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Review Article

# Post COVID-19 Syndrome. Incidence, Causes and Management

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## Abstract

**Background:** The highly infectious and pathogenic novel coronavirus has emerged causing a global pandemic. Covid-19 causes complications that affect a lot of system in the body and may be without known pathophysiology as delirium, musculoskeletal, neurological, gastrointestinal and hematological complications.

**Methods:** A literature search was performed to obtain data regarding incidence, causes, clinical presentation, and how to manage post covid-19 syndrome.

**Results:** Patients need to be rehabilitated to prevent these chronic symptoms. It was reported that 7.5% of individuals has impaired consciousness as a post covid-19 complication. On the other hand, cardiac consequences, musculoskeletal events, and hepatic impairment as a result of prolonged ICU admission may occur. Further complications like thrombotic events, psychological events, neuropathy, and GIT problems as diarrhea are likely to occur. Different anticoagulation therapies betrixaban, rivaroxaban, LMW heparin are used for thrombotic events prophylaxis/management. For pulmonary, cardiac, psychological, and musculoskeletal rehabilitation management different protocols are used.

**Conclusion:** We can conclude that post covid-19 follow-up is necessary for cured patients, as 45% of the discharged patients may require healthcare and social assistance, and 4% may require rehabilitation.

**Keywords:** Post Covid-19 Syndrome; Delirium; GI; Hepatic; Musculoskeletal; Neuropathy

## Introduction

Coronavirus disease 2019 named commonly as (COVID-19), that is caused by severe acute respiratory syndrome coronavirus 2 abbreviated as (SARS-CoV-2), has now become a global pandemic. The virus predominantly affects the respiratory tract, resulting in lung damage and followed by acute respiratory distress syndrome. Although the pathogenesis of COVID-19 remains unclear, systemic inflammation is the most commonly recognized and accepted mechanism [1,2].

After being infected with COVID-19, the vast majority of patients recovered entirely. However, a significant number of individuals infected with SARS-CoV-2 continue to have symptoms even after they have recovered from the first stages of COVID-19 illness. Clinicians all around the globe referred to these long-term CO-

VID-19 consequences as "Long-term COVID-19" or "Post covid-19 syndrome." Long-term COVID-19 patients are those who have had SARS-CoV-2 infection but do not recover totally within a few weeks (typically 2-3 weeks). According to the COVID-19 Symptom Study, a study conducted on over 4 million people in the United States, the United Kingdom, and Sweden, approximately 10% of patients who tested positive for the SARS-CoV-2 virus remain ill for more than three weeks, and a smaller proportion for months. As a result, it is becoming evident that some patients with SARS-CoV-2 infections, even those classified as "mild", continue to experience persistent or cyclical symptoms [3].

## Methods

A literature search with no language restrictions was performed to obtain published studies regarding incidence, causes, clinical presentation, and how to manage post covid-19 syndrome. The data collection was performed for all related studies from the time period of 2019 and 2020. The inclusion criteria refer to published papers of any design evaluating individual or population incidence, causes and management of post COVID-19 complications. Exclusion criteria included unpublished reports, unreported long-term COVID-19 symptoms, studies with an unclear date or location or suspicion of duplicate reporting, coronavirus strains other than COVID-19, and studies that merely speculate post-COVID-19 sequelae.

## Results

## Incidence

Coagulopathy is a considered as one of the clinically important consequences of inflammation. As a result of this consequence, patients are found to be at increased risk of venous thromboembolism. The incidence rate of different thrombotic events in COVID-19 patients ranged from 7.7 to 49 percent [1,2]. This is considerably greater than the incidence in COVID-free patients. Male patients with diabetes mellitus, hypertension, and cardiovascular diseases are at highest risk of complications of COVID. A history of prior venous thromboembolism (VTE) was noted in about 3-5% of patients [2,4]. However, there were reports of infrequent events of arterial thrombosis, characterized by ischemic strokes or acute coronary syndrome. Intensivists also encountered frequent clotting of circuits in the continuous renal replacement therapy or extracorporeal membrane oxygenation machines in these critically ill patients. The mortality rate in these patients with COVID-19 and thrombotic events varied across studies, from 8 to 26% [5,6]. A recent study describing autopsy reports from 12 patients with COVID-19 showed that four of the 12 patients died as a result of a massive pulmonary embolism; the source of the embolism was in the deep veins of the lower extremity [7].

Also, other incidences have been recognized among patient with COVID 19 and have ICU- acquired weakness, ICU-acquired weakness (ICU-AW) is an important growing clinical problem among patients admitted to the ICU.

It is also reported that 25 to 50 percent of patients who require mechanical ventilation for more than 5 days are at greater risk for developing ICU-AW.

Also, one of the complications of the COVID-19 is delirium, in an early retrospective report from Wuhan, Mao., *et al*. reported that only 7.5% has impaired consciousness [8,9].

According to the literature, 75 percent of delirium episodes in patients are overlooked unless objective delirium monitoring is used to detect this type of severe brain malfunction [2,3,10]. In the United Kingdom, it has been recommended that up to 50% of COVID-19 hospitalized patients may require continuous medical care in order to improve long-term results [5].

## Causes

The cause behind the thrombolytic events is showed to be due to capillary endothelitis with formation of microthrombi in alveolar capillaries, and small pulmonary vessels. Microthrombi develop in the pulmonary arteries as a result of diffuse alveolar injury and inflammation, interstitial inflammation, and widespread pulmonary macrophage activation [11,12].

The result behind this thrombotic event is the alteration of the balance between coagulation and fibrinolytic pathways that cause fibrin deposition. The cause of increased D-dimer in patients with COVID-19 is not clear yet. According to research studies, elevated D-dimer levels are caused by increased inflammation, critical illness, immobility, numerous comorbidities, mechanical ventilation, and vascular access catheters, all of which exacerbate thrombotic complications [11-13].

Delirium represents another complication resulted from covid-19, advanced age is an independent risk factor for delirium and

those who are at the greatest risk for severe pulmonary disease related to COVID-19 are likely at the greatest risk for delirium as well.

The use of sedating agents, such as sedative-hypnotics and anticholinergic drugs, in critically ill patients has been linked to the development of delirium.

ICU-acquired weakness (ICU-AW) represent a very big problem among patients admitted to ICU the factors such as prolonged mechanical ventilation (MV), increased length of ICU-stay, prolonged immobility, the use of neuromuscular blockers or corticosteroid therapy, hyperglycemia, shock, sepsis, and renal failure and systemic inflammatory-mediated pathology (interleukin-1 (IL-1), interleukin-6 (IL-6), and C-Reactive Protein (CRP)) represent the most significant risk factor for ICU-AW [14,15].

Cardiac consequences from viral myocardial injury, ACE2-receptor downregulation, hypoxia, hypotension, an increased systemic inflammatory load, or therapeutic toxicity are highly probable to be complex. Proinflammatory mediators implicated in COVID-19 play an important role, resulting in vascular inflammation, myocarditis and arrhythmic complications [16,17].

Psychological events happened after the infection with covid-19 is due to Corticosteroid treatment, life-threatening nature of the virus, worries for family members and concern with becoming a vector for infecting others [18].

The cause for musculoskeletal events is the prolonged mechanical ventilation and immobilization associated with ICU admissions result in musculoskeletal changes [19,20].

Neuropathy may occur after the infection with covid-19 due to the fact that SARS-CoV-2 enters the human body through ACE2 receptors on the surface of human cells, expressed on the surface of the spinal cord, as well as the respiratory tract. Suggestions from animal studies show that covid-19 may reach the CNS directly through the olfactory bulb. This might be the source of the hyposmia mentioned in COVID-19 [21-23].

GI problems as diarrhea may happened during the infection of covid-19 and may continue after the infection the cause of that is the using of steroid therapy [24].

Cause for hepatic impairment is septic response, hepatic congestion due to mechanical ventilation [24,25].

## Clinical presentation

In patients with worsening tachypnea, decreased oxygen saturation 90 percent, increasing supplemental oxygen requirement, and hemodynamic instability in the presence of imaging findings inconsistent with worsening COVID-19 pneumonia, the clinical presentation warranting a diagnosis of VTE is critical [26].

Asymmetric limb pain or swelling might raise clinical suspicion for deep vein thrombosis (DVT). Recognizing relevant symptoms and signs is critical, and while a precise diagnosis cannot be established without imaging, these patients should be placed on appropriate anticoagulant treatment [27].

Patients with delirium are at great concern, the majority of whom are elderly may suffer from an evolving neurocognitive disorder, be hypoactive or aphasic and cannot express their emotional or spiritual needs, and would typically receive comfort from relatives, friends, and caregivers, during a medical crisis [27].

Respiratory problems should be evaluated in COVID-19 patients since they may present with some degree of impairment and functional disability, including but not limited to reduced respiratory function. COVID-19 is also associated with cardiac complications, in particular, arrhythmias and myocardial injury.

While for psychological complication Examining the impact of historical CoV outbreaks on mental health reveals significant levels of emotional distress due to anxiety, sadness, fearfulness, and stigmatization [18].

For musculoskeletal complication, muscle atrophy and loss of muscle mass begin within the first week of intensive care unit admission and are exacerbated in patients with multiorgan failure, sepsis, or a protracted intensive care unit stay [28,29]. Other musculoskeletal problems that lead to decreased fitness include heterotopic ossification, muscle atrophy, chronic discomfort, weakness, and dyspnea [5].

There are neurological symptoms among patients, which are more evident in severe instances than in non-severe situations. Overall, neurological symptoms were classified into 3 categories: Central nervous system (CNS) symptoms or disease like dizziness (16.8%), headache (13.1%), impaired consciousness (7.5%), epilepsy (0.5%), and acute cerebrovascular disease (2.8%) [30]. Also peripheral nervous system symptoms including hypogeusia (loss

of taste) (5.6%), hyposmia (loss of smell) (5.1%) and neuralgia (2.3%); and musculoskeletal symptoms (10.7%) [30]. Furthermore, case studies have reported COVID-19 complications such as encephalitis, encephalopathy [31], acute necrotizing encephalopathy [32], and post infectious myelitis leading to acute flaccid paralysis of both lower limb [21].

Other individuals may suffer from GI complication indicated by diarrhoea, which can be a presenting complaint of COVID-19, so ensuring any diarrhoea and vomiting is quickly separated, and a CoV test evaluated is sensible.

The clinical presentation of COVID-19 patients with hepatic complications shows abnormal liver function tests (LFTs) (transaminases, gamma-GT, bilirubin) during the acute phase [24,25].

## Management

Regarding in-hospital prophylactic anticoagulation therapy, the (International Society on Thrombosis and Hemostasis) has advised that all hospitalized patients get antithrombotic prophylaxis with low-molecular-weight heparin unless a contraindication exists. Fondaparinux is indicated in the treatment of heparin-induced thrombocytopenia [33,34]. In ambulatory individuals with acute medical disease or respiratory symptoms, routine thromboprophylaxis is not indicated [2]. Importantly, the usage of heparin is beneficial not only for its anticoagulant activity, but also for its anti-inflammatory action in COVID-19 patients [35]. Heparin also has some protective effects on the endothelium. So, direct administration of heparin into the lung tissue through nebulization may be an attractive therapeutic approach to investigate [36]. *In vivo* models of coronavirus infection have demonstrated the anti-viral effect of unfractionated heparin [37]. The choice of heparin over low-molecular-weight heparin is clinically relevant in patients with underlying renal dysfunction. Extremely ill COVID-19 patients may also develop liver failure, aggravating their coagulopathy.

These patients are more likely to encounter haemorrhage. As a result, the kind and amount of AC should be tailored to the patient's clinical profile [37,38]. In patients with a body mass index ≥ 40 kg/m2, a higher dose of thromboprophylaxis has been shown to Decrease the odds of symptomatic VTE by 50% [39]. This strategy may be useful when treating obese patients with COVID-19.

Post discharge patients who are admitted to the hospital for an acute medical condition have a higher risk of VTE for up to 90 days following hospital discharge. A comparable risk should be addressed for COVID-19 patients. It may be appropriate to consider continued therapy to avoid thromboembolic events following hospital discharge.

It is possible to use a regulatory-approved regimen (betrixaban 160 mg on day 1, followed by 80 mg once per day for 35 to 42 days, or rivaroxaban 10 mg once per day for 31 to 39 days). Increased bleeding risk should be considered depending on the patient's clinical condition and comorbidities [33].

## Therapeutic anticoagulation

A full dosage of AC may be useful for individuals who fulfil the requirements for a SIC score or have a significantly high d-dimer level. In a retrospective analysis comprising 449 severe COVID19 patients, 99 of them were given heparin (mainly LMW heparin) for 7 days or more. In multivariate analysis, prothrombin time, dimer, and age were positively linked with 28-day mortality, whereas platelet count was negatively correlated. There was no difference between heparin users and nonusers regarding 28-day mortality rates (30.3 percent versus 29.7 percent, P = 0.910). However, in patients with SIC score 4.0 (40 percent versus 64.2 percent, P = 0.029) or D-dimer more than 6-fold of upper normal limit (32.8 percent versus 52.4 percent, P = 0.017), heparin users had a 28-day mortality rates less than the nonusers [40].

It has been recommended to start therapeutic AC in patients with COVID-19 who have experienced an incident thromboembolic event or have a high suspicion of thromboembolic disease. COVID-19 patients who require extracorporeal membrane oxygenation or continuous renal replacement treatment, or who have catheter or extracorporeal filter thrombosis, should receive therapeutic AC in accordance with standard institutional procedures [41]. A recently published study has found evidence of heparin resistance in critically ill patients with COVID-19. Measurement of the anti-factor Xa level may be useful in these patients [42,43].

Also Tissue Plasminogen Activator Few preclinical and clinical studies have postulated that fibrinolytic treatment might improve survival in individuals with acute lung damage and ARDS. A recently published case series reported the effect of tissue plasminogen activator on patients with COVID-19 experiencing ARDS and respiratory failure. Oxygen partial pressure-to- oxygen fraction inspired ratio improved initially in all three cases. However, the effect was transient. More research is needed to determine the effect of tis-

sue plasminogen activator on the survival of COVID-19 patients [44,45].

While the Oral Anticoagulation, Patients taking warfarin and those who can take oral medication should be transitioned to the same depending on the indication. If there is an option for switching to direct oral ACs (DOACs), it should be done, because during isolation for COVID-19, regular international normalized ratio monitoring would likely be difficult. The DOACs can be used in patients with COVID-19 as per the usual indications. To date, the use of DOACs in patients with COVID-19 admitted to a hospital is not routinely recommended. Tocilizumab and lopinavir, ritonavir, or Darunavir have drug-drug interactions with direct oral anticoagulants. Furthermore, in the presence of renal impairment, which is a frequent consequence in critically ill COVID-19 patients, decreased excretion of direct oral anticoagulants might increase bleeding risk [33,46].

While regarding delirium management historically, delirium rates in mechanically ventilated intensive care unit populations were consistently 70 to 75 percent, and delirium duration has been shown to be an independent predictor of longer stay lengths, higher mortality, higher care costs, and alarming rates of acquired dementia that lasts years after illness. Given these facts, it is critical to carry into the pandemic the knowledge that delirium in mechanically ventilated patients can be reduced dramatically to 50% by implementing the safety bundle known as the ABCDEFs, which is promoted by the Society of Critical Care Medicine (SCCM) in their ICU Liberation Collaborative. Limitations in the ability to conform to this approach are a major component of the burden of the isolation required to limit the spread of COVID-19, prompting us to discuss specifics related to bedside care that one might keep in mind in organizing busy triage units and routine ICU care during the pandemic. Delirium screening only takes 30 s. As such, delirium screening and treatment should follow well established international guidelines, such as the e CASH concept and the SCCM clinical practice guidelines. Although routinely used in clinical practice, some sedation- and delirium-associated issues may be especially Important when using limited resources. Standard non pharmacological measures to treat or prevent delirium may not be possible in isolation environments, and these environments may themselves worsen delirium. Pain Management remains a priority for all patients and requires the widespread implementation of behavioral pain scales (CPOT or BPS) for sedated and mechanically ventilated patients. After pain control is satisfactory, we must focus on the overlapping issues that cause a person's brain to fail in critical illness, the most serious of which are abuse of strong sedatives and excessive immobility. It would be easy to dismiss patients' brains as unimportant at such horrific moments as the respiratory failure that is occurring with COVID-19. This would be a serious mistake, according to the critical care literature. Evidence suggests that delirium is not only a strong predictor of poor immediate survival, but also of the cost of treatment and the quality of survival. As a result, healthcare practitioners should adhere to local standards and regulations for the monitoring and management of delirium. Implementing simple delirium screening methods is critical, especially given the high workload, since without proven evaluation tools, 75 percent of delirium will be overlooked during the COVID-19 crisis. It is critical to decrease ICU delirium risks by conventional care techniques such as appropriate pain management, preventing urine retention and gastro-intestinal issues (constipation), detecting and treating nosocomial infection, and maintaining enough oxygenation. Non-pharmacological measures, such as frequent orientation despite social isolation and a lack of interaction with family and carers, would be critical. In terms of pharmacological treatments, no medications other than avoidance of misuse of powerful psychoactive agents such as sedatives and neuromuscular blockers (NMB) may be suggested for the prevention or treatment of ICU delirium unless patients really require such therapy. This aspect of the discussion is especially important given the early anecdotal recommendations to treat COVID-19 patients in the prone position, which will be uncomfortable and thus likely be met with even higher than usual amounts of sedation, potentially leading to very high rates of delirium in the management of these already high-risk patients. It is also critical to evaluate prior medicines in order to avoid withdrawal symptoms. The ease of transmission of COVID-19 and the danger of injury to others (healthcare professionals, family, carers) may outweigh the risk of harm to the individual. This is an isolated case that supports the early use of sedatives for hyperactively delirious individuals who are endangering themselves and others. ICU beds and ventilators are valuable and required resources, thus it is critical to investigate strategies to prevent the unneeded extension of ventilation time and ICU length of stay associated with deeper sedation [47,48].

For pulmonary rehabilitation management Low intensity exercise (≤3 METs or similar) should be considered first, especially for individuals who require oxygen treatment, while vital signs are monitored continuously (heart rate, pulse oximetry and blood

pressure). Exercise should be gradually increased based on their symptoms.

For cardiac rehabilitation management According to the British Association for Cardiovascular Prevention and Rehabilitation, the six key components of CR are as follows: health behaviour change and education, lifestyle risk factor management, psychological health, medical risk management, long-term solutions, and audit and assessment [49].

For psychological management. Referral to psychological services and consideration of trauma focused cognitive behavioural therapy, cognitive processing therapy or eye movement desensitisation and reprocessing is appropriate for those with moderate to severe symptoms of acute stress disorder.

For musculoskeletal management The physical therapy strategy for patients with post-ICU related weakness includes exercise-based interventions such as muscle stretching, weakness and joint range of motion to avoid contractures and pressure sores. Pain management should be patient-centred and involve education, and non-pharmacological and pharmacological interventions [50].

## Conclusion

It is expected that 45 percent of patients discharged from hospitals would require healthcare and social care assistance, while 4 percent will require rehabilitation in a bed setting. As a result, there is a need to prepare for post-acute and chronic care of COVID19 patients. However, COVID-19 is a novel illness that has only been in circulation since late 2019. As a result, several of the mentioned publications are in preprint and merely present observational case series, with certain journals expediting publication of COVID-19-related research.

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