RECOVERED: WHAT DOES IT MEAN POST-COVID-19?

Abstract

On March 11, 2020, the World Health Organization officially declared COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), to be a pandemic. According to the Johns Hopkins Coronavirus Resource Center dashboard,[1] more than 82 million people worldwide have been infected (approximately 20 million in the U.S. alone), upward of 1.8 million have died of it, and the spread shows no signs of slowing.

On the plus side, close to 47 million cases have recovered, meaning that most who get COVID-19 do not die. Recovery, however, has not turned out to mean restoration to full health in many cases.

From an insurance standpoint, when someone is underwritten for life insurance after a medical event, it is usually only done if that person is considered "fully recovered" – that is, if it can be inferred that no lasting health problems or symptoms exist. Any residual impairments can be accounted for with a substandard premium. However, this may not be simple when underwriting living benefits products, particularly disability insurance.

In this article, the unique aspects of coronavirus recovery are examined across the spectrum of individuals who have recovered from these viruses, including from COVID-19 – whether asymptomatic, severe, or critical – and their health outcomes.

COVID-19: It's Not "Just the Flu"

Research thus far is showing that COVID-19 has the potential to affect multiple organs in the body. It is best known for causing a range of degrees of respiratory symptoms, including respiratory failure and Acute Respiratory Distress Syndrome (ARDS). It also has cardiac, cardiovascular, thromboembolic, and inflammatory complications, and autopsies have shown that the virus can disseminate systemically: in addition to the respiratory tract, SARS-CoV-2 RNA has been found in the kidneys, liver, heart, and brain.

It is not yet clear whether the presence of the virus at these sites has a direct cytopathic effect.[2, 3] Presently, the data regarding long-term effects of COVID-19 are limited, but given its potential for multisystem involvement and the range of severity of infection, variable recoveries and the possibility of long-term sequalae can and should be expected.

Severe COVID-19 Infection

COVID-19 is characterized by its many degrees of respiratory symptoms. Cough and shortness of breath can progress to "severe." Severe is generally thought of as respiratory failure and ARDS, requiring admission to an intensive care unit (ICU), intubation, or mechanical ventilation.

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Autopsy studies on COVID-19 deaths have shown varying degrees of diffuse alveolar damage, similar to what was seen with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). The autopsies also revealed marked fibrotic lung parenchymal remodeling. The cause of this fibrosis is not currently clear but it is likely multifactorial in nature and occurring as a result of the virus, the ensuing cytokine cascade, and the treatments (primarily ventilation). Researchers are concerned that these fibrotic changes are unlikely to regress in survivors of severe COVID-19.[4, 5] Therefore, it is important to consider the long-term mortality and morbidity implications of this fibrosis in those who survive a severe COVID-19 infection.

Recovery From Non-COVID-19 ARDS

To ascertain the long-term effects of ARDS due to COVID-19, it would be reasonable to look at the long-term effects of ARDS that are not due to COVID-19 (non-COVID-19 ARDS). A literature review by Chiumello, et al.[6] of 26 studies on long-term outcomes of patients with ARDS concluded that those who survived non-COVID-19 ARDS had only mild radiological pulmonary abnormalities and had recovered pulmonary function. However, despite the paucity of clinical abnormalities, ARDS survivors had a reduced quality of life, characterized by persistent exercise limitations (shown in the six-minute walk test) and neuropsychological disorders up to five years after recovery.[6] Data from a study by Burnam, et al. also suggests that pathological fibroproliferation in the lungs plays a critical role in both short-term and longer-term outcomes in ARDS patients, along with extrapulmonary complications such as depression and neuromuscular weakness.[7] The following sections will outline some of the significant findings in survivors of non-COVID-19 ARDS.

Radiographic Abnormalities

Radiologic studies of the lungs of non-COVID-19 ARDS patients show ground glass opacity (GGO) in the early phases (7.7 +/- 6.2 days after intubation), usually in nondependent regions, and consolidation in dependent regions. In the late phase (median five months post-ARDS resolution), the reticular pattern is the most frequent pattern seen in 85% of subjects, primarily in the nondependent regions.[8] The more time spent receiving mechanical ventilation, the greater is this late reticular pattern.[8]

These lung abnormalities involve only a small fraction of lung parenchyma, with one study showing that the fine reticular pattern was seen in <25% of total lung volume at six months after an ARDS diagnosis.[9] Five years post-ARDS, the majority (75%) of survivors showed only minor nondependent fibrotic abnormalities on high-resolution CT (HRCT) scans.[10, 11] This may suggest that ongoing post-ARDS functional impairments are more likely due to a neuromuscular component than significant structural lung changes.[10]

Pulmonary Dysfunction

The three main methods used to evaluate pulmonary function are: spirometry, which evaluates static and dynamic lung volumes; lung diffusion capacity for carbon monoxide, which looks at the capacity for gas exchange across the alveolar barrier; and the six-minute walk test, which depends on lung and cardiac function along with muscle strength.

Spirometry values in non-COVID-19 ARDS survivors can be quite variable. Normal values at six months have been reported,[12] with other studies showing 6% to 43% of ARDS survivors having an obstructive pattern and 15% to 58% having

a restrictive pattern within the first year after recovery.[9, 13, 14] The restrictive pattern could be due to structural lung changes, such as fibrosis, and a neuromuscular component. It should be noted that at three to five years follow-up, normal or near-normal volumes via spirometry were seen.[11]

Diffusion capacity appears to be the single functional variable most often compromised in ARDS survivors.[6] Studies show a slight improvement in year one, from 62% to 63% of predicted value to 72% to 77%.[12] At three and five years follow-up, the values were just slightly below or at the lower limits of normal, at 77% and 80% of predicted, respectively.[11]

Despite normal to minimal findings on HRCT and pulmonary function testing, six-minute walk test results showed a reduction in function that persisted at five years post-ARDS. In the first year post-discharge, the distance walked increased from 49% to between 66% and 75% of predicted. However, at five years post-discharge, no further improvement was seen.[11, 12]

Health-Related Quality of Life

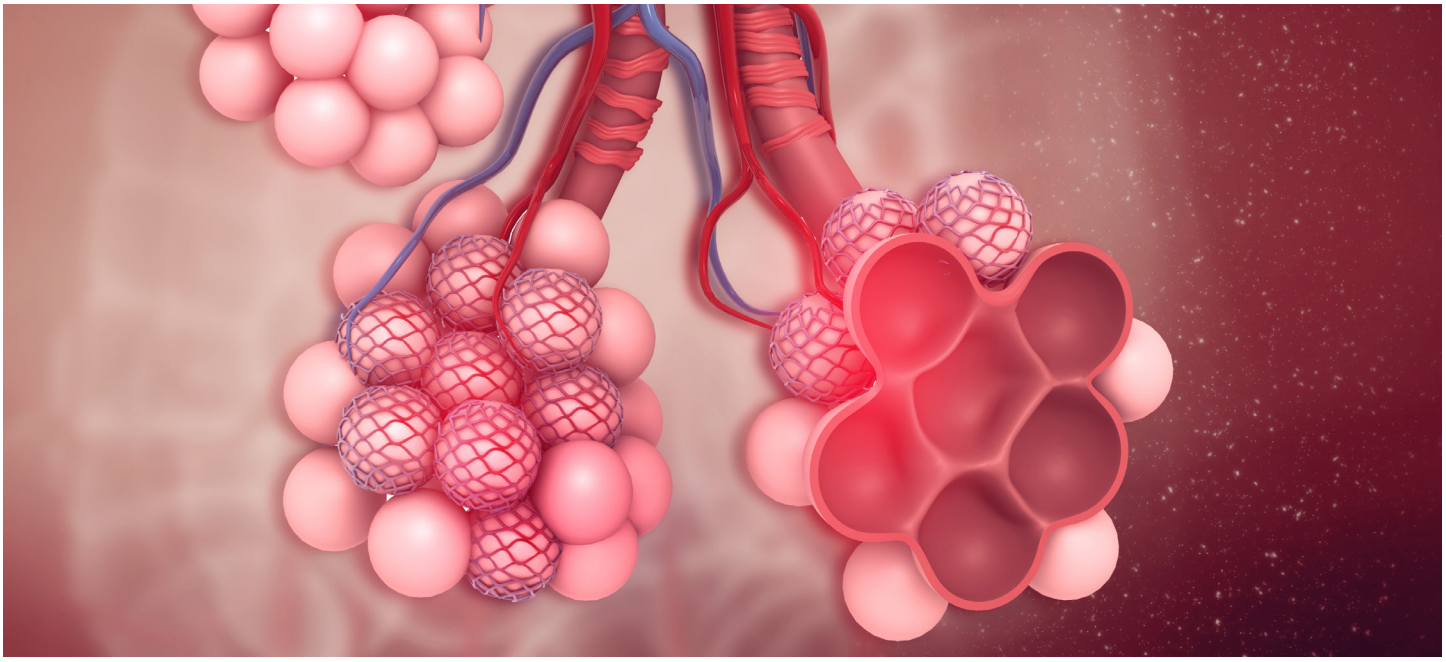
Studies show that most survivors of non-COVID-19 ARDS experience impaired health-related quality of life (HRQL) for years after their acute illness. At six months after hospital discharge, 38 survivors of non-COVID-19 ARDS showed lower HRQL compared to the general population. This was mainly due to lower scores in relation to mobility, energy, and social isolation.[7] Survivors did not return to their predicted levels of physical function at five years follow-up. As for younger survivors, they did have a greater rate of recovery than did older, but they never did return to normal.[11]

Neuropsychiatric Disability

Several psychiatric and neurocognitive issues can occur both in non-COVID-19 ARDS survivors who would have been admitted to an ICU and in persons admitted to the ICU who did not have non-COVID-19 ARDS. This condition is known as post-intensive care syndrome.

Post-ARDS psychiatric dysfunction primarily manifests as post-traumatic stress disorder (PTSD) and depression. Incidence of PTSD after non-COVID-19 ARDS has been shown to be highest at time of discharge from the ICU or hospital (43.5% in one group). Over time, this number has improved, but 23.9% still reported PTSD at eight years post-discharge.[15]

Depression has also been reported at significantly higher rates in non-COVID-19 ARDS survivors, with 50% reported in these survivors one year after discharge.[16] Longer-term studies have shown that 51% of survivors reported an episode of physician-diagnosed depression, anxiety, or both, between two and five years after discharge.[11]



The causes of these long-term psychological issues are multifactorial and due to the nature of the critical illness prompting admission to the ICU. Factors can include hypoxemia, activation of the hypothalamic-pituitary axis, elevated cytokines, and organ dysfunction, as well as administration of medications such as epinephrine, norepinephrine, and sedatives.[6] This would suggest that some of the psychiatric dysfunction could be organic in nature and may not improve in the long term.

Long-term neurocognitive dysfunction can also be seen in non-COVID-19 ARDS survivors and has been shown to manifest as issues with attention, memory, mental processing speed, and executive function. Cognitive impairment, especially with executive dysfunction, was shown to be present in 55% of ARDS survivors at one year after discharge.[17] Another study showed that 100% of ARDS survivors at discharge experienced cognitive impairment, which included issues with memory, attention, concentration, and/or global loss of cognitive function. Follow-up testing of this group one year later showed 30% of the survivors still exhibited a global cognitive decline and 78% had issues with at least one of the following: impaired memory, attention, concentration and/or decreased mental processing speed.[18] The cognitive impairments seen in these survivors included problems remembering appointments, remembering what to buy at the store, recalling what people said to them, recalling whether they took their medications, and remembering and following directions.[18] The causes of the brain injury leading to this cognitive impairment are multifactorial and may be due to hypoxemia, emboli, inflammation,[18] drug toxicity, and/or other etiologies.

Health care utilization in survivors of non-COVID-19 ARDS does not return to baseline levels after discharge.

Post-ARDS Insurance Implications

Several issues can prevent full recovery after ARDS. From an insurance standpoint, what does this mean when a person is applying for life or living benefits coverage?

Long-Term Mortality

Over the years, there has been a significant decrease in hospital mortality due to ARDS, but do ARDS survivors have a higher long-term mortality rate? Although their long-term mortality would appear to be higher than expected, this could be due to previous comorbidities and age and not the acute illness.[6, 19] Research from Chiumello, et al. and Wang, et al. showed 44% mortality one year after hospital discharge versus hospital mortality of 24%, irrespective of the ARDS etiology. Those more likely to die in the first year were significantly older and were more likely to have been discharged to a nursing home or another hospital.

A prospective matched parallel cohort study from Davidson, et al., with a longer follow up period (median 753 days; range 8 to 1,503 days), showed similar findings. This study looked at patients with ARDS associated with trauma or sepsis who survived and compared them to a control group of critically ill discharged patients who did not develop ARDS. Again, it was shown on follow-up that patient mortality was not influenced by the severity and presence of ARDS but rather by their age and comorbidities.[20]

Return to Work

The inability to return to work is common in persons who have survived an ARDS-related stay in the ICU. One large meta-analysis of 51 studies (7,267 patients) found that only 33%, 55%, and 56% of previously employed patients returned to work by three, six, and 12 months, respectively, post-discharge.[21]

Another systematic review and meta-analysis of 10,015 persons who were previously employed and discharged after an ICU admission found that at three, 12, and 42 to 60 month follow-ups, return to work prevalence was 36%, 60%, and 68% respectively. There was no significant difference in outcomes for ICU stays between ARDS and non-ARDS patients. Following return to work, 20% to 36% of the ICU survivors experienced job loss, 17% to 66% changed their occupation, and 5% to 84%

incurred worsening employment status (e.g., their work hours were cut).[22] Similarly, 5,762 ICU survivors in Denmark reported a cumulative incidence of job loss after return to full-time work of nearly 50% at a three-year follow-up after discharge from the ICU.[23]

From these studies, it can be inferred that for COVID-19 patients who had ARDS or were admitted to the ICU, return to work may not be sustainable long-term. This would imply that a certain period of employment stability in COVID-19 survivors who were diagnosed with severe disease may be necessary before disability insurance can be offered.

Post-ARDS Hospital Care Utilization

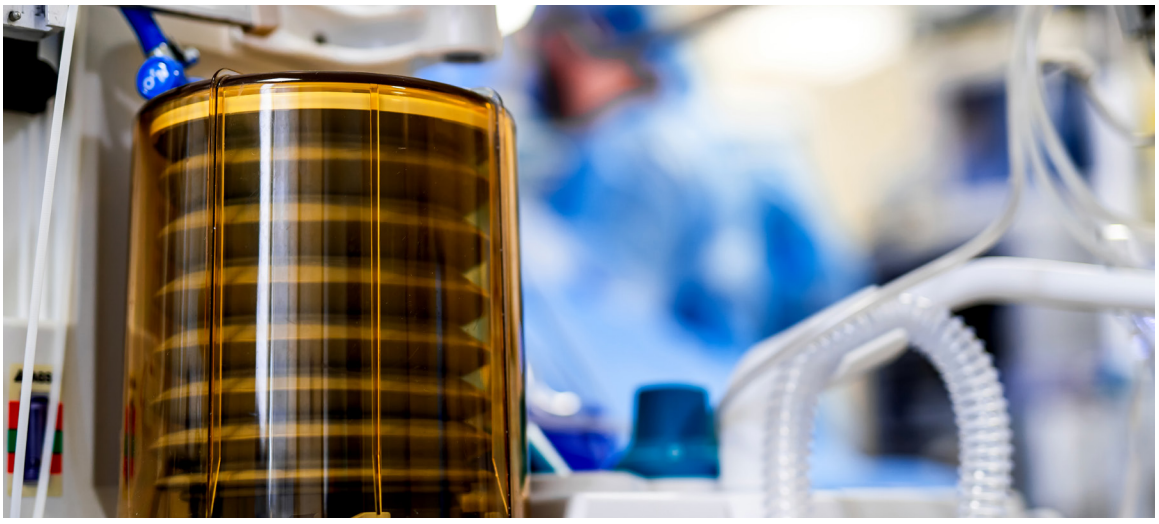
Based on the previous findings, it would not be surprising to find that health care utilization in survivors of non-COVID-19 ARDS does not return to baseline levels after discharge. A five-year follow-up of 109 ARDS survivors after discharge from the ICU found their health care costs were higher than those incurred by healthy workers and closer to the low end of the range of costs among patients with chronic disease.[10] This group was relatively young (median age at enrollment 45 years), previously working, and had only modest coexisting disorders.

The same study also showed that health costs after discharge were associated with the burden of illness at the time of ARDS. The conclusion was that ARDS survivors do suffer long-term from chronic disease, the degree of which is dependent on the development of new disability and/or the worsening of preexisting organ dysfunction.[11]

Long-Term Outcomes in Non-COVID-19 Coronavirus Infection Survivors

Long-term outcomes for persons with severe SARS and MERS (severe being admission to the ICU, intubation, or mechanical ventilation) are similar to the findings above. A meta-analysis of 23 studies which included 2,820 patients reported high rates of mental health outcomes, including PTSD (39%), depression (33%), and anxiety (30%), at six months following infection. Impaired diffusion capacity for carbon monoxide and reduced exercise capacity were also noted along with low HRQL at 12 months after discharge, with only slight improvements beyond six months.[24]

Tansey, et al.'s 2007 study reported that 17% of the SARS and MERS survivors had not returned to work and a further 9% had not returned to their pre-SARS level of work one-year post discharge. The median age of this group was 42, only 16% had been admitted to the ICU, and 9% of the total study group required mechanical ventilation. One cause of these low return-to-work levels could be chronic fatigue, which was reported in one study by 60% of SARS survivors at 12 months[25] and in another study, by 40% at their 40-month follow-up.[26]



Is there a difference in outcome between SARS survivors who required ICU admission (whether they had ARDS or not) and those treated on medical wards? A two-year follow-up study by Ngai, et al. of 55 SARS survivors, mean age 44.4, 21.8% of whom were admitted to the ICU, with 7.3% of the total study group requiring mechanical ventilation, showed that SARS survivors who had been admitted to ICUs for ARDS had significantly lower lung function versus those who had been treated on the medical wards. There was no significant difference between the results for the two groups for the six-minute walk test and the HRQL assessments. The study's findings were also similar comparing persons who had been intubated and those who had not. Significantly lower lung function in the intubated group was noted, but no significant difference was seen in the results of six-minute walk tests and HRQL assessments: both groups had measurements that were lower than those of normal subjects.[27]

Overall, SARS and MERS had significant physical and mental impacts with long-lasting consequences to survivors. This applied to people admitted to the ICU and to people with moderate disease who were only admitted to the hospital ward.

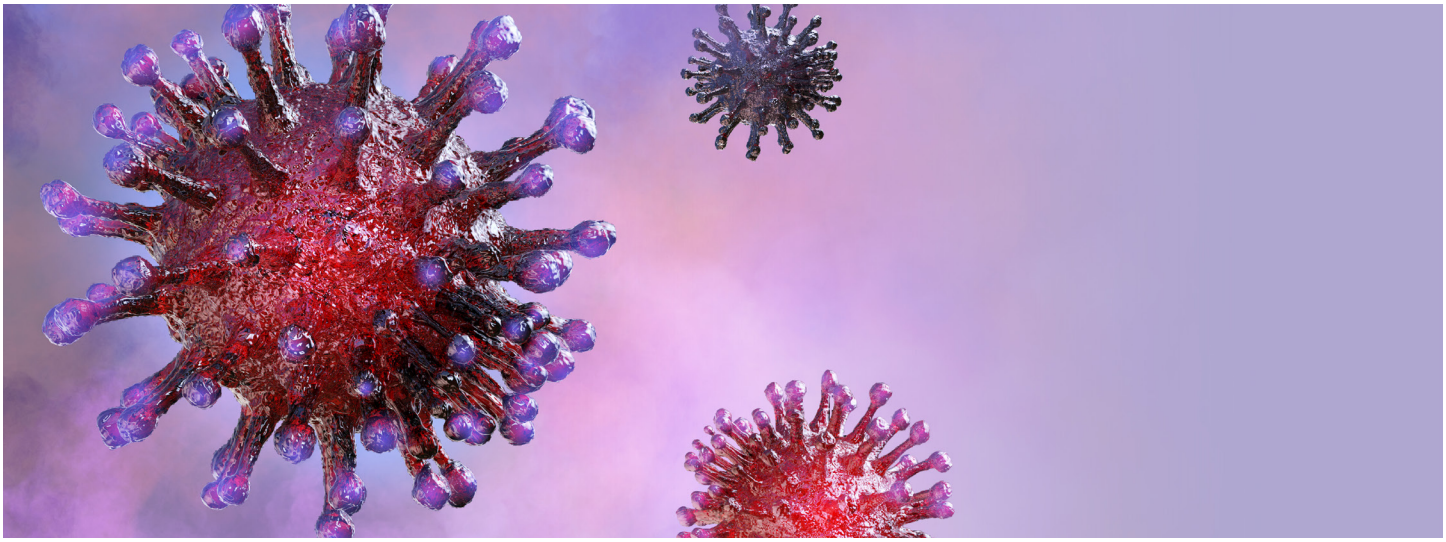
Survivors of Symptomatic COVID-19 Infection

Given the above data, it can be reasonably assumed that survivors of a severe COVID-19 infection (those who experienced respiratory failure and ARDS, and the subset of this group requiring ICU admission, intubation, or mechanical ventilation) would have similar outcomes to survivors of ARDS who did not have COVID-19. Having said this, it may well be that survivors of severe COVID-19 could suffer more chronic residual effects given the unique cardiac, cardiovascular, thromboembolic, and inflammatory complications of COVID-19.

Only a small percentage of patients with COVID-19 are ever admitted to the ICU, and data is starting to emerge about long-term sequalae occurring in COVID-19 survivors irrespective of pneumonia severity. One study of 143 COVID-19 survivors of mean age 56.5 years, only 13% of whom had been admitted to an ICU, found that nearly 90% of the study group were experiencing persistent symptoms (fatigue, dyspnea, and joint pain) two months after the onset of their illness. At a mean of 60.3 days after onset of first COVID-19 symptoms, 12.6% were completely free of any COVID-19-related symptoms, 32% had one or two symptoms, and 55% had three or more. In addition, 44.1% reported a worsened quality of life post-COVID-19 onset.[28]

The DISCOVER (Diagnostic and Severity markers of COVID-19 to Enable Rapid triage) study, an observational study from the University of Bristol in the U.K., reported similar findings. The participant sample included 110 patients, ranging from 46 to 73 years of age, who were followed for a median of 83 days after hospital admission and 90 days after onset of their COVID-19 symptoms. The median age of persons with mild symptoms (defined as no need for oxygen or enhanced care during stay) was 47 years, and 57 years for those with moderate symptoms (defined as requiring oxygen during their hospital stay). The mild group was hospitalized for a median of two days and 59% reported ongoing symptoms at follow-up. People with moderate symptoms were hospitalized for a median of five days and 75% reported ongoing symptoms at follow-up. The most persistent symptoms for both groups at the three-month follow-up were breathlessness, excessive fatigue, myalgia, and insomnia.[29]

It is worth noting that in the mild group, 48% were male, median BMI was 31.2 (obese), and comorbidities were common: 22% had heart disease, 15% had chronic lung disease, and 15% had hypertension. In the moderate group, 68% were male, median BMI was 32.5, and comorbidities were even more common: 25% had hypertension, 25% had chronic lung disease, 18% had type II diabetes mellitus, and 17% had heart disease. At follow-up, only patients with moderate to severe symptoms had abnormal findings on X-ray, clinical examination, or spirometry.[29]



The most striking finding from the DISCOVER study was the persistence of COVID-19 symptoms many weeks after onset or hospitalization, despite improvements in clinical and radiological parameters such as chest radiograph and blood tests. For instance, 59% of patients who did not require oxygen in the hospital had ongoing symptoms. HRQL scores for these individuals also demonstrated a reduction in reported health status across all domains compared to population norms, with particular deficits in perceived ability to perform their physical roles and vitality, while mental wellbeing scores were similar to U.K. population norms.[29] In contrast, more than 90% of outpatients with influenza (flu) recover within two weeks after testing positive.[30]

Survivors of Asymptomatic COVID-19 Infection

Unique to COVID-19 is that some asymptomatic infections have been linked with abnormal findings on chest computed tomography scans.[31] In addition, the presence of end organ damage has been noted in recovered persons who were reported to be asymptomatic or only experiencing minor symptoms.

One study examined the outcome of cardiovascular magnetic resonance imaging (CMR) in 100 patients who had recovered from COVID-19 at a median of 71 days after positive COVID-19 testing. Of these patients, 54 were male, the median age was 49, and only 33 had required hospitalization. Their CMRs revealed cardiac involvement in 78 patients and ongoing myocardial inflammation in 60 patients, independent of preexisting conditions, severity, overall course of the acute illness, and time from the original diagnosis.[32]

At this time it is unclear what these clinical abnormalities might mean in regard to both short- and long-term morbidity and mortality.

Summary and Recommendations

The range of outcomes that can develop after ARDS or an ICU admission can vary, with some persons reporting predominantly cognitive symptoms (memory deficits, difficulty concentrating), while others experience physical limitations (exercise intolerance, fatigue, dyspnea) or psychological sequelae (anxiety, depression, nightmares). Based on these reported outcomes, it would be prudent to postpone any type of insurance coverage for a reasonable period of time if a person has suffered from severe COVID-19 infection resulting in ICU admission, intubation, or mechanical ventilation.

Following this deferment period, life insurance coverage could be considered based on traditional risk factors such as age, comorbidities, and the degree of any residuals. Consideration for living benefits cover would vary, but should only be offered after a reasonable period of time has passed and should be based on verification of a full recovery, i.e., full-time return to work, and resumption of all previous occupational and non-occupation duties and activities without restrictions or limitations.

The finding of significant morbidity in survivors of asymptomatic, minor, mild, and moderate COVID-19 is also of significant concern. From an insurance standpoint, it is not clear what the long-term consequences of these findings might be regarding mortality and morbidity, but caution would be advised going forward until more data is collected regarding the long-term effects of COVID-19.

References

1. Johns Hopkins University of Medicine Coronavirus Resource Center dashboard. https://coronavirus.jhu.edu/map.html
2. Wichmann D, Sperhake J, Lutgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients with COVID-19: A Prospective Cohort Study. Annals of Internal Medicine. 2020 Aug 18; 173(4): 268-77. https://www.acpjournals.org/doi/10.7326/M20-2003
3. Lindner D, Fitzek A, Brauninger H, et al. Association of Cardiac Infection with SARS-COV 2 in Confirmed COVID-19 Autopsy Cases. JAMA Cardiology. 2020 July 27; 5(11): 1281-5. https://jamanetwork.com/journals/jamacardiology/fullarticle/2768914
4. Carsana L, Sonzogni A, Nasr A, et al. Pulmonary Post-Mortem Findings in a Series of COVID-19 Cases from Northern Italy: A Two-Centre Descriptive Study. Lancet Infectious Diseases. 2020 June 8; 20(10): 1135-40. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30434-5/fulltext
5. Grillo F, Barisione E, Ball L, et al. Lung Fibrosis: An Undervalued Finding in COVID-19 Pathological Series. Lancet Infectious Diseases. 2020 July 28. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30582-X/fulltext
6. Chiumello D, Coppola S, Froio S, et al. What's Next After ARDS: Long-Term Outcomes. Respiratory Care. 2016 May; 61(5): 689-99. https://pubmed.ncbi.nlm.nih.gov/27121623/
7. Burnham EL, Janssen WJ, Riches DWH, et al. The Fibroproliferative Response in Acute Respiratory Distress Syndrome: Mechanisms and Clinical Significance. Eur Respiratory Journal. 2014 Jan; 43(1): 276-85. https://pubmed.ncbi.nlm.nih.gov/23520315/
8. Desai S, Wells A, Rubens M, et al. Acute Respiratory Distress Syndrome: CT Abnormalities at Long-Term Follow-Up. Radiology. 1999 Jan; 210(1): 29-35. https://pubmed.ncbi.nlm.nih.gov/9885583/
9. Masclans JR, Roca O, Munoz X, et al. Quality of Life, Pulmonary Function, and Tomographic Scan Abnormalities After ARDS. Chest. 2011 Jun: 139(6): 1340-6. https://pubmed.ncbi.nlm.nih.gov/21330382/
10. Wilcox ME, Patsios D, Murphy G, et al. Radiologic Outcomes at 5 Years After Severe ARDS. Chest. 2013 April; 143(4). 920-6. https://pubmed.ncbi.nlm.nih.gov/23187463/
11. Herridge MS, Tansey CM, Matte A, et al. Functional Disability 5 Years After Acute Respiratory Distress Syndrome. New England J. Med. 2011 Apr 7; 364(14): 1293-304. https://pubmed.ncbi.nlm.nih.gov/21470008/
12. Herridge MS, Cheung AM, Tansey CM, et al. One-Year Outcomes in Survivors of the Acute Respiratory Distress Syndrome. New England J Med. 2003 Feb 20; 348(8): 683-93. https://pubmed.ncbi.nlm.nih.gov/12594312/
13. Cooper A, Ferguson N, Hanly P, et al. Long-Term Follow-up of Survivors of Acute Lung Injury: Lack of Effect of a Ventilation Strategy to Prevent Barotrauma. Critical Care Med. 1999 Nov 30; 27(12): 2616-21. https://europepmc.org/article/med/10628599
14. Linden V, Lidegran M, Frisen G, et al. ECMO in ARDS: A Long-Term Follow-Up Study Regarding Pulmonary Morphology and Function and Health-Related Quality of Life. Acta Anaesthesiol Scand. 2009 Apr; 53(4): 489-95. https://pubmed.ncbi.nlm.nih.gov/19226296/
15. Kapfhammer H, Rothenhausler H, Krausneck T, et al. Post-Traumatic Stress Disorder and Health-Related Quality of Life in Long-Term Survivors of Acute Respiratory Distress Syndrome. Am. J. Psychiatry. 2004 Jan; 161(1): 45-52. https://pubmed.ncbi.nlm.nih.gov/14702249/
16. Angus DC, Musthafa AA, Clermont G, et al. Quality-Adjusted Survival in the First Year After the Acute Respiratory Distress Syndrome. American Journal of Respiratory Critical Care Med. 2001 May; 163(6): 1389-94. https://pubmed.ncbi.nlm.nih.gov/11371406/
17. Mikkelsen M, Christie J, Lanken P, et al. The Adult Respiratory Distress Syndrome Cognitive Outcomes Study: Long-Term Neuropsychological Function in Survivors of Acute Lung Injury. American Journal of Respiratory Critical Care Medicine. 2012 Jun 15; 185(12): 1307-15. https://pubmed.ncbi.nlm.nih.gov/22492988/

18. Hopkins R, Weaver L, Pope D, et al. Neuropsychological Sequelae and Impaired Health Status in Survivors of Severe Acute Respiratory Distress Syndrome. American Journal of Respiratory Critical Care Medicine. 1999 Jul; 160(1): 50-6. https://pubmed.ncbi.nlm.nih.gov/10390379/

19. Wang CY, Calfee CS, Devon PW, et al. One-year Mortality and Predictors of Death Among Hospital Survivors of Acute Respiratory Distress Syndrome. Intensive Care Med. 2014 Mar; 40(3): 388-96. https://pubmed.ncbi.nlm.nih.gov/24435201/

20. Davidson TA, Rubenfeld GD, Caldwell ES, et al. The effect of acute respiratory distress syndrome on long-term survival. Am J Respir Crit Care Med. 1999 Dec; 160(6): 1838-42. https://pubmed.ncbi.nlm.nih.gov/10588594/

21. McPeake, J, Mikkelsen ME, Quasim T, et al. Return to Employment After Critical Illness and its Association With Psychosocial Outcomes. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. 2019 Oct; 16(10): 1304-11. https://pubmed.ncbi.nlm.nih.gov/31184500/

22. Kamdar BB, Suri R, Suchyta MR, et al. Return to Work After Critical Illness: A Systematic Review and Meta-Analysis. Thorax. 2020 Jan; 75(1): 17-27. https://pubmed.ncbi.nlm.nih.gov/31704795/

23. Riddersholm S, Christensen S., Kragholm K, et al. Organ Support Therapy in the Intensive Care Unit and Return to Work: A Nationwide, Register-Based Cohort Study. Intensive Care Med. 2018 Apr; 44(4): 418-27. https://pubmed.ncbi.nlm.nih.gov/29616288/

24. Ahmed H, Patel K, Greenwood DC, et al. Long-term Clinical Outcomes in Survivors of Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome Coronavirus Outbreaks after Hospitalisation or ICU Admission: A Systematic Review and Meta-Analysis. J. Rehab Med. 2020 May 31; 52(5): jrm00063. https://pubmed.ncbi.nlm.nih.gov/32449782/

25. Tansey CM, Louie M, Loeb M, et al. One-year Outcomes and Health Care Utilization in Survivors of Severe Acute Respiratory Syndrome. Arch Intern Med. 2007 Jun 25; 167(12): 1312-20. https://pubmed.ncbi.nlm.nih.gov/17592106/

26. Lam M, Wing YK, Yu M, et al. Mental Morbidities and Chronic Fatigue in Severe Acute Respiratory Syndrome Survivors: Long-Term Follow-up. Arch Intern Med. 2009 Dec 14; 169(22): 2142-7. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/415378

27. Ngal JC, Ko FW, Ng SS, et al. The Long-term Impact of Severe Acute Respiratory Syndrome on Pulmonary Function, Exercise Capacity and Health Status. Respirology. 2020 Apr; 15(3): 543-50. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1440-1843.2010.01720.x

28. Carfi A, Bernabei R, Landi F, et al. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020 Aug 11; 324(6): 603-5. https://jamanetwork.com/journals/jama/fullarticle/2768351

29. Arnold DT, Hamilton FW, Milne A, et al. Patient Outcomes After Hospitalisation With COVID-19 and Implications for Follow-up: Results From a Prospective UK Cohort. MedRxIV. 2020 Aug 14. https://www.medrxiv.org/content/10.1101/2020.08.12.20173526v1

30. Petrie JG, Cheng C, Malosh RE, et al. Illness Severity and Work Productivity Loss Among Working Adults With Medically Attended Acute Respiratory Illnesses: US Influenza Vaccine Effectiveness Network 2012-2013. Clinical Infectious Diseases. 2016 Feb 15; 62(4): 448-55. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4725387/

31. Hu Z, Song C, Xu C, et al. Clinical Characteristics of 24 Asymptomatic Infections With COVID-19 Screened Among Close Contacts in Nanjing, China. Sci China Life Sci. 2020 May; 63(5): 706-11. https://pubmed.ncbi.nlm.nih.gov/32146694/

32. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Jul 27; e203557. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7385689/