



## A Study on Post-Covid-19 Condition Research Challenges, Strategies and Importance Related To Human Health

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### Abstract

The pandemic of COVID-19, which first appeared in Wuhan, China, is now infecting millions across the globe. This is a review of the widespread effects of COVID-19 on virtually all organs. It causes swelling, inflammation, endotheliosis, vasoconstriction, and hypercoagulability. There is lymphocytopenia, elevated D-dimer and fibrin degradation products (FDPs), as well as disseminated intravascular coagulation (DIC). The following conditions are reported: deep vein thrombosis (DVT), venous thromboembolism (VTE), pulmonary embolism (PE), systemic and pulmonary arterial thrombosis and embolism, ischemic stroke, and myocardial infarction (MI). It can cause acute coronary syndrome, cardiac failure, myocarditis, and arrhythmias in the heart. Typically, kidney damage is secondary to systemic abnormalities. Stroke can even occur in younger patients. Seizures and delirium are prevalent. Anosmia and taste impairment are reported. Psychological issues are prevalent among both patients and providers. feces may harbor a pathogen. Lactate dehydrogenase levels could be elevated. Multiple cutaneous manifestations are reported, including a patchy erythematous rash.

**KEY WORDS: COVID-19, Challenges, Strategies, Importance, Human Health.**

### INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has demanded prompt responses from healthcare systems and research networks worldwide. Although a large quantity of comprehensive data on acute symptoms and clinical management has been collected and analyzed, there is no established clinical definition or Core Outcome Sets (COS) at this time. In fact, even the terminology of the condition is contested, with various terms and definitions for the post-COVID-19 condition, such as long COVID, "long haulers", post-acute sequelae of SARS-CoV2 infection (PASC), and post-COVID-19 condition, the term used by the World Health Organization (WHO). With over 217 million confirmed COVID-19 cases worldwide, the post-COVID-19 condition has the potential to affect millions of individuals worldwide, making it a top priority for research. Although widespread vaccination may eventually contribute to a decline in the number of COVID-19 cases, the pandemic is far from over as cases continue to rise worldwide. There is an urgent need for consensus regarding the fundamental outcomes that must be measured in the post-COVID-19 era. Establishing a COS will ensure that critically important outcomes are measured and reported in research and practice settings in a consistent manner. The consistent use of the most significant outcomes across studies and clinical practice is essential for comparing and collating the research findings and translating them into recommendations for patient care.

Following WHO's systematic approach to identifying research gaps and with the primary purpose of suggesting and outlining the implementation of a COS for the post-COVID-19 condition (i) to allow for the assessment of outcomes that are of the greatest relevance and importance to stakeholders and relevant target populations, including patients, families, clinicians, researchers, and policymakers, Given the urgent need for an accepted post-COVID-19 condition COS, the development of a COS for the post-COVID-19 condition could serve as a guide over the next few years until more is known and/or a review or reassessment is warranted.



## POST-COVID CONDITION REPERCUSSIONS ON HEALTH

Recent editorials and conferences sponsored by the National Institutes of Health (NIH) and the World Health Organization have called for research into the risk factors, clinical features, diagnosis, management, and outcomes of SARS-CoV-2 infection in the acute phase. Consequently, funding opportunities have increased. It is essential to note that most post-COVID-19 data were generated prior to the announcement of the condition definition. Consequently, previous studies might not meet the proposed definition criteria. Post-COVID-19 condition extends beyond the cardiorespiratory system to affect most other anatomical and physiological bodily systems. Although the causes of post-COVID-19 illness are unknown, persistent immune activation may play a role. Risk factors for various syndromes of post-acute SARS-CoV-2 sequela have not been identified, but it has been hypothesized that several post-COVID-19 condition phenotypes may exist, even though pathophysiology, management, and outcomes remain unknown.

Unknowns are the long-term health effects of COVID-19, but reports indicate that protracted symptom duration and functional limitations are common among hospitalized and non-hospitalized adults and children. The spectrum of long-lasting symptoms is broad, ranging from modest discomfort to severe adverse effects on physical, cognitive, and psychosocial health, with significant broader implications for functioning, such as employment and school attendance.

Multiple international studies discovered that six months after contracting COVID-19, many individuals continued to experience symptoms, with fatigue or muscle weakness, sleep difficulties, and anxiety or depression being the most prevalent. A recent study suggests that although most COVID-19 survivors recover physically and functionally one year after acute infection, some still experience difficulties with mobility, pain or discomfort, and anxiety or depression compared to non-COVID-19 controls. The results of the controlled investigations are consistent with the findings of earlier studies. A recent analysis of data from over 250,000 electronic health records revealed that more than one-third of individuals had one or more symptoms of post-COVID-19 condition recorded between 3 and 6 months after a diagnosis of COVID-19, which was significantly higher than in influenza patients. Post-COVID-19 condition development was correlated with disease severity, female gender, and lower age.

However, it is unknown if persistent symptoms and associated abnormalities will resolve completely or if some will result in permanent dysfunction. Notably, investigations into the post-COVID-19 condition can be challenging due to high loss to follow-up, frequent use of unvalidated measurement instruments, lack of inclusion of controls during the pandemic, and censoring of data (e.g. for death) that is not always fully considered in published studies. Certain symptoms attributed to a post-COVID-19 condition are indicative of an ongoing problem (e.g., dysautonomia in individuals reporting heart rate variability), making differential diagnosis difficult.

The investigation of potential treatments for post-COVID-19 conditions is still in its infancy. Most approaches concentrate on rehabilitation and symptom management. Some experts believe that antibodies and T cells able to recognize SARS-CoV-2 induced by vaccination "may help the immune system to stop the virus during its first few replications before it can establish hidden reservoirs in the body"; however, the evidence regarding the efficacy of SARS-CoV-2 vaccines in post-COVID-19 condition treatment is somewhat contradictory. The absence of agreed-upon clinical trial outcomes is one of the most significant obstacles to the development of intervention strategies for post-COVID-19 condition.



As a result of isolation, economic instability, job insecurity, illness/death of infected family members, COVID-19-related stigma, lack of trust in government agencies, and constant media attention focused on the pandemic threats, many people have experienced anxiety and depression. Care disruption for those with pre-existing conditions has also had a significant effect. According to the WHO Pulse survey on continuity of essential health services during the COVID-19 pandemic, in the first quarter of 2021, 45% of countries reported disruptions in services for mental, neurological, and substance use disorders. On a similar scale, 53% (of 89 countries) continue to report disruptions in rehabilitation services.

In addition, indirect effects of COVID-19 on mental health, psychosocial, and neurological sequelae have been reported in adults following COVID-19, and many patients are facing a variety of consequences, including fatigue, shortness of breath, cognitive dysfunction, and decreased quality of life, all of which have an impact on day-to-day functioning even months after acute infection.

With millions of people affected by COVID-19, even a small proportion developing the post-COVID-19 condition will have a negative impact on society and public health, necessitating long-term monitoring, management, and support for many individuals. A recent study found that previously hospitalized COVID-19 patients had higher rates of multiorgan dysfunction than the general population.

### **CLINICAL TERMINOLOGY AND DEFINITIONS**

In light of the numerous unresolved issues associated with this condition, the incorporation of patients' perspectives into the development of a COS has become increasingly crucial. Notably, there is presently no consensus on a clinical definition and which outcomes and how they should be measured. WHO recently concluded a Delphi consensus to finalize a clinical case definition for post-COVID-19 condition. This official WHO definition was recently published and is as follows: "post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARSCoV-2 infection, typically three months after the onset of COVID-19 with symptoms that last at least two months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, and cognitive dysfunction, but there are many others that have a significant impact on daily functioning. After initial recovery from an acute COVID-19 episode, symptoms may be new or continue from the initial illness. In addition, symptoms may fluctuate or recur over time".

Other organizations have also proposed interim definitions, including the National Institute for Health and Care Excellence (NICE) in the United Kingdom, which defines post-COVID-19 syndrome as "signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and cannot be explained by alternative diagnoses". Due to the scarcity and high degree of heterogeneity of extant studies, the definition may change as new evidence emerges; however, diversity in diagnostic criteria, methodology, and outcomes measured may impede progress. There is a need for terminology standardization, and a consensus should be reached between significant public health and government research organizations and professional bodies for the benefit and convenience of clinicians, researchers, and, most importantly, patients. With growing evidence on the effects of COVID-19, there is a risk that the number of terms used to describe the post-COVID-19 condition will increase alongside the phenotyping of this condition.

### **DEFINITION AND VALUE OF CORE OUTCOME SET**

In clinical research or practice, outcomes are measured to evaluate relevant associations, safety and efficacy, risk factors, and the efficacy of interventions. The absence of agreed upon



outcomes and associated measurement instruments may complicate the evidence synthesis due to the inability to pool data in meta-analyses, resulting in a heterogeneous, incomplete, and low-quality evidence base and a barrier to the development of clinical guidelines and policymaking. A COS is a minimum list of outcomes recommended for assessment in all studies, clinical practice settings, or both, for a particular condition, and is required to harmonize research outputs and increase their comparability, quality, and generalizability to ensure their relevance to all interested parties. Failure to consider the perspectives of patients and their families when selecting outcomes may result in the evaluation of less pertinent outcome measures, while the most essential outcomes are overlooked.

### **CORE OUTCOME SETS FOR COVID-19 AND CONDITIONS POST-COVID-19**

The Core Outcome Measures in Effectiveness Trials (COMET) Initiative web-registry of planned, ongoing, and completed COS studies includes several COVID-19-related COS studies. These initiatives provide clinicians, researchers, and policymakers with essential information on the pertinent aspects of COVID-19 and enable the generation of harmonized, high-quality data. Notably, COVID-19 COS development initiatives were initiated quickly, in contrast to the typical COS development process, which takes several years.

Although none of the available COVID-19-related COS projects are solely focused on the post-COVID-19 condition, some include outcomes for the "rehabilitation period", "longer term impacts", and "recovery". Despite a well-established and standardized approach to COS development, which is generally guided by the COMET Handbook, the development of COS for the post-COVID-19 condition may be a difficult undertaking due to the diversity and multisystem nature of infection sequelae. COS previously developed for other conditions, which may be pertinent for people recovering from COVID-19, should be considered a potential option for certain populations (e.g., survivors of acute respiratory failure/acute respiratory distress syndrome after hospital discharge).

### **CONSIDERATIONS AND CONSTRAINTS FOR POPULATIONS AT RISK**

The development of a COS in vulnerable populations, such as those with disabilities/comorbidities, undergoing complex treatment (e.g., chemotherapy or transplantation), the elderly, racial and ethnic minority groups, pregnant women, and children, presents unique challenges that require additional consideration. These obstacles involve not only the constellation of symptoms, but also the optimal time for assessment and the individual being evaluated. Any adverse birth outcome, such as preterm birth, stillbirth, or pregnancy complication (e.g., preeclampsia or gestational diabetes), may or may not be part of the post-COVID-19 condition for an expectant woman who was infected in the first trimester and recovered completely before delivery. Consideration is required to determine whether congenital anomalies in the neonate or any neonatal complication following maternal COVID-19 can be classified as a potential post-COVID-19 condition for the neonate or infant. It is crucial to distinguish between adverse birth outcomes that could be attributed to maternal COVID-19 and those that would have occurred regardless of maternal COVID-19 status due to other risk factors. This is comparable to eliminating other causes in the general population (adults who are not expectant).

### **CONSIDERATIONS AND CONSTRAINTS IN LOW-TO-MODERATE INCOME SETTINGS**

Multiple consequences of the COVID-19 pandemic for low- and middle-income countries (LMICs) include insufficient healthcare resources to meet the requirements of the local population, not only for COVID-19 infection but also for other acute and chronic conditions. An



additional anticipated difficulty for LMICs is the identification of the post-COVID-19 condition. Post-acute care of physical, cognitive, and mental health disabilities may be under-recognized, particularly in low-resource contexts where all efforts are focused on containing the spread of COVID-19 and providing appropriate care for critically ailing patients. This may have an impact on post-COVID-19 disease research as well as identification and management in LMICs.

Current definitions for the evaluation of outcomes entail advanced laboratory and imaging techniques, which necessitate the application of resources and expertise. Such talents and resources may not be readily accessible in settings with limited resources. While compiling the COS, an inclusive approach should be adopted by including alternative definitions and methods of measurement that may be acceptable in low- to middle-income settings. Extraordinary care must be taken to establish a balance between the assessment's precision and its global applicability. The development of a COS for post-COVID-19 condition should take into consideration cultural and social differences as well as access and resource restrictions. Clinicians, researchers, and patient representatives from LMICs should be involved in the development of the COS to assure its global applicability and future relevance.

### **EXISTING LIMITATIONS IN THE INVESTIGATION**

Although the problem of the post-COVID-19 condition is receiving more attention, there are still numerous unresolved questions and significant limitations affecting the quality of research and comprehension of COVID-19 sequelae.

These as well as potential mitigation strategies following a systematic approach or defining research priorities through the phases of planning, implementation, publication, and evaluation. DM drafted the table, which was then evaluated critically and approved by all authors. Post-COVID-19 disease lacks a consensus definition, well-defined clinical phenotypes, and a clear explanation of the underlying physiological mechanisms. WHO has highlighted "three Rs" related to post-COVID-19 condition: recognition, research, and rehabilitation, and has initiated working groups aiming to provide a post-COVID-19 condition clinical definition and outline plausible explanations of the physiological mechanisms, in addition to proposing an interim clinical case definition through a multi-disciplinary, gender-based, international Delphi consensus.

The number of studies assessing post-COVID-19 condition is rising, resulting in a vast quantity of data whose validity is unknown. The reporting and quantification of post-COVID-19 condition symptoms vary considerably between studies. Not only is the presence of symptoms essential, but also their duration and severity must be considered. One of the main limitations of post-COVID-19 condition research is the absence of comparative pre-morbid data. Assuming the patient did not have asymptomatic aberrant testing prior to infection, any abnormalities are typically attributed to post-COVID-19 condition.

Few international initiatives have developed data collection instruments. The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) has devised follow-up protocols and surveys for adults and children to assess the prevalence and risk factors for long-term physical and psychosocial health consequences following a diagnosis of COVID-19. The WHO has designed a post-COVID-19 condition case report form for reporting standardized clinical data from individuals after hospital discharge or after the acute illness to study the medium- and long-term effects of COVID-19. Even though these instruments facilitate harmonized data collection, the proliferation of tools from reputable organizations may lead to data heterogeneity, as various centers prioritize different instruments.



Few ongoing initiatives are addressing the problem of data heterogeneity by systematically evaluating available evidence in the live format, which could inform COS initiatives and aid in the development of a lengthy list of outcomes. However, systematic reviews do not resolve the instrument validity issue. Validity evaluation may require a considerable amount of time, and a COS should be developed in the interim.

Because post-COVID-19 condition research on pediatric and adolescent development may have lifelong consequences, there is a significant lacuna and limitation. Children and adolescents may have very distinct outcomes of interest than adults, and COS for this age group should be developed in collaboration with the children and adolescents themselves, as well as their parents and caregivers.

## CONCLUSION

This manuscript was authored by a multidisciplinary (allergists, critical care specialists, ENT specialists, infusionists, immunologists, neurologists, psychiatrists, pediatricians, pulmonologists, experts in global and public health, epidemiologists, methodologists, rehabilitation specialists, and people with lived experience of post-COVID-19 condition), gender-balanced, international group of experts, including members of the ISARIC Consortium, US Centers for Disease Control and Prevention, and the World Health Organization. Prior research in a variety of medical disciplines has demonstrated the significance and utility of COS in both research and clinical practice. There is an urgent need to develop a COS for the post-COVID-19 era that will enable for the improvement of data quality, harmonization, and comparability across geographic regions. All relevant stakeholders, including but not limited to healthcare professionals, researchers, methodologists, patients, and caregivers, are required to contribute to the joint initiative. We urge local and international funding agencies to support coordinated efforts to develop COS for adults and children with post-COVID-19 conditions.

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