ReFlections

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Dr. Adela Osman
Chief Medical Research Officer, South Africa
adela.osman@rgare.com

Dr. Daniel D. Zimmerman, DBIM
Senior Vice President, Head of Global Medical
dzimmerman@rgare.com

IN THIS ISSUE

FROM THE EDITORS

As always, we hope this issue of *ReFlections* finds you safe and well. While the pandemic and its challenges are far from over, we look forward to the new year with hope and optimism. We don't yet know what the coming "new normal" will be, but we do know life will be different.

This issue features our first father-daughter collaboration. Dr. John Lefebre, Vice President, Global Medical Director, a frequent contributor to *ReFlections*, teamed up with his daughter, Lauren Lefebre, Director, E-Underwriting Rules, to produce a comprehensive and detailed article on recovery from COVID-19 which examines emerging trends and addresses important underwriting and claims considerations. We also welcome back Dr. Radhika Counsell, Consulting Medical Officer, who offers a deep dive into the growing complexity of differentiated thyroid cancers and discusses this topic in the context of critical illness claims assessment.

In addition, *ReFlections* editor Dr. Daniel D. Zimmerman, Senior Vice President, Head of Global Medical, provides a Brief Report on therapeutic monoclonal antibodies, which are rapidly growing in importance for a multitude of disorders for both prevention and treatment.

Our update on the **Longer Life Foundation**, RGA's research collaboration with Washington University School of Medicine in St. Louis, features an interview with grantee Meredith Jackrel, Ph.D. Dr. Jackrel's lab is leading exciting research into protein misfolding – work with great relevance to diseases such as Alzheimer's, Parkinson's, and ALS.

Beginning with this issue, we will be publishing *ReFlections* in an electronic format only, which will enable it to be even more timely. A printable PDF will continue to be made available.

We remain committed to bringing our readers the best medically-focused thought leadership in the industry. Please do not hesitate to let us know how we can best serve you.

Dan and Adela

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.

ABOUT THE AUTHORS

Dr. John J. Lefebre, M.D., FRCP(C)
Vice President, Medical Director
RGA International, Toronto, Canada
jlefebre@rgare.com

Dr. Lefebre is a member of RGA's Global Medical team. He is responsible for case consultation, product development, internal and external education, client support, and representing RGA to key industry professional organizations. A graduate of the University of Alberta, where he earned his Medical Doctor (M.D.) degree, he completed his postgraduate residency with a specialty in Emergency Medicine at the University of Toronto and has extensive clinical experience in teaching hospitals in Halifax and Toronto. Dr. Lefebre is a member of the Canadian Life Insurance Medical Officers Association.

Lauren Lefebre
Director, E-Underwriting Rules
RGA International, Toronto, Canada
lauren.lefebre@rgare.com

Lauren Lefebre joined the Underwriting Business Solutions team in 2018. Her focus is on adapting the questionnaires and rules for RGA's proprietary AURA e-underwriting solution for the Canadian and International markets. Prior to joining RGA, Lauren was a Senior Underwriter for the Group Insurance Market at Sun Life Financial, and before that, was an underwriter of living benefits and life insurance products for ANZ Wealth, in Melbourne, Australia. She is a graduate of Brock University in Ontario, Canada.

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

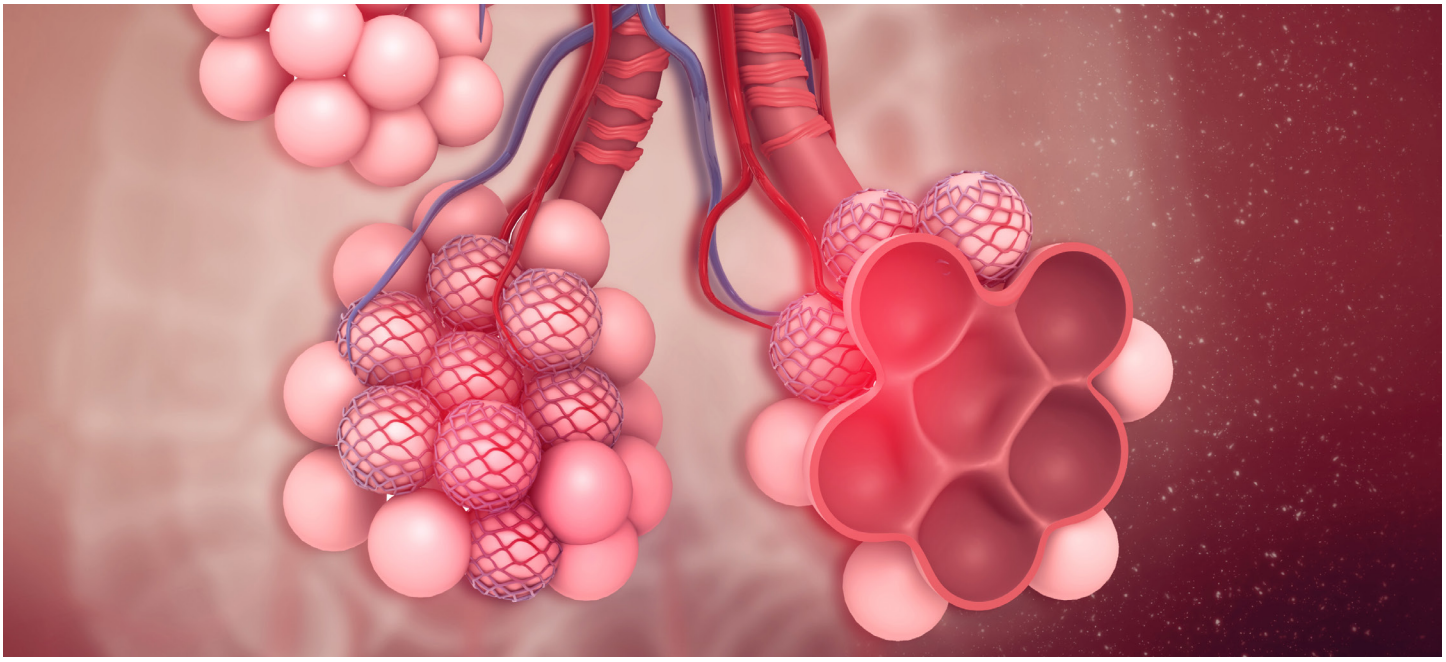
Studies show that most survivors of non-COVID-19 ARDS experience impaired health-related quality of life (HRQL) for years after their acute illness. At six months after hospital discharge, 38 survivors of non-COVID-19 ARDS showed lower HRQL compared to the general population. This was mainly due to lower 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

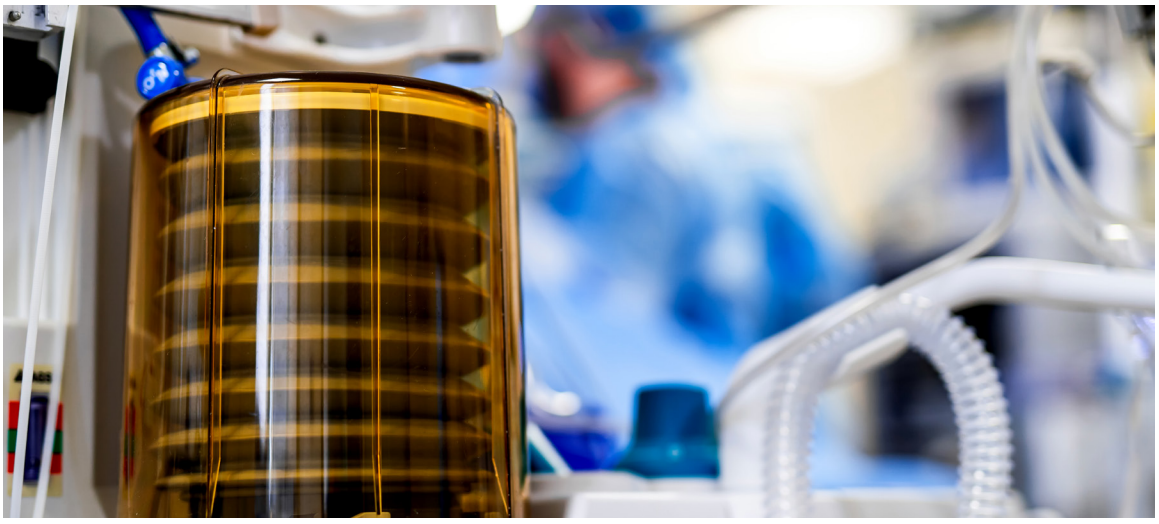
Based on the previous findings, it would not be surprising to find that health care utilization in survivors of non-COVID-19 ARDS does not return to baseline levels after discharge. A five-year follow-up of 109 ARDS survivors after discharge from the ICU found their health care costs were higher than 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.

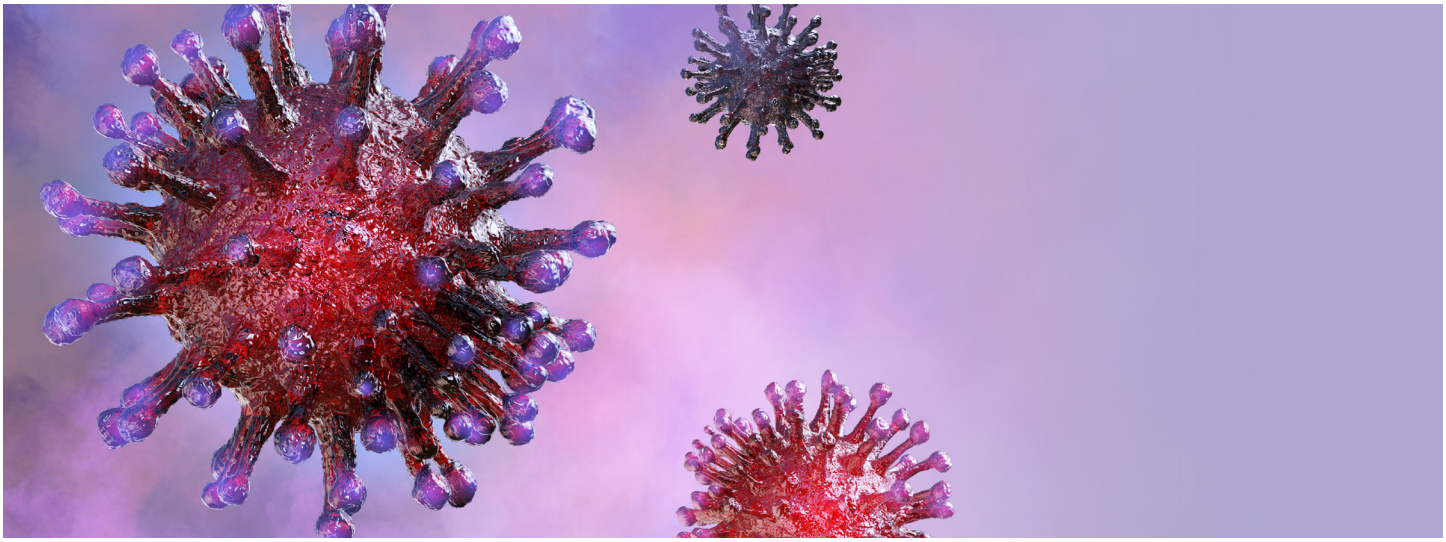
Survivors of Symptomatic COVID-19 Infection

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.

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ASSESSING DIFFERENTIATED THYROID CANCERS AND VARIANTS

Abstract

Incidence of thyroid cancer has been increasing worldwide, largely due to greater use of body imaging with ultrasound and subsequent fine needle aspiration (FNA) for incidentally discovered thyroid nodules.[1] Papillary thyroid cancer (PTC), a type of differentiated thyroid cancer (DTC), is solely responsible for the increase in cases,[2] accounting for nearly 90% of all thyroid cancers.[2, 3] Another important factor has been the increased diagnosis of a PTC variant – follicular variant papillary thyroid cancer (FVPTC). However, it was recently recognized that a percentage of these cases were tumors with very low potential for malignancy, and so were reclassified from a cancer to a neoplasm. This article explores some of the newer nomenclature for differentiated thyroid cancers and current issues in assessing critical illness claims for them.

Introduction

Thyroid cancer can arise from thyroid follicular or parafollicular C cells. Differentiated thyroid cancer (DTC) arises from the follicular cells and includes papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and variants of both. These cancers generally have excellent prognoses, with 10-year survival rates in excess of 90% to 95%.[3] Poorly differentiated thyroid cancers, which probably arise from either PTC or FTC, have worse outcomes, with 10-year survival rates of around 50%. Anaplastic thyroid cancer, one such cancer, is a rare but aggressive undifferentiated tumor arising from thyroid follicular cells with less than 10% survival at five years.[4]

Differentiated Thyroid Cancers

The histology of PTC is characterized by a papillary growth pattern. Papillae are tongue-shaped structures with one or two layers of tumor cells surrounding a well-defined fibromuscular core. Follicles are usually absent. The nuclei of the malignant cells appear large, oval, crowded, and overlapping, and may contain hypodense powdery chromatin, pseudoinclusions, or nuclear grooves (also called “orphan Annie eyes”). PTC is typically unencapsulated.

PTC is also often multifocal, either due to lymphatic spread within the thyroid gland or field change, with the development of synchronous tumors which are locally invasive and can spread to local lymph nodes in the neck. Distant spread may also be present in up to 10% of cases at the time of diagnosis, with lung and bone being common sites.

A scoring system based on tumor size and shape, membrane irregularities, and characteristics of the chromatin is used to make the diagnosis of PTC.

FTC has a completely different histological appearance from PTC. The architecture in good prognosis tumors shows well-differentiated epithelium forming follicles containing colloid. In poor prognosis tumors, the cells are poorly differentiated, growing as a solid mass without forming follicles. The

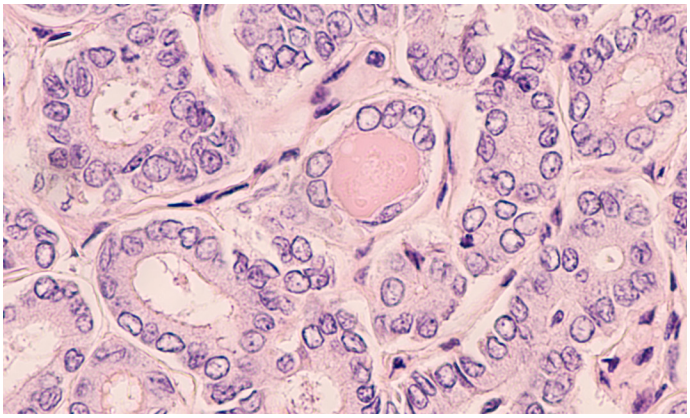
ABOUT THE AUTHOR

Dr. Radhika (Radi) Counsell, MBBS
Consulting Medical Officer,
RGA UK Services Limited
rcounsell@rgare.com

Dr. Radhika (Radi) Counsell, MBBS, MD, is a Consulting Medical Officer with RGA UK Services Limited. A specialist in gynecological and breast cancers, she provides direct case consultation for annuities, critical illness, terminal illness, and medical insurance claims, and review and input for RGA Global Underwriting Manual’s oncology guidelines and for new products under development in Asia. Dr. Counsell’s managerial role in the National Health Service (from which she recently retired) included the launching of the NHS Trust’s Acute Oncology Outreach Service, which provides opinions on cancer patients presenting with acute problems, and leadership of the regional gynecological brachytherapy service. She has also taught and trained medical students, acute medicine doctors, oncology specialty trainees, and therapy radiographers. She continues to work as an appraiser for NHS Trust medical consultants.

Dr. Counsell’s qualifications include obtaining Membership of the Royal College of Physicians (MRCP) of the United Kingdom and Fellowship of the Faculty of the Royal College of Radiologists (FRCR). Her Bachelor of Medicine & Bachelor of Surgery (MBBS) degree, and her medical doctorate (M.D.) for research on magnetic resonance spectroscopy in breast cancer, are from University of London Medical School. She has lectured on oncology at both medical and insurance events.

nuclei do not have the features seen in PTC. There can be invasion of the blood vessels and also the tumor capsule.

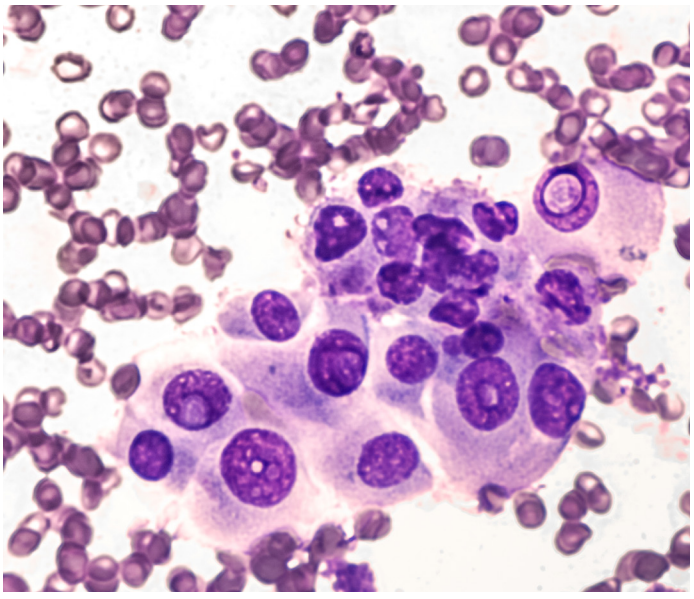


Histopathology of Follicular Thyroid Cancer – good prognosis subtype showing follicular architecture

Diagnosis of Differentiated Thyroid Cancer

When thyroid cancer is suspected, an ultrasound exam is performed, followed by fine needle aspiration of the thyroid lump. Microscopic examination of the cells enables the pathologist to recognize the typical changes of the nuclei associated with PTC.

For follicular tumors, however, it is not possible for a pathologist to tell the difference prior to surgery between a benign follicular adenoma and malignant FTC. Examination of the thyroid lobe after surgery to identify the tumor capsule and assess vascular invasion is required for a diagnosis of FTC.



Fine Needle Aspiration from papillary thyroid cancer with the cancer cells showing the typical appearance of Orphan Annie eyes

Staging and Prognosis

There are several systems for staging DTC. Each uses a core set of data that usually includes age at diagnosis, size of the primary tumor, extent of local extrathyroidal extension, and the presence or absence of distant metastases. However, there are sufficient differences among the systems that they are not interchangeable. The TNM system shown in Table 1 appears to be the best for predicting disease-specific mortality.[5]

Outcomes, stage for stage, are very similar for PTC and FTC. Mortality from PTC increases progressively with advancing age, starting around age 35. Using the cut-off of age 55 appears to be the most reliable for categorizing risk.[6] Thyroid cancers arising from the follicular cells of the thyroid gland, however, display a spectrum of biological behaviors ranging from papillary microcarcinoma in the elderly, for which prognosis is generally excellent, to the highly lethal anaplastic thyroid cancer, which has a 10% to 20% survival rate at one year.

The subtypes of PTC and FTC have important influences on outcomes. Excellent outcomes are associated, for example, with non-invasive encapsulated FTC and with follicular variant papillary thyroid cancer (FVPTC). The more aggressive variants – poorly differentiated thyroid cancer, tall cell variant, hobnail variant, and columnar cell variant – tend to have poorer outcomes. Several other histological features, such as perineural invasion, multifocal disease, and high mitotic rate, may influence the prognosis as well. However, these histological features are not included in the staging system of the American Joint Committee on Cancer (AJCC) as there are no absolute pertinent cut-points.

Tables 1 and 2 illustrate the AJCC staging system,[7] which is based on TNM (tumor, node, metastasis) parameters (Table 1) and uses the age 55 cutoff for the prognostic subgroups (Table 2). Pathological staging of cancers is based on findings at surgery for extrathyroidal spread and the pathology of the surgical specimen. Nodal involvement and distant metastatic spread may only be detected by radioactive iodine scans which are performed one to three months after surgery.

In addition to staging at diagnosis, the American Thyroid Association[8] also recommends additional staging to predict risk of recurrence, risk of persistent disease, and to modify the risk estimate based on response to therapy. Factors such as serum thyroglobulin four to six weeks after initial surgery, calculated thyroglobulin doubling time,

radioactive iodine uptake, and avidity of FDG uptake on PET scans may also influence the prognosis.

Table 1: AJCC TNM Staging for PTC, FTC, Poorly Differentiated, Hurthle, and Anaplastic Thyroid Cancers

Category	Criteria
T1	Tumor 2 cm or less limited to the thyroid gland
T2	Tumor >2 cm and up to 4 cm limited to the thyroid gland
T3	Tumor >4 cm limited to the thyroid gland or gross extrathyroidal extension invading only infrahyoid (strap) muscles
T4	Includes gross extrathyroidal extension
N0	No evidence of locoregional lymph node metastasis
N1	Metastasis to regional nodes
M0	No distant metastasis
M1	Distant metastasis

Source: AJCC Cancer Staging Manual 8th Edition

Table 2: AJCC Prognostic Stage Groups for Differentiated Thyroid Cancer (PTC and FTC) Incorporating Age With TNM Staging

When age at diagnosis is…	And T is…	And N is…	And M is…	Then the stage group is…
<55 years	Any T	Any N	M0	I
<55 years	Any T	Any N	M1	II
55+ years	T1	N0/ NX	M0	I
55+ years	T1	N1	M0	II
55+ years	T2	N0/ NX	M0	I
55+ years	T2	N1	M0	II
55+ years	T3	Any N	M0	II
55+ years	T4a	Any N	M0	III
55+ years	T4b	Any N	M0	IVA
55+ years	Any T	Any N	M1	IVB

Source: AJCC Cancer Staging Manual 8th Edition

Most patients with DTC do not die of it: long-term cancer-related mortality is less than 5%.[3] Multiple studies confirm that DTC mortality increases progressively with advancing age but even older patients (65+ years) in the SEER database still demonstrate 95% survival at five years.

Tumor size is important for prognosis. Tumors of less than 1.5 cm in size are universally cured, but mortality increases with tumor size. Twenty-year mortality for tumors measuring between 2.0 cm and 3.9 cm, for example, is 6%, and increases to 50% for tumors 7.0 cm or larger.[9] Involvement of the regional lymph nodes is also an important adverse factor, particularly when associated with T4 tumors or M1 disease. However, small volume nodes have little impact on survival particularly at younger ages (<45 years), as they can be effectively eradicated by radioactive iodine therapy.

Follicular Variant PTC (FVPTC)

There are more than 10 variants of PTC,[10] including follicular (the most common), tall cell (more aggressive), insular, hobnail, and diffuse sclerosing variants (Table 3). FVPTC, which represents 30% to 40% of all cases,[11] has an architecture of follicles rather than papillae, and the malignant follicular cells show the characteristic features of PTC.

There are two main subtypes of FVPTC: encapsulated (EFVPTC), which represents the majority of FVPTC, and non-encapsulated or infiltrative (NFVPTC). The two subtypes have clearly different clinical and biological behaviors. They also differ in their molecular profiles, with the BRAF V600E mutation seen in the infiltrative tumors and the RAS mutation in the encapsulated tumors.

Two-thirds of infiltrative FVPTC cases exhibit lymph node spread, whereas EFVPTC rarely (5%) involves lymph nodes. EFVPTC may also show signs of invasion of the tumor capsule, of blood vessels within the capsule, or of the adjacent thyroid tissue. Minimal invasion of the capsule slightly increases the risk of recurrence, but invasion of the lymphatics and/or blood vessels – particularly if extensive (>4 foci) – greatly increases the risk of recurrence, spread, and mortality.

A substantial number of FVPTCs are neither encapsulated nor infiltrative, but instead are partially encapsulated or well-demarcated. They have a similar molecular profile to EFVPTC, with the RAS mutation seen in nearly half the cases (46%) and no BRAF V600E mutation seen.

Table 3: PTC Variants[12]

Variant	Molecular Alteration	Clinical Behavior
Papillary microcarcinoma <1 cm	BRAF V600E	Excellent
Encapsulated	Not specified	Excellent
Follicular	RAS mutation	Excellent
Diffuse sclerosing	RET/PTC	Less favorable
Tall cell	BRAF V600E	High risk
Columnar cell	Not specified	High risk
Cribriform-morular	APC	Excellent
Hobnail	BRAF V600E	High risk
Fibromatosis/Fasciitis-like stroma	Not specified	No information
Solid/Trabecular	RET/PTC3	High risk
Oncocytic	Not specified	Less favorable
Spindle cell	Not specified	No information
Clear cell	Not specified	No information
Warthin-like	Not specified	No information

Source: WHO Classification for Thyroid Tumors, fourth edition.

Non-Invasive Follicular Thyroid Neoplasm with Papillary Nuclear Features (NIFTP)

In the last 20 to 30 years, incidence of encapsulated thyroid tumors has risen two to threefold and now represents 10% to 20% of all thyroid cancers in Europe and North America. These tumors generally have an indolent course and following limited surgery (removal of the affected lobe rather than the whole thyroid gland), they very rarely relapse or spread to distant sites. To avoid overdiagnosis and overtreatment, these tumors were downgraded from cancer to neoplasm in 2017.

The subtypes of PTC and FTC have important influences on outcomes.

In 2016, an international working group of expert thyroid pathologists convened by the National Cancer Institute reported on a study of 109 patients diagnosed with EFVPTC.[13] At a median follow-up of 13 years there were no episodes of recurrences or spread in these patients. This was not, however, the case for patients with the invasive form of FVPTC. Because of these results, the working group recommended that EFVPTC be called "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP).

This change in nomenclature and classification was subsequently accepted by the World Health Organization (WHO) and was included in the 4th edition of the WHO Classification of Tumors of Endocrine Organs, published in 2017.[14] NIFTPs are now usually treated by removal of one lobe of the thyroid and radioactive iodine treatment is omitted.

Diagnosis of NIFTP is based on strictly defined inclusion and exclusion criteria, which are outlined in Table 4. The assessment of whether a tumor is non-invasive or invasive cannot be made until the tumor and its surrounding capsule have been removed by lobectomy. The pathologist needs to examine the entire capsule carefully to determine if there is any invasion

by cancer cells or any lymphovascular invasion.Thus, the diagnosis can only be made after surgery, not pre-operatively.

The average size of an NIFTP is 3 cm, but they can vary from microtumors (<1 cm) to as large as 10 cm. They can also be multifocal or affect both lobes, and can be found in a thyroid gland containing an invasive tumor.

From the perspective of assessing critical illness (CI) claims, it is important to be aware that not all EFVPTC cases have been downgraded from cancer to NIFTP. The strict criteria for diagnosing NIFTP highlight that there should be no invasion into the capsule or into the adjacent thyroid gland for well-circumscribed tumors.

Tumor size is important for prognosis.

Table 4: NIFTP Inclusion and Exclusion Criteria[13]

Inclusion Criteria
The tumor must be well-demarcated, with discrete interface with the surrounding thyroid tissue. There can be three scenarios:
• Well-defined fibrous capsule
• Partly encapsulated
• Unencapsulated but clearly delineated from the adjacent thyroid tissue
Appearance of the nuclei as seen in PTC. The features can be subtle and are often easier to assess in areas of small follicles or near the tumor periphery.
Exclusion Criteria
Invasion with complete tumor capsule penetration. For well-circumscribed tumors lacking a fibrous capsule, infiltration of tumor cells into adjacent uninvolved thyroid tissue. Also, lymphatic and/or vascular invasion defined by tumor cells within an endothelial lined space in the tumor capsule or in vessels outside the tumor.
Pattern of growth not showing follicular architecture although up to 30% solid, trabecular, or insular appearance is allowed.
Papillary structures.
High-grade features with psammoma bodies (dead calcified papillae), tumor necrosis, or high mitotic index (i.e., three or more mitoses per 10 high-power fields).

Source: Nikorov et al. Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma: A Paradigm Shift to Reduce Overtreatment of Indolent Tumors.

Case 1: EFVPTC that does not meet NIFTP criteria

History: A 25-year-old man presented with a persistent non-tender 4-5 cm lump in the right lobe of the thyroid gland. There were no palpable lymph nodes in the neck. Following a multidisciplinary team (MDT) discussion of the ultrasound and fine needle aspirate cytology results, the right lobe of the patient's thyroid gland was removed.

Pathology: Gross pathology revealed a well-defined lesion extending through the entire right lobe, measuring 45 x 35 x 26 mm. Microscopy determined that it was an encapsulated follicular lesion predominantly consisting of microfollicles, many containing colloid, and that there were a few rudimentary papillae. The capsule was relatively thin and in two blocks (sections) there was suspicion of possible capsular invasion. In several blocks there was also suspicion of vascular invasion.

Provisional diagnosis: EFVPTC confined to the thyroid gland with a clearance of 0.1 mm. There were no lymph nodes present. Stage: pT3a and R0 (clear margins).

The case was also sent to an expert thyroid pathologist who agreed that the tumor was a well-defined encapsulated mass. The pathologist noted that there were multiple foci of FVPTC but did not feel there was evidence of vascular invasion. However, there were some epithelial components extending into but not penetrating through the fibrous capsule.

Conclusion: Multifocal EFVPTC with tumor cells within the capsule but no vascular invasion. Stage: pT2 NX MX and R0.

The MDT recommended completion of the thyroidectomy followed by radioactive iodine treatment. Pathology examination of the left lobe did not show any cancer.

Key points for assessing the critical illness claim:

- The tumor had a complete capsule (i.e., encapsulated). Note that presence of a capsule does not exclude invasive cancer.
- The tumor was multifocal.
- Expert opinion was that vascular invasion was absent.
- There were tumor foci in the capsule (this excludes diagnosis of NIFTP).
- Size cannot differentiate between NIFTP and invasive thyroid cancer as NIFTP can be 4 cm or larger in up to 5% of cases.
- Treatment was provided as for invasive thyroid cancer.

This case was accepted as a valid critical illness claim as this cancer was showing signs of invasion with involvement of the tumor capsule.

Case 2: Partially encapsulated FVPTC

History: A 36-year-old woman with a past history of multinodular goiter and thyrotoxicosis presented with a persistent lump on the left side of her neck after a throat infection. An ultrasound scan showed an indeterminate heterogenous well-defined nodule in the left lobe of the thyroid, measuring 18 x 10 mm. Fine needle aspirate cytology showed papillary clusters of cuboidal-to-columnar cells supported by fibrovascular stroma. The nuclei showed features suspicious for PTC. She underwent removal of the left lobe of her thyroid.

Pathology: Gross pathology revealed a 15 x 12 x 22 mm nodule close to the surface of the thyroid gland. Microscopy showed a partly encapsulated follicular variant of papillary thyroid cancer. The capsule was fibrous and in areas ill-defined. The cells showed overlapping nuclei with grooves and inclusions. Vascular invasion was suspected, as several foci of intracapsular cells were seen to mingle with vessels, but interpretation was complicated by the granulation tissue response to previous fine needle aspiration. Definite evidence of vascular invasion was absent. There was also no evidence of capsular invasion or extension beyond the thyroid gland. The tumor extended to within 0.22 mm of the thyroid capsule.

Conclusion: Partially encapsulated and clearly demarcated FVPTC with suspected vascular invasion but no capsular invasion. Stage: pT2 (22 mm) NX MX.

Based on suspicion of vascular invasion, the remaining right lobe of her thyroid was removed, followed up by radioactive iodine treatment. The pathology of the right lobe was negative for cancer.

Key points for assessing the critical illness claim:

- The capsule was incomplete and ill-defined in areas, therefore partially encapsulated.
- The tumor was demarcated and there was no sign of diffuse infiltration.
- There was no invasion of the capsule.
- There was suspicion of vascular invasion as several foci of intracapsular cells were seen to mingle with vessels. The interpretation was compromised by the after-effects of fine-needle aspiration with granulation (healing/scar) tissue.
- Treatment was provided as for higher risk tumor, with completion of the thyroidectomy and radioactive iodine therapy.

This case was accepted as a valid critical illness claim, as it was reasonable to conclude there was vascular invasion within the tumor capsule.

Case 3: Non-encapsulated FVPTC

The current approach for assessing critical illness claims for EFVPTC without evidence of tumor capsule invasion is to view it as a non-cancer.

In another brief case example, gross pathology of a thyroid tumor showed a nodule measuring 14 x 7 x 5 mm. Microscopy revealed features typical of NIFTP, with cells showing nuclear elongation, overlapping, grooves, and occasional intracytoplasmic nuclear pseudoinclusion. The tumor was well-circumscribed and demarcated but non-encapsulated. No vascular invasion or extrathyroidal extension was seen.

Upon review of the claim, the terminology in the pathology report was felt to be consistent with what is acceptable for the diagnostic criteria of a NIFTP. This claim was therefore determined not to meet the definition of cancer as defined by the policy provision, as there was no evidence of invasion nor was the neoplasm diffuse in nature.

Case 4: Tumors with uncertain malignant potential

History: A 41-year old woman presented with a 4 cm lump in the left side of her thyroid. She had previously undergone a right hemithyroidectomy 24 years earlier for a benign lesion. Ultrasound was indeterminate and fine needle aspirate cytology could not distinguish between follicular neoplasm and a benign lesion. The pathologist was also of the opinion that papillary thyroid cancer could not be excluded. She underwent removal of the remaining left lobe of her thyroid.

Pathology: Gross pathology showed a well-circumscribed nodular lesion measuring 27 x 33 mm. Microscopy confirmed a circumscribed and encapsulated nodule with closely packed follicles and a predominantly microfollicular growth pattern. There was a well-formed thick fibrous capsule, and no cytological features to suggest papillary carcinoma. There were also three separate small nodules just outside the capsule with similar appearance to the main tumor nodule, suspicious for extracapsular spread although extensive examination of the capsule did not show any growth within the capsule. It was noted that the background thyroid tissue had a vaguely nodular appearance with some nodules appearing similar morphologically to the main nodule although at some distance from it. The extracapsular nodules could represent compressed background nodular hyperplasia.

The tumor was limited to the thyroid gland and was clear of the surgical margin by 0.1 mm. No lymphovascular invasion was seen and all three lymph nodes were clear.

The report noted that at worst, the appearance could be consistent with minimally invasive follicular carcinoma, provisional stage pT2 N0. The case was sent to an expert thyroid pathologist.

Conclusion: Following discussion among members of the MDT, the surgeon wrote that this tumor was best described as “tumor of unknown malignant potential,” but that some features would fit with the diagnosis of minimally invasive thyroid carcinoma. This was therefore accepted as the final working diagnosis.

Key points for assessing the critical illness claim:

- The tumor was an encapsulated lesion with three separate nodules of similar appearance outside the tumor capsule within the adjacent thyroid gland.
- Although the capsule was intact, it was deemed reasonable to assume that these nodules represented invasive spread within the thyroid gland. Although the pathologist could not see invasion of the capsule, it was impossible to assess the whole capsule in detail, so it was possible to miss an area of invasion.
- The final claim decision was in alignment with the MDT's decision that this was a minimally invasive cancer.

This case highlights the difficulty of making a clear diagnosis even for an expert thyroid pathologist. The key clinicians in this MDT (surgeon, pathologist, radiologist, and oncologist) took into consideration the clinical findings and pathology in order to reach a final diagnosis and decide upon a treatment plan. If there was doubt about the pathological diagnosis, they could have also asked for an opinion from a regional or national expert.

For follicular patterned thyroid tumors, such as this case, the WHO classification system recognizes there are tumors of "unknown malignant potential," which describes the uncertainty of the biological behavior of these tumors. The recognized types are called:

- Follicular tumors of uncertain malignant potential
- Well-differentiated tumors of uncertain malignant potential

Summary

For DTC CI claims, assessment of cancer invasion depends upon evaluation of the tumor capsule, vascular invasion, and local spread within the adjacent thyroid and the lymph nodes.

EFVPTC meeting strict inclusion and exclusion criteria, defined by an expert international panel of pathologists, are now known as NIFTP. Downgrading these tumors from cancer to neoplasm recognizes that many of the cases are non-invasive tumors with excellent prognoses and so can be safely managed by limited surgery. This will enable these patients to avoid the complications of removal of the whole thyroid gland and radioactive iodine therapy. From the insurance point of view, these neoplasms generally would not meet the strict definition of "cancer" as defined by most CI policy provisions. Nonetheless, these cases should be reviewed carefully to ensure accurate and fair adjudication.

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THE MONOCLONAL ANTIBODY REVOLUTION – WHAT INSURERS NEED TO KNOW

Abstract

Monoclonal antibodies (mAbs) were first produced in the laboratory in the mid-1970s. At the time they were hailed as a modern advance in medicine, but their application to clinical medicine came slowly. Recently, however, there has there been a rapid development of new and diverse medical indications for mAbs – nothing short of a therapeutic revolution. According to The Antibody Society, antibody-based therapeutics are advancing in clinical development at a rapid rate and are being approved for use in record numbers. This Brief Report will define mAbs, review their clinical indications, and examine the potential impact of this fast-growing class of therapeutics on insurance medicine. mAbs are also playing an emerging role in the treatment of COVID-19, and this will be addressed.

What are Monoclonal Antibodies?

Monoclonal antibodies (mAbs) are specialized proteins produced by immune system B cells. Their unique structure and function allow them to bind to highly specific targets or receptors. Therapeutic mAbs are designed specifically to prevent or treat particular diseases or clinical conditions. Their mechanisms of action are varied and can include killing of cells, immune modulation, or neutralization of an infectious agent.

mAbs can be produced in large quantities via the hybridoma technique, which was introduced in 1975. In this technique, B cells are "immortalized" by fusing them with myeloma cells which then leads to continuous mAb production and cell growth. Additional methods have now been developed to produce mAbs and, depending on the method, mAbs can be described as human, humanized, chimeric, or murine. Fully humanized mAbs have human biological properties and so can carry out their therapeutic functions with better clinical tolerance and without generating undesirable allergic reactions or side effects.

Clinical Applications and Indications for mAbs

The first therapeutic mAb, muromonab CD3, was approved by the U.S. Food and Drug Administration (FDA) in 1986 to prevent acute organ transplant rejection. Since then, mAb engineering has evolved significantly, leading to the growth of this major class of drugs. As of December 21, 2020, nearly 100 therapeutic mAbs have been approved by the U.S. FDA and by 2025, the global market is projected to be valued at US$300 billion.

The list of clinical indications for mAbs is also growing rapidly, both preventatively and therapeutically. These include several hematologic and solid cancers, autoimmune disorders such as rheumatoid arthritis, certain types of asthma, multiple sclerosis, bone loss, macular degeneration, and psoriasis, to name a few. mAbs can also

ABOUT THE AUTHOR

Dr. Daniel D. Zimmerman, DBIM
Senior Vice President, Head of Global Medical
dzimmerman@rgare.com

Dr. Daniel D. Zimmerman is responsible for thought and medical leadership, case consultation, product development, client support, and internal and external education at RGA and serves as editor of *ReFlections*, RGA's global medical newsletter. He is also Managing Director of The Longer Life Foundation, www.longerlife.org. This not-for-profit collaboration between RGA and Washington University in St. Louis School of Medicine funds the study of factors that either predict the mortality and morbidity of select populations or influence improvements in longevity, health, and wellness. Before joining RGA in 2014, Dr. Zimmerman was a medical director with Northwestern Mutual Life Insurance Company for eight years. Previously, he practiced primary care internal medicine and pediatrics in Tampa, Florida.

Dr. Zimmerman received his medical degree from the University of Wisconsin School of Medicine and Public Health and his undergraduate degree in Medical Microbiology and Molecular Biology from the University of Wisconsin – Madison. He has held leadership positions with the American Council of Life Insurers (ACLI), participated in program committees of the American Academy of Insurance Medicine (AAIM), and frequently represents RGA to key industry professional organizations. He has also contributed several articles to the *Journal of Insurance Medicine*, *On The Risk*, and *Best's Review*.

be designed to deliver a toxin or drug to a particular site such as a cancer cell. Figure 1, below, provides a more comprehensive list of therapeutic indications and applications of mAbs.

Figure 1: High-Level Clinical Indications and Uses of Monoclonal Antibodies
Asthma
Autoimmune disorders
Blood disorders
Drug reversal
Hematologic malignancies
Hypercholesterolemia
Infectious diseases
Macular degeneration
Migraine
Muckle-Wells syndrome
Multiple sclerosis
Organ transplant rejection
Osteoporosis
Prevention of blood clotting
Solid tumors
X-linked hypophosphatemia

Monoclonal Antibodies and COVID-19

Any discussion regarding mAbs would be incomplete without mentioning their emerging and significant role in the fight against COVID-19. The majority of mAb compounds under development for SARS-CoV-2 target the virus' well-described spike protein. Inpatient and outpatient trials are ongoing.

On November 9, 2020, the U.S. FDA granted an Emergency Use Authorization (EUA) for bamlanivimab for outpatient use. Bamlanivimab is authorized for patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older, weigh at least 40 kilograms (about 88 pounds), and are at high risk for progressing to severe COVID-19 and/or hospitalization. This includes individuals 65 years of age or older or those who have certain chronic medical conditions, such as cardiovascular disease or COPD. Additionally, on November 21, 2020, the U.S. FDA issued an EUA for the combination casirivimab and imdevimab for the treatment of mild to moderate COVID-19 and applies to similar patients outlined in the bamlanivimab EUA. The hope is that more therapeutic mAbs may be approved for the treatment of COVID-19 in the coming weeks and months, as at least nine are currently undergoing human testing.

How Are mAbs Impacting Insurance Medicine?

While there has clearly been expansion and growth of new and innovative mAb therapies in clinical medicine, the translation into long-term improvements in mortality and morbidity remains the focus of insurance medicine. Some benefits may only be measured in months, but others may result in positive effects of much longer duration. Insurers, especially those covering medical reimbursement, will need to monitor the costs associated with mAb therapies. One recent review concluded the average annual cost of mAb therapy was US$96,731 and those used for oncology or hematology indications were US$100,000 higher.

Conclusion

The addition of mAbs to therapeutic regimens is definitely a major medical advance and will hopefully lead to significant improvements in long-term morbidity and mortality outcomes. Expect to see further advancements in this field of research as well as a growing spectrum of diseases for which it may be applicable – both preventatively and therapeutically. The general population as well as insurers will benefit from these developments, but as in all new technologies, costs and benefits should be reviewed carefully. R&F

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Longer Life Foundation

An RGA/Washington University Collaboration

Meredith Jackrel, Ph.D., is an Assistant Professor of Chemistry at Washington University in St. Louis. Her laboratory researches the biochemistry of protein misfolding with a focus on the role of disaggregases. The Longer Life Foundation, a collaboration of RGA and Washington University School of Medicine in St. Louis, is proud to be a 2018-2019 and 2019-2020 supporter of Dr. Jackrel in her research, "Restoring Proteostasis to Counter Human Disease." Below is a recent and informative Q&A with Dr. Jackrel about her work conducted by Dr. Daniel D. Zimmerman, Managing Director of the Longer Life Foundation.

How did you first become interested in scientific research, and in your area of interest?

I have long had an interest in science. When I was an undergraduate at the College of New Jersey, I became interested in understanding how science progresses, and how people can better understand basic life processes. From there I got involved with laboratory research and became increasingly interested in biochemistry.

Your current research focuses on the misfolding of proteins and the numerous disorders and disease processes it influences. Indeed, protein misfolding underpins many devastating neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). How much is known about what actually causes proteins to misfold in the first place? Might it be due to a common pathway or could the cause be unique to each disease?

Protein misfolding is implicated in numerous disorders.

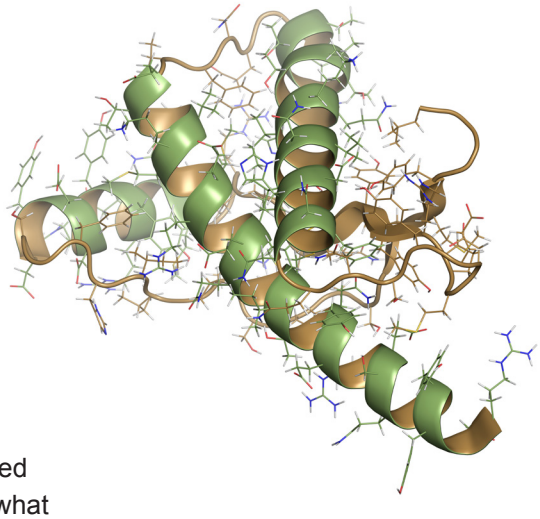
We still do not really understand what specifically initiates protein misfolding. In some cases, genetic mutations are present that increase the likelihood of a specific protein to misfold. This is particularly true for disorders such as Huntington's disease. However, in most of these disorders, it remains unclear what triggers misfolding to initially occur. There are certain common pathways implicated in multiple disorders, but there are also unique aspects to each disorder.

You are particularly interested in disaggregases, which aid in the solubilizing (dissolving) of misfolded proteins, as well as in the employment of protein engineering techniques to fine-tune the properties and capabilities of these disaggregases. How did you come upon this path of research and at what point are you now?

When I was a postdoctoral fellow at the University of Pennsylvania, I was in a group that was studying Hsp104, a protein found in baker's yeast which can eliminate misfolded proteins. Yeasts are unusual in that they can use different types of protein conformations to rapidly adapt to changing conditions. The proteins that yeast regulate in this process are strikingly similar in shape to those that aggregate in human disease. We became very interested in understanding how the yeast proteins do this. At the time, it was thought that humans did not possess these disaggregases, but we now know that humans do have different types of disaggregases. One hypothesis is that disaggregases preserve proteins in their proper shape but are prone to failure with age. We are continuing to research the utility of Hsp104 as a possible therapeutic or even as a probe to help us better understand how we might counter these disorders. We also are interested in studying and improving the activity of various human disaggregases.

For what conditions besides neurodegenerative diseases might your research be applicable?

Protein misfolding is implicated in numerous disorders. We recently published work on proteins that aggregate in sarcoma, a type of cancer. We are also interested in applying our work to protein misfolding that can drive cardiovascular disease and antimicrobial resistance.



Is there any evidence to suggest that reversing or removing misfolded proteins could improve or resolve clinical symptoms once manifested or is it too early to say?

At this point, it is a bit too soon to say if reversing misfolding might improve or resolve clinical symptoms, but recent results have been very promising. There is also some evidence that certain forms of these misfolded proteins may be toxic, while others may be protective, so it could be somewhat complicated to determine precisely which species (protein types) must be eliminated.

I understand you are in the earlier stages of research, but do you believe disaggregases might someday be used both preventatively and therapeutically?

We are eager to explore this idea. It is a bit too soon to say if disaggregases will find clinical use, but we are very optimistic that they may ultimately be used therapeutically.

To read about Dr. Jackrel's latest work on developing vaccine technologies for seniors, please click here.

LLF NEWSLETTER

We are proud to announce the November debut of the Longer Life Foundation Newsletter. This periodic publication provides news and information about the foundation, including the latest research from current and former grant recipients, events sponsored by the LLF, and more. If you would like to read the first edition and join the e-mail subscription list, please click here.

UPDATE ON LLF-SUPPORTED COVID-19 RESEARCH

The Longer Life Foundation's Scientific Review Committee leadership met with Jeffrey Henderson, M.D., Ph.D., on December 8, 2020, to discuss interim results from his ongoing study, "Prognostic Biomarkers of Severe Disease in COVID-19 Patients." His study is looking to discover predictive biomarkers using metabolic parameters to identify COVID-19 patients who have a higher likelihood of requiring mechanical ventilation or experiencing death. It is hoped that being able to do so will allow these patients to be triaged to more aggressive surveillance and therapeutic interventions.

To date, results are informative, and validation of the data continues. The next step will be to apply the data to a broader sample set, which will include non-COVID-19 specimens, and identify the key predictive metabolites. Eventually, the predictive testing will be applied in a clinical therapeutic trial. Dr. Henderson indicated that preliminary data could be ready for publication in early 2021.

RGA THOUGHT LEADERSHIP PUBLICATIONS

RGA publishes content on many topics of interest to insurers. Here are links to some recent publications:

Emerging Trends Shaping the Future of Health and Wellness
By Matt Berkley, Strategic Research Communications Lead, Global Actuarial Pricing and Research
Part I: Wearables Get Smart(er)
https://www.rgare.com/knowledge-center/media/articles/emerging-trends-shaping-the-future-of-health-and-wellness-part-i-wearables-get-smart(er)

Part II: Financial Well-Being
https://www.rgare.com/knowledge-center/media/articles/emerging-trends-shaping-the-future-of-health-and-wellness-part-ii-financial-well-being

Obesity: A Silent Pandemic
By Hilary Henly, CHARTERED INSURER / FCII (DLDU/DLDC), Global Medical Researcher
https://www.rgare.com/knowledge-center/media/research/obesity-a-silent-pandemic

Covid-19 Brief: Change and Continuity in U.S. Disability Claims
By Kari Briscoe, Director, Claims Consultant, and Jill Underhill, Senior Disability Claims Consultant, U.S. Group Reinsurance
https://www.rgare.com/knowledge-center/media/covid-19/covid-19-brief-change-and-continuity-in-u.s.-disability-claims

Growth in Telehealth: Is It Here to Stay Beyond the Pandemic?
By Dr. Steve Woh, Chief Medical Officer and Claims Manager, Global Health
https://www.rgare.com/knowledge-center/media/covid-19/growth-in-telehealth-is-it-here-to-stay-beyond-the-pandemic

ReCite

Interesting and relevant articles to the field of insurance medicine recently appearing in the literature...

Effective interventions for potentially modifiable risk factors for late-onset dementia: a costs and cost-effectiveness modelling study

Mukadam N, et al.
The Lancet Healthy Longevity. 2020 Oct; 1; E13-E20
https://doi.org/10.1016/S2666-7568(20)30004-0

An estimated 47 million people worldwide currently live with dementia, and that number is predicted to increase to 131 million by 2050. People today are living longer, particularly in low-income and middle-income countries. The annual global cost of dementia is already estimated to be US$1 trillion.

Over the past two decades, incidence of age-specific dementia has decreased in some countries, suggesting that the risk of dementia may be modifiable. In this study, a combined population-attributable fraction (PAF) was calculated for nine potentially modifiable risks for all-cause dementia from National Institute for Health and Care Excellence and National Institutes of Health guidelines.

The researchers used previously established relative risks for the nine prespecified risk factors associated with dementia (hypertension, diabetes, hearing loss, obesity, physical inactivity, social isolation, depression, cigarette smoking, and fewer years of childhood education) and searched PubMed and Web of Science systematically up to March 12, 2020, for research about effective interventions feasible in the adult population. The study then modeled potential costs and cost-effectiveness of late-onset (age 65 years and older) all-cause dementia prevention through such interventions. Focusing on England only, the study calculated potential costs and savings, accounting for risk clustering in individuals, and associated effects on Quality Adjusted Life-Years (QALYs).

The study found effective interventions for four of the nine risk factors – hypertension, smoking cessation, diabetes prevention, and hearing loss. Three of the interventions (treatments for stopping smoking, provision of hearing aids, and treatment of hypertension) if fully implemented would save £1.863 billion annually in England, reduce dementia prevalence by 8.5%, and produce QALY gains. Intervention for diabetes, however, was unlikely to be cost-effective in terms of effect on dementia alone.

Editor's Note: *There is a strong case for implementing the three cost-effective interventions into clinical settings on grounds of quality-of-life gains as well as improvements in general health. The insurance sector (especially wellness programs) will need to focus on dementia in the future.*

Prioritising primary care patients with unexpected weight loss for cancer investigation: diagnostic accuracy study

Nicholson BD, et al.
BMJ. 2020 Aug 13; 370: m2651
http://dx.doi.org/10.1136/bmj.m2651

Unexpected weight loss (WL) is recorded for about 1.5% of adults receiving treatment at primary care facilities. The likelihood of a cancer diagnosis in such people is increased in the three to six months after the first recorded unexpected WL compared with people without unexpected WL. Both early- and late-stage cancers are associated with unexpected WL. The greatest risks are lymphoma, cancer of unknown primary, or cancers of the pancreas, gastroesophageal tract, lung, bowel, or urinary tract.

The aim of this study was to quantify the predictive value of unexpected WL for cancer according to patient's age, sex, smoking status, and other concurrent clinical features (symptoms, signs, and abnormal blood test results).

The study accessed Clinical Practice Research Datalink electronic health records data linked to the National Cancer Registration and Analysis Service in primary care in England of 63,973 adults (≥18 years) with a code for unexpected WL from January 1, 2000, to December 31, 2012. The aim was to identify a cancer diagnosis in the six months after the earliest weight loss code (index date). Codes for additional clinical features were identified in the three months before and the one month after the index date.

Of the cohort, 37,215 (58.2%) were women, 33,167 (51.8%) were age 60 years or older, and 16,793 (26.3%) were ever smokers (individuals reporting smoking >100 cigarettes in their lifetimes). A diagnosis of cancer within six months of the index date was found for 908 (1.4%), of whom 882 (97.1%) were age 50 or older.

The most common diagnosed malignancies were cancers of the lung (24.2%), bowel (12.6%), gastroesophagus (11.3%), and pancreas (8.81%), and lymphoma (7.49%). In multivariable analysis, features selected to be positively associated with cancer in people with unexpected WL were abdominal pain, appetite loss, abdominal mass, iron deficiency anemia, jaundice, chest symptoms, and lymphadenopathy. Dysphagia, hemoptysis, and non-cardiac chest pain were associated with cancer only in men with unexpected WL, and back pain, change in bowel habits, dyspepsia, and venous thromboembolism were associated only in women with unexpected WL.

The risk of cancer in adults with unexpected WL presenting to primary care is 2% or less and does not merit investigation under current U.K. guidelines. However, in male ever smokers age 50 years or older and in patients with concurrent clinical features, the risk of cancer warrants referral for invasive investigation.

Editor's Note: *Clinical features typically associated with specific cancer sites are markers of several cancer types when they occur with unexpected WL. Underwriters would be advised to pay attention to these specific groups.*

Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62,354 COVID-19 cases in the USA

Taquet M, et al.
The Lancet Psychiatry. 2020 Nov 09
https://doi.org/10.1016/S2215-0366(20)30462-4

From the early days of the COVID-19 pandemic, adverse mental health consequences, including anxiety and depression, have been widely predicted but have not yet been accurately measured. There are a range of physical health risk factors for COVID-19, but it is not known if there are also psychiatric risk factors. In this U.S. electronic health record network cohort study using data from 69 million individuals, 62,354 of whom had a diagnosis of COVID-19, it was assessed

whether a diagnosis of COVID-19 (compared with other health events) was associated with increased rates of subsequent psychiatric diagnoses, and whether patients with a history of psychiatric illness might be at higher risk of being diagnosed with COVID-19.

The study used data from the TriNetX Analytics Network, a global federated network that captures anonymized data from electronic health records in 54 healthcare organizations in the U.S. The selected data included 62,354 patients diagnosed with COVID-19 between January 20 and August 1, 2020 and created several cohorts of patients who had been diagnosed either with COVID-19 or with certain other health events (influenza, other respiratory tract infections, skin disorders, cholelithiasis [gallstones], and bone fractures).

Between 14 and 90 days after a COVID-19 diagnosis, 5% to 8% of the survivors had their first recorded diagnoses of psychiatric illness, compared with 2.5% to 3.4% of patients in the comparison cohorts. Thus, adults have approximately double the risk of being newly diagnosed with a psychiatric disorder after a COVID-19 diagnosis. The hazard ratio was greater for anxiety disorders than for mood disorders. Data also showed increased diagnoses in all major anxiety disorder categories, but it remains unclear whether post-COVID-19 anxiety might have a particular post-traumatic stress disorder-like profile. Rates of insomnia diagnosis were also markedly elevated, in agreement with predictions that circadian disturbances would follow COVID-19 infection. The study found two to three times higher risk of dementia after COVID-19 infection as well, which was concerning, but some of this excess might reflect misdiagnosed cases of delirium or transient cognitive impairments due to reversible cerebral events.

The study also found that a diagnosis of psychiatric disorder in the year before the COVID-19 outbreak was associated with a 65% increased risk of COVID-19 compared with a cohort matched for established physical risk factors for COVID-19 but without a psychiatric diagnosis. This result was not related to any specific psychiatric diagnostic category and was similar whether the diagnosis was made within one or three years of infection and whether or not known physical risk factors for COVID-19 were present. The risk persisted even when controlled for problems related to housing and economic circumstances.

Editor's Note: *Survivors of COVID-19 appear to be at increased risk of psychiatric sequelae, and a psychiatric diagnosis might be an additional independent risk factor for COVID-19. The impact of COVID-19 on anxiety, insomnia, and dementia is in line with expectations and highlights the need for effective and accessible interventions as well as appropriate review at both claims and underwriting stages.*

Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review

Okoth K, et al.
BMJ 2020 October 07; 371
https://doi.org/10.1136/bmj.m3502

Globally, one-third, or 17.9 million, of total annual deaths are attributable to cardiovascular disease (CVD). Incidence of CVD has declined since the middle of the last century, but less so in women than in men.

Although many commonalities exist, several differences are apparent between men and women in terms of risk factors for CVD. Traditional risk factors, such as smoking and diabetes, affect women more than men, and risk factors specific to women, such as adverse pregnancy

outcomes and fertility complications, are under-recognized. Women experiencing adverse pregnancy outcomes and issues related to fertility have been shown to often have early manifestations of vascular changes.

The aim of this study was to consolidate evidence from systematic reviews and meta-analyses investigating the association between reproductive factors in women of reproductive age and their subsequent risk of CVD. The data was sourced from Medline, Embase, and Cochrane databases from inception of the databases until August 31, 2019.

Preterm birth, pre-eclampsia, and stillbirth were associated with a twofold increase in the risk of composite CVD; premature ovarian insufficiency, placental abruption, gestational hypertension, and gestational diabetes mellitus were associated with a 1.5- to 1.9-fold increase in the risk; and polycystic ovary syndrome, early menopause, early menarche, and ever parity (giving birth to a fetus gestation age >24 weeks at least once) were associated with a less than 1.5-fold increase in risk. Breastfeeding for longer durations was also associated with reduced CVD risk. No association was found between CVD outcomes and fertility treatment, current use of the progesterone-only pill, or use of non-oral hormonal contraceptive agents.

Editor's Note: *Reproductive factors from menarche to menopause were associated with CVD in women. These causal associations could account for a large proportion of unexplained risk among women, and the risk might be modifiable. Identifying reproductive risk factors at an early stage in the lives of women might facilitate the initiation of strategies to modify potential risks, and perhaps the insurance industry could consider incorporating reproductive risk factors as part of CVD risk assessment going forward.*

Loss of life expectancy from air pollution compared to other risk factors: a worldwide perspective

Lelieveld J, et al.
Oxford Academic. Cardiovascular Research. 2020 Sept 1; 116(11): 1910-7.
https://doi.org/10.1093/cvr/cvaa025

Global burden of disease studies have assessed major health impacts and excess mortality rates from ambient (outdoor) air pollution, building on a growing database from epidemiological cohort studies. The aim of this study was to investigate to what degree long-term exposure to air pollution contributes to mortality due to non-communicable diseases (NCDs), including cardiovascular (CVD) and respiratory disease, lung cancer, and lower respiratory tract infections (LRI).

Main health risk factors for NCDs include tobacco smoking, unhealthy diets, being overweight, hypertension, diabetes, high cholesterol, and air pollution. The mortality attributable to air pollution can be estimated with disease-specific hazard models, linked to information about exposure to ambient concentrations.

A global atmospheric chemistry model was used to estimate exposure to ozone and fine particulate matter (particles of diameter <2.5 µm), combined with the new Global Exposure Mortality Model (GEMM) (Burnett, et al.). Using this model, the effects of different pollution sources were investigated, distinguishing between natural (e.g., wildfires, dust storms) and anthropogenic emissions, including fossil fuel use. Global excess mortality from all ambient air pollution is estimated at 8.8 million per year, with a loss of life expectance (LLE) of 2.9 years, a factor of two higher than earlier estimates and exceeding that of tobacco smoking.

A comparison of different global risk factors shows that ambient air pollution is a leading cause of excess mortality and LLE, in particular due to CVD. Globally, LLE from air pollution surpasses those of HIV/AIDS, parasitic, vector-borne, and other infectious diseases by large margins. The global mean LLE from air pollution also strongly exceeds that by all forms of violence (2.9 vs. 0.3 years) and that of smoking by approximately 33%.

Editor's Note: *Based on the results of studies of this type, it is possible that air pollution levels in geographic locations might become a significant risk factor when assessing cases should levels of pollution continue to rise.*

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