Aeromedical Implications of Long-Term COVID-19 Sequelae

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BACKGROUND: While many COVID-19 studies focus on acute effects of the infection, few examine the intermediate and long-term sequelae of the illness. Studies have shown that a good portion of patients have chronic effects in several body systems for several months or longer. Such effects can potentially adversely impact pilot performance in flight. We sought to determine the long-term effects of COVID-19 infection, how such effects can affect pilot performance, and how to best evaluate pilots for aeromedical flight clearance.

METHODS: We used the PubMed literature search engine to review peer-reviewed articles that focused on the intermediate and long-term effects of COVID-19 infection. Chronic signs and symptoms were subdivided based on the particular body organ system affected. Merging information obtained from case reviews, article reviews, and aeromedical standards, we created a risk stratification guide to assist with the aeromedical disposition of affected pilots.

RESULTS: Long-term effects of COVID-19 infection can last for several months or longer. The most common effects are fatigue, weakness, pulmonary diffusion defects, depression, and anxiety.

DISCUSSION: This review article focuses on the most common intermediate- and long-term COVID-19 conditions of aeromedical significance and the corresponding course of actions recommended for the aeromedical examiner. Aeromedical evaluation should take into consideration factors related to the pilot, aircraft type, and specific aviation environment. Such evaluation may include diagnostic testing, medical specialist consultation, preflight simulation in an altitude chamber, human centrifuge testing, and/or a flight simulator checkride.

KEYWORDS: COVID-19 long-term sequelae, waiver, post-COVID-19, pilot, aviator, astronaut, flight medicine.

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While many COVID-19 studies focus on acute effects of the infection, only a few examine the intermediate and long-term sequelae of the illness. Studies have shown that a good portion of patients have long-term effects in several body systems. In a study of 1733 hospital discharged COVID-19 patients, the most common symptoms 6 mo from the onset of illness were fatigue or muscle weakness (63%), sleep difficulties (26%), and anxiety or depression (23%). Pulmonary diffusion impairment (22%) was a fairly common finding.[33] An aviation medical examiner (AME) should be aware of these long-term symptoms when evaluating a pilot for return to flight, particularly after a complicated case of COVID-19. The data obtained from our review were used to create a risk stratification strategy that takes into account variables to determine the possibility that a pilot will suffer an adverse health consequence in flight that could jeopardize flight safety. In making our recommendations, we took into consideration the severity of the medical problem, probability of recurrence, rapidness of problem onset, and whether or not early warning signs are present such that a pilot will have enough time to take appropriate action. Together, this information should help guide the AME when

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rendering aeromedical dispositions for pilots. This review article focuses on the most common intermediate and long-term COVID-19 conditions of aeromedical significance and the corresponding course of actions recommended for the AME.

METHODS

We used the PubMed literature search engine to systematically find and review peer-reviewed articles that focused on the intermediate and long-term effects of COVID-19 infection. We assessed each article searching for clinical signs and symptoms, abnormal laboratory tests, and imaging study findings that persisted for 60 d or more from the time of initial COVID-19 diagnosis. Additionally, we looked for predisposing case risk factors that were associated with long-term sequelae of COVID-19 infection. We then selected those sequelae which we felt could adversely impact pilot performance in flight, based on review of relevant Federal Aviation Administration (FAA), U.S. Air Force (USAF), and U.S. Navy (USN) aeromedical standards.

Chronic COVID-19 signs and symptoms were subdivided based on the particular body organ system affected with a few miscellaneous exceptions. The pathophysiology for such signs and symptoms were summarized. Pertinent recommended aeromedical evaluation and disposition was formulated based on FAA, USAF, and USN aeromedical standards. From the aggregate information collected, we created a table summarizing common chronic COVID-19 sequelae which also shows how far out such sequelae might persist. Finally, merging all information obtained from case reviews, article reviews, and aeromedical standards, we created a risk stratification guide to assist with the evaluation and aeromedical disposition of pilots who have had a severe case of COVID-19 infection, or who have chronic COVID-19 symptoms.

The data used in this study are publicly available and approved for unrestricted general use. No research data were collected specifically for our study. No research team member had access to subject identifiers linked to data; therefore, this study is not considered human subjects research and is IRB exempt (Code of Federal Regulations, 45CFR46, Exemption Category 4).

Mechanisms of COVID-19 Injury

The most common clinical manifestations of COVD-19 are respiratory symptoms, headache, myalgia, and arthralgia.[44,45,94] One study of 214 COVID-19 patients found that 36% developed neurological symptoms such as headache, dizziness, disturbances of consciousness, and neurological deficits. Such disturbances were more common in severely ill patients.[47]

The underlying mechanisms for injury may be due to direct effects of viral damage to cells, immune-mediated pathogenesis, coagulation dysfunction, and/or adverse side effects of treatment.[14,52,81] To gain entry into a cell, SARS-CoV-2 first binds to a receptor known as transmembrane angiotensin-converting enzyme 2, or ACE2. ACE2 is present on a wide range of cell types and tissues, including the lungs, heart, and blood vessels.[80] This receptor acts as a gateway for SARS-CoV-2 to enter type 2 pneumocytes, macrophages, perivascular pericytes, and cardiomyocytes.[28] When SARS-CoV-2 reaches its destination, it rapidly replicates and uses its own mechanisms to cause cell death or functional impairment.[26] SARS-CoV-2 can infect monocytes and macrophages, impairing the immune response. Infected monocytes migrate to tissues where they become infected resident macrophages, allowing the virus to spread to various tissues and organs.[35] C-reactive protein can remain elevated as far out as 2 mo from hospital discharge in 10% of COVID-19 cases).[51]

Not all chronic problems after severe COVID-19 infection may necessarily be due to the viral infection itself. Treatments such as prolonged ventilator use and various medications can cause problems in and of themselves. Even in non-COVID-19 patients, postintensive care syndrome is a recognized term used to describe new or worsening physical, cognitive, and psychological impairments arising from critical illness and persisting after hospital discharge. It affects more than half of patients discharged from intensive care units (ICU).[32,92] Specific complications of protracted critical illness, independent of COVID-19 effects, include ICU-acquired muscle atrophy and weakness, anxiety, depression, and posttraumatic stress disorder.[29,76] Of patients who survive acute respiratory distress syndrome (ARDS), cognitive impairment ranges from 70 to 100% at hospital discharge, to 46–80% at 1 yr, and 20% at 5 yr.[31] AMEs should also consider possible psychosocial reasons for chronic problems after COVID-19 infection.

Impairments of Aeromedical Significance by Body System

Pulmonary effects of COVID-19. SARS-CoV-2 damages the two main functional components of alveolar gas exchange: the integrity of the alveolar epithelium, and the patency of the alveolar microcirculation. This damage decreases alveolar gas exchange by diffusion.[54,57] Additionally, SARS-CoV-2 also causes airway inflammation that reduces airflow, as evidenced by scintigraphy of the upper respiratory tract.[65] The lung damage is caused directly by SARS-CoV-2 as well as the release of proinflammatory cytokines and chemokines that leads to pulmonary fibrosis.[30,43] A postulated mechanism of viral entry is through the host ACE2 receptors that are abundantly present in type 2 alveolar cells.[38] Histopathologic evaluation of eight COVID-19 disease patients who died from the disease revealed significant fibrotic pulmonary parenchymal remodeling, as characterized by fibroblast proliferation, microhoneycombing, and airspace obliteration.[25] Fortunately, overall cardiopulmonary symptoms improve significantly over time.[79]

Prolonged respiratory symptoms in COVID-19 patients include dyspnea, cough, and fatigue.[22,51] One study found that 36% of patients still had dyspnea 100 d after disease onset, with 21% having reduced diffusing capacity, correlating with low exercise capacity.[79,84] Weerahandi et al. found that 74% of patients still had shortness of breath 30–40 d after hospital discharge; 35% of patients without pre-COVID oxygen requirements needed home oxygen after discharge.[89] To get an idea of

how far out COVID-19 related pulmonary problems might occur, one can look at related coronaviruses. Clinical symptoms of COVID-19 are not very different from those of Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), though the fatality rate of 2.3% is much lower than that of MERS and SARS, which are reported to be 34.4% and 9.5%, respectively.[69] If COVID-19 pulmonary symptoms are indeed similar to those of MERS and SARS, one could expect chronic symptoms to persist as far out as 6 mo from diagnosis. A meta-analysis of 28 studies that reviewed long-term clinical outcomes of MERS and SARS revealed that impaired diffusing capacity for carbon monoxide and reduced exercise capacity were common even 6 mo after hospital discharge.[5]

Beyond supportive respiratory therapy, COVID-19 therapy may include combination immunosuppressive therapy consisting of dexamethasone and baricitinib.[12] Long-term corticosteroid exposure can cause hypertension, bone fracture, cataract, weight gain, hyperglycemia, and type 2 diabetes.[72] The most common side effects with baricitinib that are of aeromedical concern are both arterial and venous thromboembolic events.[37] Since most COVID-19 patients will typically not require such long-term use, these side effects will likely not pose aeromedical issues once a patient has recovered from active infection.

Recommended aerospace medical disposition—pulmonary. Pilots are exposed to low ambient pressure and oxygen concentration at high altitude. Since COVID-19 infection adversely affects alveolar gas exchange, the AME should check for dyspnea and fatigue, assess breath sounds, and obtain oxygen saturation via pulse oximetry for any pilot who has had a symptomatic COVID-19 infection. An oxygen saturation of 96% or greater is reassuring. If a pilot has persistent dyspnea, limited exercise tolerance, or an oxygen saturation of less than 96%, a pulmonary medicine consult should be obtained.[27] A pilot with a pulmonary diffusion impairment which adversely affects oxygen and carbon dioxide exchange in the lungs might benefit from an altitude chamber testing prior to return to flight.

If the pilot required hospitalization, this implies that a more severe infection occurred. In such a case, the examiner should find out whether or not supplemental oxygen, a ventilator, and/or ICU care was required. Daher et al. found that 6 wk after hospital discharge, patients who did not require mechanical ventilation are unlikely to develop long-term pulmonary impairments, cardiac impairments, or thromboembolic complications.[17]

The AME should review any available pulmonary imaging studies. A pulmonary function test with diffusion capacity should be obtained. Values of greater than 75% predicted without impairment are reassuring. For values less than 75%, the pilot should be referred to pulmonary medicine for assessment. An exercise tolerance test might also prove useful. Finally, the AME should assess whether or not the pilot is still on any COVID-19 medications that could cause side effects of aeromedical concern.

Cardiac effects of COVID-19. Cardiovascular manifestations of COVID-19 include arrhythmias, acute cardiomyopathies, reduced left ventricular function, myocarditis, thromboembolic disorders, and shock.[21] Cardiac arrhythmias may occur for several reasons. A number of ion channels can be adversely affected in COVID-19, leading to alterations in cardiac conduction and/or repolarization properties, as well as calcium handling. This can predispose to cardiac arrhythmogenesis.[87] In addition, several agents employed for treating COVID-19 infection, including chloroquine/hydroxychloroquine and azithromycin, may prolong the QT interval and lead to polymorphic ventricular tachycardia in the form of torsades des points.[73] Azithromycin, other macrolides, and fluoroquinolones can cause lethal arrhythmias as a potential consequence of QT-interval prolongation.[60]

COVID-19 patients may develop myocardial or vascular dysfunction. Underlying mechanisms include inflammation and renin angiotensin system activation with increased sympathetic outflow, ischemia, and vasculitis. Pre-existing cardiovascular disease is a major risk factor for adverse cardiac outcomes associated with COVID-19 infection.[53,79]

In a prospective study of 100 patients who had severe COVID-19 infection, cardiac magnetic resonance imaging revealed that 78% had cardiac involvement 64–92 d after diagnosis. Independent of preexisting conditions, severity, and overall course of acute illness, 60% had ongoing myocardial inflammation. High-sensitivity troponin T was detectable in 71% of patients and significantly elevated in 5% of patients.[71] Atrial fibrillation (a-fib) and heart failure are two of the most common COVID-19 cardiac complications.[48] While clinically stable patients have a low prevalence of arrhythmias, critically ill patients are at much higher risk.[41,75] ICU admission has been associated with a higher rate of arrhythmias.[86,88]

Recommended aerospace medical disposition—cardiac. Despite a frequent history of cardiovascular disease, 1 study of 3011 hospitalized patients showed that the incidence of cardiac complications during hospital admission is low. Of these patients, 349 were diagnosed with cardiac complications during their hospital stay. These patients tended to be older than those who did not exhibit cardiac problems. The median age of patients with cardiac complications was 72 yr, while the median age of those without cardiac complications was only 66 yr. Patients that developed these complications tended to have a history of dyslipidemia, hypertension, chronic obstructive pulmonary disease, and chronic kidney disease.[48] After an active COVID-19 infection, the AME should review all medications that were given during treatment to see if any might predispose to arrhythmias. The pilot should be asked about cardiac symptoms such as palpitations, chest discomfort, or exercise intolerance. The AME should obtain an electrocardiogram to assess for arrhythmias and ischemia. Any abnormal findings should prompt cardiology evaluation. For pilots who have been hospitalized, an exercise tolerance test should be obtained. If it is abnormal, a referral to a cardiologist should be made. COVID-19 patients with a history of atrial fibrillation may be placed on

long-term anticoagulation therapy.[10] In such cases the respective aeromedical waiver standards should be reviewed.

If more cardiac detail is needed, cardiac magnetic resonance imaging provides a noninvasive method of assessing myocardial ischemia and viability without exposure to ionizing radiation. If arrhythmias are of concern, an ambulatory electrocardiogram event monitor can be obtained 3–6 mo postevent to ensure no recurrence after all antiarrhythmic medication has been discontinued. Monitoring for a minimum of 10 d is preferred. If this is not practical, a 48-h Holter monitor could be obtained instead.[67]

Whether or not patients who have recovered from acute COVID-19 symptoms may still be at risk for cardiomyopathy and cardiac arrhythmias remains to be determined. Other viruses have been known to cause myocarditis that can evolve into overt myocardial dysfunction or sudden death.[59] Patients with preexisting cardiovascular disease are more susceptible to COVID-19 and have a more severe clinical course once infected. Heart failure occurs in at least 10% of patients hospitalized for COVID-19 disease. This percentage rises to 35% or more when patients have severe COVID-19 illness or concomitant cardiac disease.[82] Continued monitoring of cardiac damage after hospitalization may identify patients with cardiac injury and predict complications, as cardiac dysfunction has been identified as a prognostic factor.[40]

The AME should assess the pilot for symptoms of a-fib such as palpitations, lightheadedness, near syncope, dyspnea, or chest pain. Loss of atrial contribution to cardiac output with or without rapid ventricular response may result in hemodynamic symptoms. Such a compromise would be of particular concern in high-G aircraft environments. Paroxysmal and chronic a-fib predisposes a pilot to thrombosis and embolic phenomena. Thus, an echocardiogram would be useful in such cases. A minimum observation time of 60 d or more should be considered, to ensure no recurrence. The FAA requires waiver submission for nonvalvular a-fib/a-flutter whether single or multiple episodes.[27] If a patient is placed on long-term anticoagulation therapy, respective aeromedical waiver standards should be reviewed.[8]

Along with pilot evaluation, the AME should take into consideration the type of aircraft that a pilot will be in control of. High-G loading aircraft will obviously be a problem if the pilot has an arrhythmia such as a-fib, which can cause hemodynamic compromise. Such compromise may not present during sedentary activity but might declare itself upon exposure to high-G maneuvers. Pilots with a history of lightheadedness or arrhythmias who have been medically cleared by standard medical evaluation should ideally undergo human centrifuge testing prior to return to flight in high-G aircraft.

Neurological effects of COVID-19. SARS-CoV-2 is capable of infecting endothelial cells, pericytes, and possibly neurons.[58] It directly or indirectly damages neurons in the central nervous system (CNS) and peripheral nervous system.[87] SARS-CoV-2 enters the brain via the viral S protein, which binds to the ACE2 receptor which is widely expressed in neurons, astrocytes, and oligodendrocytes.[9,11] A second method by which SARS-CoV-2 enters the CNS is through nasal mucosa and olfactory fibers. The blood brain barrier provides a third possible route of entry.[66] Wang et al. showed that SARS-CoV-2 RNA was present in cerebrospinal fluid.[87]

Along with direct neural invasion by SARS-CoV-2, neurological complications are caused by excessive inflammatory responses, including upregulation of cytokines, chemokines, and proinflammatory mediators.[61] A recent case report showed that SARS-CoV-2 infection was associated with symptoms similar to those of multiple sclerosis. This correlates with the fact that SARS-CoV-2 can cause demyelination in the brain and spinal cord.[93]

A study of 214 COVID-19 hospitalized patients in Wuhan, China, found that 36% had CNS signs or symptoms. Neurological damage was predominantly ischemic. The incidence of acute cerebrovascular disease was 5.7% in patients with severe disease, but only 0.8% in those with mild disease.[52] Another study found that up to two-thirds of COVID-19 hospitalized patients had shown evidence of CNS damage. The study also found that neurological damage was mainly ischemic. In some cases, CNS damage was found to be hemorrhagic or encephalitic in nature.[58] Of patients with COVID-19 associated cerebrovascular accidents (CVAs), 5.9% had the event an average of 10 d after symptom onset.[4] A meta-analysis found that though the frequency of CVA among patients having COVID-19 infection was low, those with concomitant COVID-19 infection and stroke suffered from a more severe infection and had a poorer prognosis with a higher mortality rate (46.7%) than COVID-19 alone. Many COVID-19 patients shared the common traditional risk factors for CVA.[42]

COVID-19 neurological complications also include a high incidence of acute disseminated encephalomyelitis.[68,91] A few cases have been associated with Guillain-Barré Syndrome (GBS).[90] A literature review of 765 COVID-19 patients showed that 18% had neurological symptoms and complications, including encephalopathy, encephalitis, acute myelitis, cerebrovascular pathologies, and GBS.[91] Cognitive function can be adversely affected since cerebral white matter is particularly vulnerable to ischemia damage from COVID-19.[58] Associated neurocognitive symptoms include chronic attention and memory impairment related to hippocampal and cortical damage, as well as learning deficits.[83] Cognitive follow-up is especially important in patients who develop cerebrovascular and neurological complications during the acute illness.

COVID-19 has also been correlated with seizures; however, the risk seems to be low. A study of 6147 COVID-19 patients found that 0.08% had new onset seizures.[20] Patients with COVID-19 may develop seizures as a consequence of hypoxia, encephalopathy, neuroinvasion, cerebral damage, organ failure, metabolic derangements, or cytokine storm.[6,85] Such problems would mainly be expected to be seen in critically ill patients. COVID-19 infections are known to occasionally cause prolonged cases of anosmia.[22,34,36]

Recommended aerospace medical disposition—neurological. Per USAF standards, transient ischemic attack (TIA) and CVA

are disqualifying for all flying classes. Waivers are generally not considered unless a correctable cause is discovered and treated. Strokes leave a potential seizure focus. The incidence of new onset post-CVA seizures declines over time, with studies suggesting the risk becomes aeromedically acceptable after 2 to 3 yr. Any manned aircraft pilot waiver recommendations after a TIA/CVA are almost invariably limited to non-high-performance, multicrew aircraft, often with further restriction of another fully trained pilot to be present during aircraft operation.[2] FAA waiver requirements after TIA/CVA include neurological evaluation, magnetic resonance angiogram or computed tomography angiogram of the head and neck, carotid artery ultrasound, 24-h Holter monitor, and M-mode/2-D echocardiogram. An observation period of up to 2 yr is also frequently required.[27]

Certain biomarkers may be useful as predictors of long-term COVID-19 sequelae. Lower lymphocyte levels and platelet counts have been found to be more common in patients presenting with CNS symptoms compared to those without CNS involvement. Patients with severe disease were also found to possess higher levels of D-dimer, a marker of thrombophlebitis, hypercoagulability, and endogenous fibrinolysis. This could possibly explain why acute cerebrovascular disease more commonly develops in such patients. Some have suggested that anti-inflammatory pathways could potentially be targeted early on in the course of the illness, in order to reduce the risk of acute cerebrovascular disease.[46,52,64]

New onset COVID-19 related seizures are rare and typically of concern only during the acute phase of the disease; therefore, long-term antiseizure medication therapy is often not needed unless a subsequent seizure happens.[6] Truly provoked seizures may also be aeromedically acceptable for waiver consideration on an individual basis. Evaluation should include magnetic resonance imaging, electroencephalogram, and neurology evaluation.[2] A single seizure clearly attributable to a toxic cause may be considered for waiver.[1]

For cases of peripheral neuropathy such as GBS, the FAA requires that a pilot submit a current functional status report, including degree of impairment as measured by strength, range of motion, and pain, medications with side effects, and all pertinent medical reports.[27] Per USAF standards, GBS is disqualifying for all flying classes, including air traffic control personnel. Clearance for flight requires that GBS was limited to a single episode, subsided at least 1 yr before examination, and there are no residual effects which could be expected to interfere with normal function in any practical manner. The 1-yr observation period is specified to allow for maximal functional recovery since most GBS recurrences or transformation to chronic inflammatory demyelinating polyradiculoneuropathy will occur within this time frame.[2]

For cognitive concerns, neuropsychological evaluation should be ordered. Additionally, flight simulator check rides with various scenarios could be used. Other minor neurological symptoms could potentially cause aeromedical problems. Anosmia secondary to COVID-19 can adversely affect a pilot's ability to receive early warning of gas spills, oil leaks, or smoke. Vertigo would obviously be a contraindication for flight status.

Hematologic effects of COVID-19. A major concern with severe COVID-19 disease is the development of a prothrombotic state, which can manifest clinically as deep venous thrombosis (DVT) and pulmonary embolism (PE).[23] SARS CoV-2 targets endothelial cells and pericytes, causing endothelial cell dysfunction, vascular leakage, and immune activation. Aberrant activation of the immune system can in and of itself also cause endothelial injury, resulting in excess thrombin generation and dysregulation of fibrinolysis and thrombosis.[15] This can lead to disseminated intravascular coagulation.[58] Elevated D-dimer, which is a biomarker for intravascular coagulation, has been found to be elevated in 30% of patients as late as 2 mo after hospital discharge.[51]

A study of 1988 COVID-19 patients showed that the rate of thromboembolic complications is high. The prevalence of DVT was 19.8%, while the prevalence of PE was 18.9%. Regression models have shown that increasing age is associated with a higher prevalence of venous thromboembolic events, while a higher body mass index is associated with an increased prevalence of PE.[19]

Recommended aerospace medical disposition—hematologic. For pilot applicants with a history of DVT, PE, and/or hypercoagulopathies, the FAA requires a summary of the medical condition, treatment plan, medications, any side effects experienced, and prognosis in order to determine whether the applicant can be given a Special Issuance for flight. If the applicant is on warfarin (Coumadin), the AME should obtain a minimum of monthly International Normalized Ratio results for the immediate prior 6 mo. If using direct oral anticoagulants (DOACs) such as apixaban (Eliquis), rivaroxaban (Xarelto), dabigatran (Pradaxa), and edoxaban (Savaysa), the applicant should obtain a statement from the treating physician with details of the underlying condition, medication tolerance, the presence or absence of side effects, any bleeding episodes requiring medical attention, and any breakthrough occurrence/recurrence of DVT or PE.[27]

Per USAF standards, any history of PE is disqualifying for all flying classes. Additionally, any history of DVT is disqualifying for certain flight classes and air traffic control duty. Recurrent episodes of DVT are disqualifying for all flying classes and air traffic control duties. The use of extended anticoagulation is independently disqualifying for all flying classes.[2]

Aeromedical waivers for venous thromboembolism may be considered after completion of 3 mo of anticoagulation. Historically, warfarin was the anticoagulant of choice for pilots requiring extended anticoagulation since monitoring and reversal agents are readily available. However, the management for warfarin can be burdensome, given the need for frequent laboratory testing and dose adjustments. DOACs do not require monitoring or dose adjustments. These short-acting medications have similar safety and efficacy to warfarin. Additionally, reversal agents are available for apixaban, dabigatran, and rivaroxaban. Individuals treated with DOACs can be considered for an aeromedical waiver.[2] As a precaution, a pilot who has recovered from thrombotic complications might start out on short duration flights, and then gradually extend flight times.

Psychiatric effects of COVID-19. Due to enforced social isolation and self-quarantine measures, COVID-19 infection is predicted to promote psychiatric disease symptoms. Recent studies have shown that COVID-19 disease has the potential to cause serious mental illnesses such as depression, anxiety, and sleep disorders.[70] Psychiatric problems such as anxiety and depression were not uncommon in the early recovery phase of COVID-19; however, these improved over time in a majority of patients.[13] One-fourth of patients had posttraumatic stress disorder, which has been found to be the most prevalent long-term psychiatric condition.[50] In a study of 40,469 COVID-19 patients, 0.2% had suicidal ideation.[62]

Recommended aerospace medical disposition—psychiatric. Depressive disorders are associated with decreased concentration, inattention, indecisiveness, insomnia, fatigue, agitation, and sometimes psychosis. These are incompatible with aviation duties. While depressed patients have a 15% risk for suicide, fortunately, acute major depression is treatable in 80% of patients. The USN considers aeromedical waivers for single episodes of depression. Information needed for waiver consideration should ideally include a clinical summary by the AME documenting all prior symptoms, absence of persistent features, course of the disorder, medication use, and current level of functioning. Additionally, mental health treatment notes should be reviewed.[1] The AME should also keep in mind that flying can be stressful, which could pose a problem for COVID-19 recovering pilots who have anxiety and posttraumatic stress disorder.

Constitutional signs and symptoms of COVID-19. Persistence of symptoms or the development of new symptoms late in the course of COVID-19, is an increasingly recognized problem known as Long Haul COVID.[56] The cause of such symptoms may include unmasking of underlying comorbidities, residual damage from acute infection, persistent or restricted viral replication, or a persistent immune reaction.[63] Long Haul COVID can produce nonspecific symptoms such as breathlessness, chest pain, palpitation, and orthostatic intolerance.[18] Other symptoms include mental fogging, sleep disturbances, and exercise intolerance. Such cases may exceed 100 d.[63] One study of 384 COVID-19 patients found that 53% had persistent breathlessness, 34% had persistent cough, and 69% had persistent fatigue approximately 2 mo after hospital discharge.[18]

Numerous studies have demonstrated that COVID-19 patients have reduced levels of physical function and fitness post-infection compared to healthy controls. Some patients experienced such impairments up to 1 yr after initial infection. A randomized controlled trial found that aerobic and resistance training significantly improved physical function and fitness post-infection.[74] Rehabilitation has beneficial effects in both the acute and recovery stages, including improving respiratory function, exercise endurance, and psychological support.[45]

Recommended aerospace medical disposition – constitutional signs and symptoms. Ongoing fatigue is of clear aeromedical significance. Pilots presenting with persistent fatigue should avoid long duration flights. Those with muscle weakness and fatigue from COVID-19 and/or prolonged ICU stay should be carefully evaluated prior to return to a high-G environment, which is much more physically demanding than flying in low-G aircraft such as wide-body commercial passenger or military transport aircraft. Narcolepsy is disqualifying

	CATASTROPHIC	CRITICAL	MODERATE	MARGINAL
FREQUENT			WEAKNESS FATIGUE	HEADACHE
PROBABLE				
OCCASIONAL		THROMBOEMBOLISM SHORTNESS OF BREATH DEPRESSION		COUGH PTSD
REMOTE	ARRHYTHMIA HYPOTENSION	DIZZINESS BRAIN FOG	NEUROPATHY INSOMNIA	ANOSMIA
IMPROBABLE	SEIZURES NEUROLOGICAL DEFICITS			FEVERS

Fig. 1. COVID-19 sequelae and aeromedical risk stratification.

under all standards due to rapid onset without clear indicators. Other conditions that have insidious degradation of vigilance to the individual such as insomnia and obstructive sleep apnea, are considered disqualifying for flight duties per USAF and USN standards when not addressed. Vigilance testing may be warranted. Demonstrable orthostatic hypotension on clinical exam warrants further work-up, including cardiology referral. Pilots with Long Haul COVID should ideally not be cleared for flight status until all significant symptoms have resolved. The AME should analyze the pilot's condition holistically, in order to determine when such symptoms are mild enough to enable return to flight status. Such evaluation should include a review of recent and current COVID-19 medications. One such medication is remdesivir, which has been approved for treatment of hospitalized COVID-19 patients. It is an adenosine analog that has broad-spectrum antiviral activity.[3,49,55,77,78] Common side effects of remdesivir include rash, diarrhea, hypotension, abnormal liver function, and renal impairment. Serious adverse events include acute kidney injury, septic shock, and multiorgan failure.[24] Most likely, any pilot presenting to an AME for a return to flight duty examination would likely have completed remdesivir treatment and recovered from any serious adverse effects.

Coronaviruses may cause dysregulated host immune responses. Exploratory studies have suggested that interleukin-6 levels are elevated in cases of complicated COVID-19. A meta-analysis by Coomes et al. found that in patients with Covid-19, interleukin-6 levels are significantly elevated and associated with adverse clinical outcomes.[16] C-reactive protein, a marker of inflammation, can remain elevated in 10% of patients as far out as 2 mo from hospital discharge.[51] Multiple studies have shown increased cardiac troponin I and T in COVID-19 patients, especially those with severe disease.[8] Of particular note, repeat PCR testing is not recommended. Immunoglobulin serology also has no role in determining disposition. Positive testing may suggest past infection or even immunization, but currently there are insufficient data from which to extrapolate and determine immune status or adequate viral clearance.

Overall Aeromedical Disposition and Risk Stratification

Many COVID-19 patients will likely recover from active infection with no prolonged symptoms. For those with

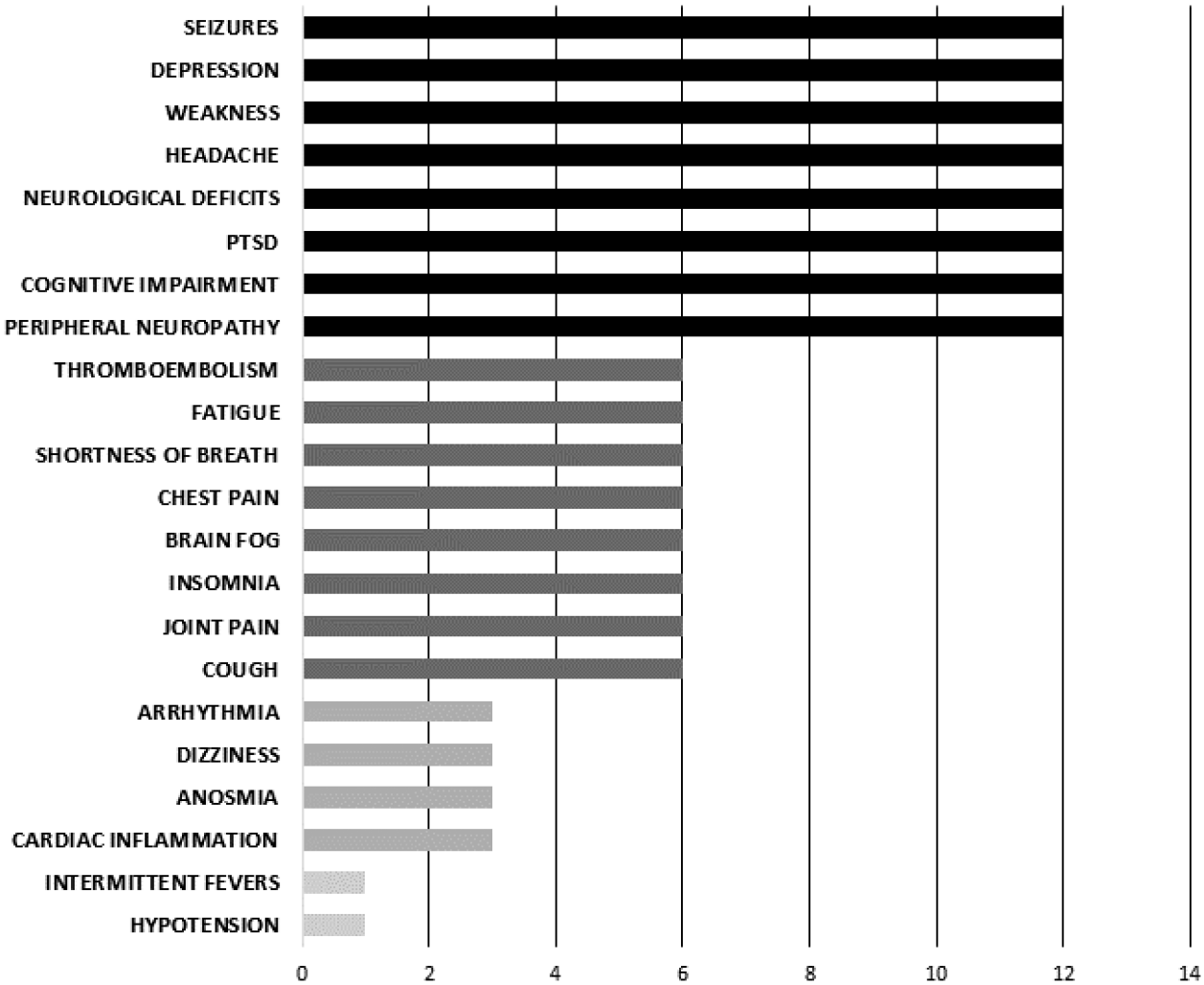

Fig. 2. COVID-19 long-term symptoms and possible duration in months.

prolonged symptoms, the AME should review fitness for flight duty, keeping in mind the basic principles of risk management as well as the concept of how man, machine, and the environment interact with one another. General factors to consider when stratifying risk include severity and probability. Severity is the amount of harm a hazard could create and is often ranked on a 4-point scale: negligible, marginal, critical, and catastrophic (see **Fig. 1**). Probability is the likelihood of the hazard occurring and is often ranked on a 5-point scale: improbably, remote, occasional, probable, and frequent. Multiplying severity and probability can give one an idea of the risk involved. Based on the results of a risk calculation, the AME can then make an informed decision as to when to medically clear a pilot for flight duty.

Medical impairments that may be fairly benign for many nonflying occupations can be problematic or catastrophic in the unique aerospace environment. With regards to the pilot, COVID-19 specific predictors of prolonged medical sequelae include clinical severity of the illness, pilot age, the presence of comorbid medical conditions, and certain medication use. Studies have shown a relationship between the presence of other comorbidities and severity of disease.[28,38] The severity of post-COVID-19 manifestations is related to the severity of acute COVID-19 infection.[39] The risk for severe infection increases with advancing age.[28] Thus, one would expect to find less serious cases within the military, where pilots are typically 18 to 35 yr old. The age factor is more of concern when evaluating civilian pilots. Recent studies show that within the United States alone, 23% of all pilots are 60 yr of age or older. Within this age group, 33,213 are commercial pilots and 43,012 are airline transport pilots.[7]

The AME should inquire whether or not the pilot required hospitalization and how long any such hospitalization was for. Additionally, one should inquire whether ICU admission and/or a ventilator was needed. The AME should find out which organ systems were critically affected during the COVID-19 illness. Such information can help predict possible system-specific problems. Medications used to treat the illness may have aeromedical significance. If after a thorough medical evaluation the aeromedical disposition remains uncertain, an AME might consider assessing global medical status through the use of a flight simulator and/or in an altitude chamber. A check ride in an actual aircraft with another qualified pilot might also be considered. The AME should also take into consideration whether or not a pilot routinely flies solo, or with another qualified pilot.

Final aeromedical clearance for flight. While the above recommendations provide generalized recommendations that AMEs may use to assist in deciding when to safely return a pilot to flight status, they are no substitute for sound clinical judgement. Additional work-up, testing, and specialty consult may be required on a case-by-case basis. Care should be taken to differentiate between new onset medical conditions due to COVID-19 illness (**Fig. 2**) and those that are due to unrelated underlying conditions. The understanding of COVID-19 disease mechanisms is still evolving. Continued data collection and research studies will enable a better prediction of long-term COVID-19 sequelae and their aeromedical implications.

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