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SYNOPSIS

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Long-Term Sequelae and COVID-19 – What We Know So Far

Introduction

PHO is actively monitoring, reviewing and assessing relevant information related to Coronavirus Disease 2019 (COVID-19). "What We Know So Far" documents are intended to provide a rapid review of the evidence related to a specific aspect or emerging issue related to COVID-19.

The development of these documents includes a systematic search of the published literature as well as scientific grey literature (e.g., ProMED, CIDRAP, Johns Hopkins Situation Reports) and media reports, where appropriate. Relevant results are reviewed and data extracted for synthesis. All "What We Know So Far" documents are reviewed by PHO subject-matter experts before posting.

As the COVID-19 outbreak continues to evolve and the scientific evidence rapidly expands, the information provided in these documents is only current as of the date of posting.

Key Findings

- At this stage of the COVID-19 pandemic, there are few peer-reviewed studies examining the occurrence or prevalence of long-term sequelae associated with COVID-19.
    - There is some evidence that olfactory dysfunction (e.g., dysosmia) and gustatory dysfunction (e.g., dysgeusia) are relatively common long-term sequelae associated with COVID-19 infection.
    - Multisystem inflammatory syndrome in children (MIS-C) has been associated with SARS-CoV-2 infection in several studies. MIS-C may have long-term sequelae.
- Cardiovascular, pulmonary and other neurological sequelae may be expected based on the pathophysiology of COVID-19 or what is known regarding other infectious diseases.
- Additional long-term sequelae that may be anticipated based on knowledge of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) include anxiety, cardiovascular system abnormalities, depression, glucose metabolism disorders, hyperlipidemia, lipid metabolism dysregulation, post-traumatic stress disorder and reduced lung capacity.

Background

As the COVID-19 pandemic has progressed, there has been growing awareness of the long-term impacts of COVID-19 infection, including cardiac, neurological, metabolic and respiratory long-term sequelae (Dasgupta et al.).[1]

For the purposes of this What We Know So Far, we consider long-term sequelae as symptoms that develop after 6 weeks or persist beyond 6 weeks of COVID-19 symptom onset, excluding symptoms and complications arising during the acute phase of infection. Current data from the World Health Organization China Joint Mission on COVID-19 suggest that the median time from onset to clinical recovery for mild cases is approximately 2 weeks and is 3-6 weeks for patients with severe or critical disease (World Health Organization).[2]

The purpose of this document is to examine what is known so far about long-term sequelae directly related to COVID-19 infection. This document does not report on indirect impacts of pandemic public health measures on long-term sequelae; e.g., impact of social distancing on mental health or the consequences of deferred health care on chronic disease management.

Reports on Long-term Sequelae by Organ System

Neurological Long-term Sequelae

There are few studies to date documenting long-term neurological sequelae related to COVID-19. However, given the similarities of COVID-19 to other coronaviruses (specifically SARS-CoV-1 and MERS-Cov), it can be hypothesized that neurological sequelae may develop in people with COVID-19, such as neurodegenerative disorders, and that cognitive monitoring should be performed on recovered patients (e.g., Abboud et al., De Felice et al., Heneka et al., Serrano-Castro et al., Troyer et al.).[3-7]

- Cothran et al. hypothesized that the immune response due to severe COVID-19 can lead to cognitive decline (due to cytokine storm syndrome) and stroke. However, currently there is no evidence for cognitive decline in recovered COVID-19 patients.[8]
- Lennon, in a commentary, noted the potential for increased risk of developing Alzheimer's disease during and after recovery from COVID-19.[9]

Numerous studies investigated the long-term persistence of sensory deficits; specifically, olfactory (smell) and gustatory (taste) dysfunction. These studies use different approaches to measuring the symptoms and most do not include follow-up periods that would be indicative of long-term sequelae (persistence >6 weeks since COVID-19 symptom onset) (Sayin).[10]

- In South Korea, Lee et al. reported that the majority of patients with anosmia and ageusia (n=488 total) recovered from these symptoms within 3 weeks.[11] The median time to symptom resolution for anosmia and ageusia in people with COVID-19 was 7.0 days (interquartile range [IQR]: 4.0-11.0, range: 1-39) and 6.0 days (IQR: 3.0-10.0, range: 1-42), respectively. The median age of patients was 36.5 years (IQR: 24.5-54.0).
- In a study of 126 people with COVID-19 and olfactory dysfunction in Italy, resolution of olfactory dysfunction by day 40 since initial symptom onset occurred in 83.4% (95% confidence interval [CI]: 89.5-76.2) of patients; it is unclear the exact proportion of patients with persistent symptoms past 6 weeks (Paderno et al.).[12] Sixteen (12%, n=135) subjects reported ongoing gustatory dysfunction at the end of the follow-up period (mean recovery time from onset was 33 ± 15 days); it is unclear the exact proportion of patients with persistent symptoms past 6 weeks. The mean age of patients was 45 years (range: 18-70).
- Kosugi et al. reported the median time to regaining sense of smell was 15 days (IQR: 10-21, n=72).[13] In several cases, hyposmia or anosmia did not fully resolve at 31 days after its onset or

at time of last follow-up; therefore, there may be cases of long-term hyposmia or anosmia in this cohort. The median age of patients was 36 (IQR: 31-34).

- Li J et al. reported that the mean time from COVID-19 symptom onset to resolution of dysosmia was 62 days (range: 25-95), in a cohort of 145 people with COVID-19 in China. The median age of patients was 49 years (range: 13-80).[14]
- In Germany, Otte et al. reported that 50% (25/50) of people with COVID-19 and olfactory dysfunction still had dysfunction 7 weeks after initial symptom onset based on a comprehensive psychophysiological smelling test, despite the fact they reported full recovery from other COVID-19 symptoms.[15] The mean age of patients was 43.2 years (range: 23-69).
- In Italy, Meini et al. noted that 9.5% (4/42) people with COVID-19 and with ageusia still had gustatory dysfunction at a mean of 32 days post-symptom onset; 4.8% (2/42) for anosmia.[16] The average age of patients with ageusia or anosmia was 63 years. The mean duration of anosmia and ageusia was 18 and 16 days, respectively.

Pulmonary Long-Term Sequelae

Post-mortem studies have noted diffuse alveolar damage, leading some to postulate that long-term pulmonary sequelae are possible from COVID-19, such as interstitial pulmonary fibrosis (Carsana et al., Schaller et al.).[17-18] In addition, based on the literature from other viral infections, reduced or abnormal pulmonary function may be expected in people with COVID-19 in the months after recovery (Salehi et al.), although there are limited studies to date evaluating pulmonary function.[19]

- In a computed tomography (CT) study of 165 patients with COVID-19 and follow-up information, Jin et al. [not peer-reviewed] reported 13.9% (23/165) showed diffuse alveolar damage on baseline CT (median time from symptom onset to baseline CT was 7 days (range: 1-44).[20] In follow-up CTs performed ≥30 days after symptom onset, 22.0% (9/41) of patients still showed diffuse alveolar damage. The mean age of patients was 49.5 ± 15.9 (range: 4-89).

Cardiovascular Long-Term Sequelae

The expression of the angiotensin-converting enzyme 2 (ACE2) receptor on myocytes, coronary endothelial cells and arterial smooth muscle increases the risk of organ damage in individuals with COVID-19, as the virus uses these receptors to gain entry into cells (Chen et al., Cormican et al., Guo et al.).[21-23] The majority of studies have focused on acute complications, but long-term sequelae may be possible based on the above mechanism.

- Driggin et al. hypothesized that the following cardiovascular sequelae and complications may develop in individuals with COVID-19 and pre-existing cardiovascular risk factors: acute coronary syndrome, myocardial infarction, arrhythmia, cardiogenic shock, heart failure, myocarditis and venous thromboembolism.[24]
- Sardari et al. reported on a case of myocarditis in a 31-year-old that developed three weeks after recovery from COVID-19; however, it is unclear how far after symptom onset this occurred to classify as short-term or long-term sequelae.[25]

MIS-C is a newly recognized illness that may be associated with SARS-CoV-2. Reports suggest that MIS-C appears weeks after potential infection with or exposure to COVID-19 (Belot et al., Cheung et al., Pouletty et al.).[26-28] Symptoms are variable, but many children have symptoms similar to toxic shock syndrome or Kawasaki disease. Kawasaki disease is a clinical diagnosis characterised by fever longer than five days, non-purulent bilateral conjunctivitis, unilateral cervical lymphadenopathy, rash,

peripheral edema of the hands or feet, cracked or dry lips, and a "strawberry" tongue (Lin et al.).[29] One of most significant long-term effects of Kawasaki disease are cardiovascular complications, specifically coronary artery aneurysms.

- Feldstein et al. reported on patients with MIS-C patients from 26 states in the United States (US).[30] Fourteen of 186 patients had a history of symptoms associated with COVID-19; the median time from initial symptom onset to MIS-C symptom onset was 25 days (range: 6-51). Most patients required intensive care unit (ICU) admission (80%, 148/186), 20% required mechanical ventilation (37/186), 8% (15/186) had coronary artery aneurysms and three children died. The median age of patients in the study was 8.3 years (IQR: 3.3.-12.5).
- In a study of patients with MIS-C in New York State, Dufort et al. reported 99 confirmed and suspected cases.[31] Prior to hospitalization for MIS-C, 24% (24/99) of patients had COVID-19-like symptoms; the median time from COVID-19 symptoms to hospitalization was 21 days (IQR: 10-31). Most patients required admission to an ICU (80%, 79/99), 10% (10/99) required mechanical ventilation, 9% (9/99) had coronary artery aneurysms and two patients died. 42% (42/99) of patients were 6-12 years old.
- In France, Toubiana et al. reported that the median time from COVID-19 symptoms and MIS-C symptoms in 21 patients was 45 days (range: 18-79).[32] The median age of patients was 7.9 years (range: 3.7-16.6).

Renal and Hepatic Long-Term Sequelae

There are limited reports evaluating renal and hepatic sequelae associated with COVID-19. The majority of studies report acute damage, which may lead to long-term sequelae, but the latter requires further study.

- Adapa et al. report acute injury to the kidneys during COVID-19 infection, which could lead to potential long-term impacts.[33]
- In contrast, Wang et al. reported that COVID-19 does not result in acute kidney injury based on a study that included 116 hospitalized patients in China with a median age of 54 years (IQR: 38-69).[34]
- In a meta-analysis, the pooled prevalence of liver injury in 4,191 people with COVID-19 was 19.5% (95% CI: 14.3-26.1) with substantial variations among the 19 studies (Samidoust et al.).[35] Given the potential for liver injury during COVID-19 infection, it is not unreasonable to assume long-term hepatic sequelae may occur in recovered patients (sequelae will depend on the type of liver injury, however, these are not specifically discussed in the article).

Reproductive Long-Term Sequelae

Little is currently known about the long-term reproductive sequelae associated with COVID-19 infection; however, there is one study that suggests that sperm quantity and function may be impacted.

- A review indicates decreased sperm concentration and motility for up to 90 days following COVID-19 infection (Segars et al.).[36]

Reports on Treatment-Related Long-Term Sequelae

In this section, we highlight long-term sequelae resulting from specific treatments for managing patients with COVID-19, such as use of mechanical ventilation. It is well-established that ICU admission and

mechanical ventilation are associated with ICU-acquired weakness, deconditioning, myopathies, neuropathies and delirium; however, much of the support for this observation with reference to COVID-19 is based on the literature for ICU-related outcomes (Candan et al., Koftis et al. , Stam et al., Vittori et al.).[37-40] Long-term sequelae related to ICU care for patients with COVID-19 include persistent and delayed-onset symptoms.

- In a meta-analysis of COVID-19 research, Rogers et al. identified one study that noted 65%, (26/40) of people in the ICU had confusion and 69% (40/58) had agitation; and another study that noted 21%, 17/82 patients had altered consciousness.[41] At discharge, 33% (15/45) of people with COVID-19 (in one study) who were assessed had a dysexecutive syndrome affecting cognition.
- In a single centre study in the US, Malik et al. [not peer reviewed] reported that 11 people with COVID-19 (mean age was 60.3 ± 15.7 years) and acute respiratory distress syndrome were placed in the prone position; all of these patients acquired focal/multifocal peripheral nerve injury.[42] The authors suggest that the peripheral nerve injury is potentially due to hyperinflammation and hypercoagulability linked to COVID-19 infection.
- In Italy, Kiekens et al. reported numerous issues related to the ICU care of patients with acute COVID-19 illness including dysphagia, impaired gait, impaired balance, muscle weakness, myopathy, neck/shoulder pain (due to placing in prone position for extended period), neuropathy, psychological problems and reduced joint mobility.[43] The authors also report the need for chest physiotherapy in recovered patients due to pulmonary fibrosis.
- A report has urged continued cardiac monitoring of those recovering from COVID-19 who have received hydroxychloroquine or azithromycin during acute infection, as these drugs have potential to cause arrhythmia (e.g., Kara et al.).[44]
- Dean et al. have noted that there will be an increased demand for physical therapists post COVID-19, specifically, therapists for prescribing a structured exercise program when the patient had returned to the community.[45]

Reports on Long-Term Sequelae from SARS-CoV-1 and MERS-CoV Infection

To supplement our existing knowledge on the long-term sequelae associated with COVID-19, we present reports on the long-term sequelae associated with similar infections; i.e., MERS (caused by MERS-CoV) and SARS (caused by SARS-CoV-1).

- In a systematic review and meta-analysis, Ahmed et al. reported that the most common sequelae during the period 6 months post-hospital-discharge in people with MERS or SARS were impaired diffusing capacity for carbon monoxide (indicative of pulmonary fibrosis or pulmonary vascular disease; prevalence 27%, 95% confidence interval [CI]: 15-45%) and reduced exercise capacity (mean 6-min walking distance = 461 m, 95% CI: 450-473 m).[46] In addition, the prevalence of post-traumatic stress disorder after 6 months post-discharge was 39% (95% CI: 31-47%), followed by depression (33%, 95% CI: 20-50%) and anxiety (30%, 95% CI: 10-61%).
- In South Korea, Park et al. reported that 42.9% (27/63) of MERS survivors reported post-traumatic stress syndrome and 27.0% (17/63) reported depression at 12 months post-MERS (unclear if this 12 months is since disease onset or since disease recovery).[47] The mean age of patients was 49.2 ± 12.6 years.

- In a meta-analysis, Rogers et al. showed that in the post-acute-illness period of people with MERS and SARS, the point prevalence of post-traumatic stress syndrome was 32.2% (121/402 patients from 4 studies (95% CI: 23.7-42.0); followed by depression, 14.9% (77/517 patients from 5 studies), (95% CI: 12.1-18.2); and anxiety disorders, 14.8% (42/284 patients from 3 studies,95% CI: 11.1-19.4).[41]
- Wu et al. examined 25 people with SARS 12 years after recovery and noted that 68% had hyperlipidemia and 44% had cardiovascular system abnormalities.[48] In addition, 60% had glucose metabolism disorders.
- Li AM et al. demonstrated children that had SARS showed long-term sequelae at 6 months post recovery.[49] Thirty four percent (16/47) of patients had persistent abnormal CT images (i.e., ground-glass opacities, air trapping). In 38 patients that underwent pulmonary function tests, four had abnormal lung function tests (i.e., mild obstructive/restrictive deficit). In addition, exercise impairment was associated with abnormal CT findings. The median age of all patients was 13.6 years (IQR: 9.9-16.0)

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