CSF) for long COVID [60].

Biomarkers for respiratory symptoms

In patients with long COVID-related pulmonary symptoms, elevated levels of IL-6, CRP, and TGF-β were associated with an increased risk of developing pulmonary fibrosis after SARS-CoV-2 infection [61].

Biomarkers for gastrointestinal symptoms

SARS-CoV-2 RNA in stool, elevated viral proteins (S, S1, N), and increased levels of zonulin, lipopolysaccharide binding protein (LBP), β-glucan, autoantibodies (La/SS-B), and CMV-specific CD8+ T cells were identified as biomarkers for gastrointestinal symptoms in long COVID [62].

As biological biomarkers are essential in understanding the development of post-COVID-19 syndrome. Table (1) presents an overview of the potential diagnostic biomarkers.

Table 1: Biological biomarkers related to post COVID-19 syndrome:

Biological biomarker	Significance	References
Systemic inflammation biomarkers	IL-6 levels were higher in post COVID-19 patients compared to healthy controls and recovered COVID-19 patients.	**(63)**
	CRP, D-dimer, LDH and leukocytes levels were elevated in Long COVID-19 patients compared to those without Long COVID.	**(48)**
Endothelial and vascular biomarkers	Increased levels of (endothelin-1) in post COVID-19 patients compared to healthy controls and post-convalescent individuals. Decreased levels of (angiopiotien-2) in both post COVID-19 patients and post-convalescent individuals in comparison to healthy controls.	**(46)**
Coagulation and fibrinolysis biomarkers	Higher levels of (platelet factor 4, VWF, α-2 antiplasmin) and lower levels of (plasma kallikrein) were detected in post COVID-19 patients.	**(44)**
Hormonal biomarkers	High level of TSH, low level of growth hormone and cortisol were observed in post COVID-19 patients.	**(49)**
Metabolic biomarkers	Quinolinic acid and kynurenine were elevated in patients suffering from cognitive impairment following COVID-19.	**(64)**
	High levels of phosphatidylcholines and sphingomyelins in post COVID-19 paients compared to controls.	**(50)**
SARS CoV-2 persistence biomarkers	SARS-CoV-2 RNA remained detectable in various anatomical sites for as long as 230 days after infection.	**(53)**
	Higher levels of circulating spike protein were detected in post COVID-19 patients up to 12 months in comparison to recovered cases.	**(65)**
Reactivation of latent viruses biomarkers	Increased IgG levels against EBV 4 months after infection.	**(55)**
	Out of 88 post COVID-19 patients, EBV reactivation was observed in 42.6% of cases, HHV6 in 25.0%, and both EBV and HHV6 in 32.4%.	**(54)**
Autoimmunity biomarkers	COVID-19 survivors showed positive ANAs one year after COVID-19 infection.	**(56)**
	High levels of antineuronal antibodies were detected in post COVID-19 patients with impaired cognitive conditions.	**(57)**
	Patients suffered from persistent respiratory symptoms had high levels of IFN-α2 autoantibodies.	**(32)**

CONCLUSION

Post-COVID Syndrome emerges as a complex, multifactorial condition that involves a wide range of clinical manifestations, including fatigue, respiratory issues, cardiovascular symptoms, neuropsychiatric disorders, and gastrointestinal complications. It has been linked to various risk factors such as severity of the initial infection, female sex, pre-existing comorbidities, and the presence of multiple symptoms during the acute phase of COVID-19. The pathogenesis of PCS involves viral persistence, immune dysregulation, endothelial dysfunction, and potential autoimmunity, contributing to long-term health complications. Biological biomarkers played a crucial role in diagnosing and predicting post COVID-19 syndrome.

Abbreviations:
Post-COVID-19 syndrome (PCS), Programmed cell death ligand 1 (PD-L1), T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain (TIGIT), Post-traumatic stress disorder (PTSD), Serum Amyloid A1 (SAA1), Vascular endothelial growth factor (VEGF), Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), von Willebrand factor (vWF), Trefoil factor 2 (TFF2), Lysosome-associated membrane glycoprotein 3 (LAMP3), Follistatin (FST), Antinuclear antibodies (ANAs), Neurofilament light chain (NFL), Glial fibrillary acidic protein (GFAP), Lipopolysaccharide binding protein (LBP), Tumor necrosis factor (TNF)-related activation-induced cytokine (TRANCE), TNF Receptor Superfamily Member 9 (TNFRSF9).

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