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Late post-COVID syndrome: clinical complications beyong 12 weeks

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Abstract

The persistent and diverse manifestations of post-COVID syndrome present a significant challenge for global healthcare. Beyond the acute phase of infection, individuals continue to grapple with lingering symptoms affecting various organ systems, including the respiratory, cardiovascular, neurological, and endocrine systems. In the respiratory realm, symptoms such as cough, dyspnea, and fatigue endure, particularly in those with a history of severe COVID-19. The cardiovascular impact manifests as chest pain, arrhythmias, and heightened risks of thromboembolic events, emphasizing the intricate connection between COVID-19 and cardiovascular complications. Neurological complications, ranging from headaches to more severe disorders, further contribute to the complex sequelae of post-COVID syndrome. Additionally, disruptions in the endocrine system, including new-onset diabetes and thyroid abnormalities, pose long-term challenges for affected individuals. The review discusses the clinical management challenges posed by the multifaceted nature of post-COVID complications and the necessity for tailored multidisciplinary approaches. A holistic and compassionate response to the long-term effects of COVID-19 requires collaboration across healthcare professionals, researchers and the broader community. By navigating these challenges collectively, we can pave the way for a more comprehensive and effective approach to post-COVID care.

Keywords: Post-COVID syndrome, respiratory complications, cardiovascular complications, neurological complications, endocrine complications, diabetes inset.

Introduction

The initial focus on COVID-19 primarily revolved around understanding and managing the acute phase of infection. However, as time has progressed, attention has shifted to the considerable number of individuals experiencing persistent symptoms well beyond the acute phase and the interest still exists [1, 2]. Termed post-COVID syndrome, this phenomenon has sparked a new frontier of research and clinical consideration. According to the WHO-lead Delphi process, post-COVID-19 syndrome is defined as a condition that emerges in individuals with a history of probable or confirmed SARS-CoV-2 infection, typically appearing three months after the onset of COVID-19, and is defined by symptoms lasting at least two months without explanation from an alternative diagnosis [3].

An early meta-analysis investigating post-COVID syndrome revealed a noteworthy statistic: more than 60% of individuals who had survived a SARS-CoV-2 infection experienced diverse complications three months after the initial infection [4]. This underscores the substantial and lasting impact of the virus on a significant portion of the population, necessitating an in-depth examination of the clinical manifestations of post-COVID syndrome (Figure 1). In alignment with the ever-evolving landscape of post-COVID healthcare and considering its effect across diverse medical disciplines, this review aims to present a thorough exploration of post-COVID syndrome's clinical manifestations.

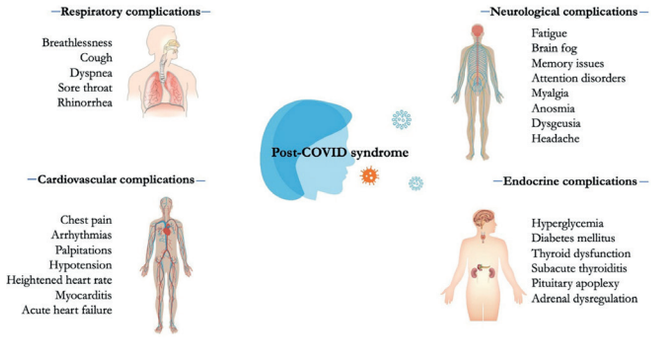

Figure 1 - Clinical complications of COVID-19 appearing after 12 weeks after the initial infection.

Effect on the Respiratory System

Considering that COVID-19 often causes problems with breathing, it's important to focus on the respiratory system when studying its lasting effects. After hospital discharge, certain symptoms, including cough, exertional dyspnea, sore throat, rhinorrhea, muscle aches, and fatigue, may persist for prolonged durations, particularly among individuals who have undergone severe COVID-19 [5]. Notably, those patients who experienced acute respiratory distress syndrome (ARDS) and had invasive mechanical ventilation (IMV) therapy face the heightened risk of developing chronic respiratory failure and enduring lung fibrosis [5, 6].

According to the prospective cohort study from the UK, 39% of patients had breathlessness symptoms and approximately 13% had a cough at 12-week follow-up [7]. A persistent cough can disrupt sleep patterns, leading to fatigue and daytime drowsiness. Sleep disturbances contribute to a decreased overall sense of well-being and can hinder the recovery process. Another prospective cohort study in the Netherlands, including 2113 participants, revealed that at the 3-month follow-up, 71% reported dyspnea (compared to 90% during the infection), 29% had a cough (compared to 68% during the infection), 26% experienced a sore throat (compared to 62% during the infection), and 24% reported pain or a burning sensation in the lungs (compared to 61% during the infection) [8]. Dyspnea can restrict physical activities, making even routine tasks challenging. Individuals may experience difficulty walking, climbing stairs, or engaging in exercise, leading to a decreased ability to participate in daily life activities.

A study from Stanford University showed that at 3-months follow-up, the rate of chest pain, cough, rhinorrhea, and sore throat did not differ significantly between severe and mild COVID groups; however, the rate of dyspnea was higher in the first group (p=0.006) [9]. This study shows the absence of a correlation between the severity of COVID-19 during hospitalization and the extent of symptoms during follow-up, as observed in previous research [10]. It highlights the need for a nuanced understanding of the varied and unpredictable nature of post-COVID effects on individuals' health.

Effect on the Cardiovascular System

While post-COVID complications commonly manifest as dyspnea and fatigue, persistent symptoms such as chest pain, olfactory and gustatory dysfunction, headaches, and gastrointestinal and cardiac-related issues may endure for up to six months [11, 12]. Within the realm of post-COVID syndrome, individuals commonly experience a range of cardiovascular events, including arrhythmias, palpitations, hypotension, heightened heart rate, venous thromboembolic diseases, myocarditis, and acute heart failure [13]. This diverse array of cardiovascular complications underscores the intricate impact that the syndrome can have on the cardiovascular system.

In a 76-patient observational follow-up study at Wuhan Union Hospital, 62% reported chest tightness and palpitations three months after infection [14]. The high levels of troponin-I, which is related to the contraction of the heart muscle, in the blood during the illness were strongly connected with feeling tired after leaving the hospital (correlation coefficient 0.782, $p = 0.008$). Additionally, having low levels of lymphocytes during the illness was linked to feelings of tightness in the chest and heart palpitations during physical activity after leaving the hospital (correlation coefficient: -0.285, $p = 0.027$; correlation coefficient: -0.363, $p = 0.004$, respectively) (14). Recently, a meta-analysis of seven studies involving 8,126,462 participants showed that combined odds ratios for cardiovascular outcomes were notably higher in post-COVID cases ($OR > 1$, $p < 0.05$) compared to controls [15].

A long-term study conducted in China examined the post-COVID in patients who had been hospitalized and released from Renmin Hospital of Wuhan University. The study compared this group with a set of volunteers who did not have COVID-19 and lived in the urban area of Wuhan during the outbreak. Three months post-discharge, 11.2% of COVID survivors exhibited an increased resting heart rate, 4.8% reported discontinuous flashing, and 1.3% were diagnosed with new hypertension (16). In the comparison group, there was no significant increase in heart rate ($p<0.001$), only one case of discontinuous flashing ($p<0.01$), and no instances of newly diagnosed hypertension ($p=0.20$) [16].

The potential link between cardiovascular complications post-COVID and angiotensin-converting enzyme 2 (ACE2) expression in the heart is plausible. SARS-CoV-2, the virus causing COVID-19, binds to membrane-bound ACE2, leading to internalization by the host cell [17]. These findings suggest COVID-19-induced cardiovascular damage, although discerning whether these symptoms are part of the general post-COVID aftermath or a result of a complex interplay of factors poses a challenge for clinicians.

Neurological Complications

In addition to respiratory and cardiovascular complications, post-COVID patients commonly exhibit neurological manifestations such as headaches, peripheral neuropathy symptoms, memory issues, difficulties in concentration, and sleep disorders. A comprehensive meta-analysis of studies conducted from January 1st, 2020, to August 1st, 2021, involving a total of 10,530 patients, revealed the prevalence of post-COVID-19 neurological symptoms. The overall prevalence rates were as follows: 37% fatigue, 32% brain fog, 28% memory issues, 22% attention disorders, 17% myalgia, 12% anosmia, 10% dysgeusia, and 15% headache [18]. Notably, the prevalence of neurological symptoms tended to be lower in hospitalized patients compared to non-hospitalized individuals. Furthermore, the occurrence of fatigue, brain fog, and headaches was higher in assessments conducted at or beyond six months (long-term) compared to assessments between three and six months (mid-term) [18].

In a prospective cohort study, Rass et al. identified the emergence of neurological disorders in 17% of patients during the 3-month follow-up post-COVID-19 [19]. This prevalence exhibited a pronounced elevation among patients in the Intensive Care Unit (ICU), encompassing conditions such as polyneuro/myopathy, mild encephalopathy, and parkinsonism. This research indicated that individuals with severe COVID-19 were more predisposed to enduring neurological symptoms at follow-up compared to those with milder courses [19]. A

similar trend was observed by Taquet et al., who identified a significantly heightened prevalence of neurological disorders among hospitalized COVID-19 patients, particularly those requiring ICU admission [20].

In the realm of Post-COVID Neurological Syndrome (PCNS), there exists a spectrum of less common yet noteworthy disorders, including Guillain-Barré syndrome (GBS), polyneuropathy, myopathy, encephalopathy, post-infectious transverse myelitis, seizures, parkinsonism, orthostatic hypotension associated with vasovagal syncope, strokes, and neuro-ophthalmological issues such as post-infectious optic neuritis [21]. These less frequent manifestations reveal a nuanced neurological landscape in the aftermath of COVID-19, extending beyond the commonly observed symptoms. During the 12-week follow-up period, a subset of individuals exhibited these disorders, shedding light on the diverse and potentially prolonged neurological impact attributed to post-COVID complications [19]. This delineation serves to underscore the multifaceted nature of post-COVID neurological sequelae, necessitating comprehensive exploration for a holistic understanding and effective management.

Effect on the Endocrine System

Similar to its impact on various organ systems, COVID-19 influences the human endocrine system in several ways [22]. The recognized endocrine manifestations of COVID-19, primarily observed during the acute phase, encompass dysglycemia, new-onset diabetes mellitus, euthyroid sick syndrome, subacute thyroiditis (SAT), and pituitary apoplexy. Post-COVID syndrome disrupts endocrine regulation, affecting various mechanisms such as those related to the thyroid [22, 23], pituitary [24, 25], adrenal [26, 27], and gonadal [28]. Reduced thyroid function (hypothyroidism) can lead to symptoms such as fatigue, weight gain, intolerance to cold, dry skin, and constipation. As it was discussed before, one of the most prevalent cases of post-COVID syndrome is fatigue. The connection between COVID-19 and the pituitary gland lies in the expression of Angiotensin-Converting Enzyme-2 (ACE-2) receptors on the surface of pituitary cells [25, 26]. The pituitary gland is a crucial part of the endocrine system, regulating the release of various hormones that control essential bodily functions. Post-COVID syndrome may impact the normal functioning of the gland and disrupt the hormonal balance.

The binding of SARS-CoV-2 to angiotensin-converting enzyme-2 (ACE-2) receptors results in an overexpression of angiotensin II, potentially impairing insulin secretion and contributing to disruptions in glucose metabolism, which may lead to the development of diabetes [29]. According to a prospective observational study, 10% of initially non-diabetic patients developed new-onset pre-diabetes, and 14% developed new-onset diabetes mellitus (DM) within three months after the infection [30]. Additionally, at the same follow-up time, 17% of initially pre-diabetic patients had developed DM. The consequences of new-onset diabetes mellitus following SARS-CoV-2 infection are particularly concerning for individuals with pre-existing predispositions. Predisposed individuals, such as those with a family history of diabetes or other risk factors, may experience exacerbated challenges in glucose regulation due to the added burden of COVID-19-induced diabetes [31, 32]. This dual impact could lead to a more complex and difficult-to-manage metabolic condition, posing heightened risks for adverse outcomes and potentially complicating the overall health status of these individuals.

A recent study revealed that, after a 3-month follow-up, 10% of initially non-diabetic patients developed new-onset diabetes mellitus (DM). The most common risk factors associated with this development were a high dose of steroids ($p<0.001$), a family history of DM ($p=0.001$), excess weight ($p<0.001$), and fungal infection ($p<0.001$) (32). The results of this study also indicated that individuals experiencing new-onset diabetes exhibited a more severe infection, necessitating oxygen supplementation and ICU admission. Additionally, they demonstrated elevated levels of inflammatory markers compared to non-diabetic patients. These findings align with those of Li et al., who reported that individuals with newly diagnosed diabetes and hyperglycemia frequently presented with more severe symptoms and higher inflammatory marker levels [33]. As per a comprehensive meta-analysis, individuals with COVID-19-associated new-onset diabetes mellitus (NODM) exhibited the highest mortality rate (24.96%), surpassing patients with pre-existing diabetes mellitus (DM) (16.03%) and non-diabetic patients (9.29%) (29). Moreover, COVID-19-associated NODM patients experienced the most significant adverse effects, followed by individuals with pre-existing DM, COVID-19-associated hyperglycemia, and non-diabetic patients.

Implications and Future directions

The diverse and persistent nature of post-COVID complications poses significant challenges for clinicians. Tailored and multidisciplinary approaches are essential to address the range of symptoms affecting the respiratory, cardiovascular, neurological, and endocrine systems. Developing comprehensive clinical guidelines that integrate evolving knowledge about post-COVID manifestations is crucial for optimizing patient care. Moreover, the long-term nature of post-COVID syndrome implies continued healthcare resource utilization. Hospitals and healthcare systems need to anticipate and plan for ongoing support, including specialized clinics, rehabilitation services, and mental health resources. This necessitates a strategic allocation of resources to meet the evolving needs of individuals experiencing persistent symptoms.

As the understanding of post-COVID syndrome advances, public health strategies must adapt to address the long-term health consequences. Education campaigns should focus on raising awareness about the potential for lingering symptoms and the importance of seeking medical attention for persistent health issues. Public health interventions should extend beyond the acute phase of the pandemic to provide sustained support for those affected. In addition, the psychological impact of persistent symptoms should not be underestimated. Mental health support must be integrated into post-COVID care plans, acknowledging the potential for anxiety, depression, and other mental health challenges. Research into effective mental health interventions for individuals grappling with the psychological toll of post-COVID syndrome is imperative.

Conclusion

Considering the abovementioned complexities, a comprehensive understanding of post-COVID syndrome's diverse manifestations is crucial for effective clinical management. Continued research and exploration of the long-term effects of COVID-19 are essential for developing targeted interventions and support strategies for individuals experiencing persistent symptoms. The evolving landscape of post-COVID healthcare underscores the need for a multidisciplinary approach to address the intricate interplay of symptoms across different organ systems.

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