Looking Toward the Medical Underwriting Evidence in COVID-19

Risk Factors in Disease Development and Early Perspectives in Complications

RGA

Looking Toward the Medical Underwriting Evidence in COVID-19

Good day,

I hope all are staying safe and well. As the COVID-19 pandemic continues to rapidly unfold and evolve, we have heard from clients about several challenges around the development of underwriting guidelines not only for those deemed at higher risk of mortality from the disease but for the growing number of survivors of COVID-19 infection. The emerging data is complex yet incomplete and often contradictory.

To aid in this endeavor, RGA recently published the COVID-19 content page in the U.S. Global Underwriting Manual. (If you do not yet have access to the manual, please click here for registration instructions, and email the RGA Client & Marketing Services Team at CMSTeam@rgare.com if you need any assistance). Soon, we anticipate the addition of guidance for the assessment of individuals who have recovered from COVID-19.

As an intermediate step, we wanted to share with you a research review of the medical evidence surrounding COVID-19 to assist in risk stratification, both from the perspective of disease development, as well as early perspectives of long-term complications. Each of our USMM medical directors has contributed to this piece, which is organized to reflect their medical specialty and interest. I also thought this would be an excellent way to introduce our two newest medical directors, Drs. Maryam Shapland and Preeti Dalawari. They have responded admirably to the challenges of beginning a new position amid all this turbulence!

We will of course continue to follow this evidence closely and welcome your feedback as always.

Dave Rengachary, MD, DBIM, FALU, FLMI
Senior Vice President & Chief Medical Director
RGA U.S. Mortality Markets
drengachary@rgare.com

COVID-19 and Comorbidities: Introduction

Since the December 2019 identification of a novel coronavirus (later named SARS-CoV-2) in Wuhan, China, and characterization of the disease known as COVID-19 in the early months of 2020, there has been a substantial body of literature detailing the effect of age and chronic conditions on disease severity and mortality. One of the earliest studies[2] of the clinical features of novel coronavirus cases in Wuhan prospectively collected and analyzed the data on 41 patients with laboratory-confirmed infection who were admitted from December 16, 2019 to Jan 2, 2020. The median age of these patients was 49 years. Associated underlying disease included diabetes (20%), hypertension (15%), and cardiovascular disease (15%).

As the virus continued to spread, it became more evident that the elderly and those with underlying comorbidities were more likely to develop critical illness and experience a higher fatality rate. A recent meta-analysis[4] revealed that the proportion of underlying diseases were significantly higher in critically ill and fatal cases compared to non-critically ill patients; in particular, having diabetes (OR 3.68), hypertension (OR 2.72), cardiovascular disease (OR 5.19) and respiratory disease (OR 5.15) put patients at high risk for severe disease and mortality. Patients with cancer – particularly those with hematologic, lung and metastatic malignancies – have also been found to be at significant risk of severe outcomes from coronavirus disease, with higher observed death rates (OR 2.34) and higher rates of intensive care unit (ICU) admission (OR 2.84).[1] The odds ratio (OR) is a measure of the association of an exposure to an outcome; for example, an odds ratio of 2 doubles the odds of an outcome if there is a particular exposure.

In the US, the CDC has published the Morbidity and Mortality Weekly Report[3], which includes the characteristics of patients whose COVID-19 infection was lab-confirmed in March 2020. It is evident from this report that comorbidities play an important role in disease severity, as 89.3% of hospitalized patients have underlying disease:

Table 1. COVID-NET, Comorbidities of 1482 US-Hospitalized Patients Ages ≥ 18, March 1-30, 2020.	
Comorbidity	**Percentage (Ratio)**
Any Comorbidity	89.3 (159/178)
Hypertension	49.7 (79/151)
Obesity (BMI≥30)	48.3 (73/151)
Chronic metabolic Disease Diabetes	36.1 (60/166) 34.6 (55/159)
Chronic lung Disease Asthma COPD	34.6 (55/159) 17.0 (27/159) 10.7 (17/159)
Cardiovascular Disease[1] CAD CHF	27.8 (45/162) 14.2 (23/162) 6.8 (11/162)
Neurologic Disease	14.0 (22/157)
Renal Disease	13.1 (20/153)
Immunosuppressive condition	9.6 (15/156)
GI/Liver Disease	6.6 (10/152)
Blood disorder	5.8 (9/156)
Rheumatologic/Autoimmune disease	1.9 (3/154)

Table adapted from Garg et al.

[1] Cardiovascular disease excludes hypertension

References

1. Dai, M et al. Patients with cancer appear more vulnerable to SARS-COV-2: a multi-center study during the COVID19 outbreak. *Cancer Discov* April 28 2020 DOI: 10.1158/2159-8290.CD-20-0422
2. Huang, C et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet;* 395(10223): 497-506, 2020 02 15.
3. US Department of Health and Human Services/Centers for Disease Control and Prevention. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019-COVID-NET, 14 States, March 1-30, 2020. MMWR/April 17, 2020/Vol 68/No 15
4. Zheng Z, Peng F, Xu B et al. Risk factors of critical and mortal COVID-19 cases: A systematic literature review and meta-analysis. *Journal of Infection* (2020), doi: https://doi.org/10.1016/j.jinf.2020.04.021

Pulmonary Considerations in COVID-19

Preeti Dalawari, MD, MSPH
Medical Director
RGA U.S. Mortality Markets
preeti.dalawari@rgare.com

The virus aptly named SARS-CoV-2, or severe acute respiratory syndrome coronavirus 2, can cause a wide array of pulmonary symptoms and complications, of which acute respiratory distress syndrome (ARDS) is the most severe. SARS-CoV-2 enters cells by binding its spike protein to the angiotensin converting enzyme 2 (ACE2) receptor on the host. These ACE2 receptors are found on alveolar lung and upper respiratory tract epithelial cells (as well as endothelial cells of arteries and veins, arterial smooth muscle, small intestine epithelium, immune cells) and correlates with COVID-19 pulmonary symptoms and organ dysfunction.[1-3] Suppression of ACE2 expression is thought to have a role in the pathologic changes (e.g., interstitial and alveolar exudative inflammation), leading to pneumonia and ARDS.[1,2] Pulmonary involvement (e.g., coughing, sneezing) also aids in high viral transmission.

Intuitively, it makes sense that those with preexisting lung conditions are at an increased risk for severe disease. The CDC guidelines include those individuals with chronic lung diseases such as moderate-to-severe asthma, COPD, pulmonary fibrosis, and cystic fibrosis.[4] According to surveillance data, about one-third of admitted US patients have chronic lung disease.[5] Data from March 1 - April 4 of 5,700 COVID-19 positive hospitalized patients within the Northwell Health system in New York, found respiratory comorbidities of: asthma 9%, COPD 5.4%, and obstructive sleep apnea 2.9%.[6]

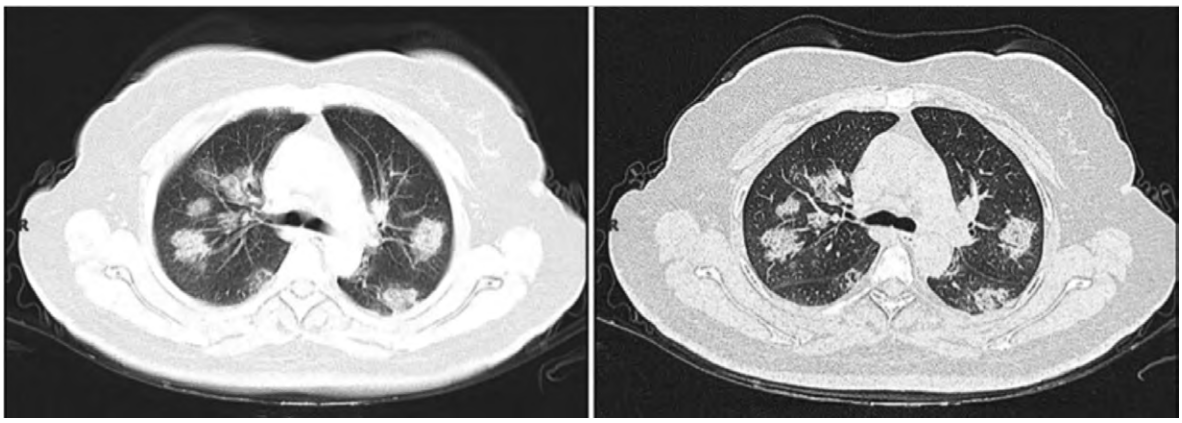
While predominant symptoms vary among countries and regions, most studies indicate initial nonspecific viral symptoms such as fever, cough, myalgias/fatigue.[7,8] Current US data obtained through COVID-NET[§] notes cough and shortness of breath are among the predominant respiratory symptoms upon admission to the hospital, indicating a progression of disease from upper to lower respiratory tract.[6] The median time interval from symptom onset to hospitalization was seven days.[5]

Earlier studies from China show a similar clinical course for those hospitalized; with dyspnea occurring at the beginning of the second week (days 5-8) corresponding with hospitalization.[7]

Most infected individuals are asymptomatic or pauci-symptomatic. Of 44,415 confirmed COVID-19 cases, the Chinese CDC found 81% were mild (no or mild pneumonia). However, 14% were severe, defined as dyspnea, hypoxemia with oxygen saturations ≤ 93%, respiratory rate of ≥ 30, >50% lung involvement on imaging in 24-48 hours of hospitalization, or partial pressure of arterial oxygen to fraction of inspired oxygen ration < 300 mm Hg (a finding of early acute respiratory distress syndrome), and 5% were critical (respiratory failure, shock, and multiple organ dysfunction).[9]

[§] per CDC website/MMR weekly: COVID-NET (COVID-19-Associated Hospitalization Surveillance Network) data arises from population-based surveillance for laboratory-confirmed COVID-19 hospitalizations in 14 states (California, Colorado, Connecticut, Georgia, Iowa, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah). This area distribution represents 10% of the US population.

Chest CT of Rapidly Progressing Phase in COVID-19 Pneumonia



https://commons.wikimedia.org/wiki/File:COVID19CT1.webp Creative Commons Attribution 4.0

A few studies have looked at prognostic factors for disease progression and hospitalization. A systematic review by Zheng et al. noted that shortness of breath/dyspnea was significantly associated with progression of disease in those critical patients (OR 4.16) compared to noncritical hospitalized patients.[10] Another study in the US found an admission pulse-oximetry reading of <88% was positively associated with admission and critical illness (OR 6.99), along with certain inflammatory markers and older age.[11] Of the 1,099 hospitalized patients with an outcome (discharged alive or dead), 28% required invasive mechanical ventilation and 18.5% died or were discharged to hospice. Among critical cases, the fatality rate was 45%, similar to the findings by the Chinese CDC of 49%.[11]

There are many contributing factors to morbidity and mortality of COVID-19, one of which is ARDS. Lung injury in ARDS arises from an intense host cytokine-mediated inflammatory response with resultant cell death leading to alveolar flooding, diminished lung compliance, and ventilation perfusion mismatches.[12] This leads to respiratory failure, hypoxemia, and mechanical ventilation.[13] Because there have been reports of preserved lung compliance with hypoxemia, there is speculation on whether the pulmonary pathophysiology in critical COVID-19 patients is consistent with ARDS.[14] Newer studies show many critical COVID-19 patients having a similar hyperinflammatory response and downstream effects as traditional ARDS patients.[12,15] Thus, from an underwriting perspective, the long-term sequelae of ARDS needs consideration.

Studies have shown parenchymal lung changes on CT scan of the chest in 75-87% of patients six months to five years post-ARDS but involving less than 25% of the lung.[16] The coarse reticular pattern and ground glass opacities noted is thought to be fibrosis of the lung. Accordingly, those patients whose ARDS was due to pulmonary pathology, who spent more time on a ventilator, and had higher positive end expiratory pressure, were more likely to develop fibrosis.[16] While many patients may be left with radiographic changes, the clinical impact of these findings are unclear.

There are conflicting studies on the long-term residual effects to lung function as measured by pulmonary function tests (six-minute walk test, spirometry, carbon monoxide diffusing capacity, etc.). Some studies find residual restrictive (range in studies of 15% to 58% of patients), obstructive (range of 6% to 43% of patients), or mixed-pattern disease on PFTs; others indicate resolution of these findings within six months to a year and remaining stable five years post-ARDS.[16,17] Median diffusion capacity

returned to near normal levels at 12 months and resolved by four years and remained stable. It is also important to note that muscular weakness, as opposed to or in addition to pulmonary dysfunction, may contribute to abnormalities, if noted on spirometry or the six-minute walk test.[16,17] Given the conflicting evidence, it seems reasonable at this time, to be cognizant of possible long-term complications of ARDS associated with COVID-19.

Underwriting Takeaways

- Those with COPD, pulmonary fibrosis, cystic fibrosis, and moderate to severe asthma are at greater risk of morbidity and mortality related to SARS-CoV-2
- Long-term pulmonary complications are not currently known but may be similar to long-term respiratory sequelae found in ARDS:
    - Coarse reticular pattern and ground glass opacities on CT chest
    - Pulmonary function tests are very often abnormal, but the pattern is quite variable. If complications develop, they typically are apparent by one year's time.

It is worth mentioning that many of the current data and studies, especially within the US, are case series or hospitalized-population based with incomplete data or lack of final outcomes. Thus much of the data is preliminary and subject to change as more information or outcomes are known.

References

1. Jain A. COVID-19 and lung pathology. Indian J Pathol Microbiol [serial online] 2020 [cited 2020 Apr 29]; 63:171-2. Available from: http://www.ijpmonline.org/text.asp?2020/63/2/171/282688
2. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential Effects of Coronaviruses on the Cardiovascular System: A Review. *JAMA Cardiol.* Published online March 27, 2020. doi:10.1001/jamacardio.2020.1286
3. Liu Peter P., Blet Alice, Smyth David, and Li Hongliang. "The Science Underlying COVID-19: Implications for the Cardiovascular System." *Circulation* 0, no. 0. Accessed April 30, 2020. https://doi.org/10.1161/CIRCULATIONAHA.120.047549.
4. CDC. "Coronavirus Disease 2019 (COVID-19)." Centers for Disease Control and Prevention, February 11, 2020. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html.
5. Garg, Shikha. "Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020." *MMWR. Morbidity and Mortality Weekly Report* 69 (2020). https://doi.org/10.15585/mmwr.mm6915e3.
6. Richardson, Safiya, Jamie S. Hirsch, Mangala Narasimhan, James M. Crawford, Thomas McGinn, Karina W. Davidson, Douglas P. Barnaby, et al. "Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area." *JAMA*, April 22, 2020. https://doi.org/10.1001/jama.2020.6775.
7. Huang, Chaolin, Yeming Wang, Xingwang Li, Lili Ren, Jianping Zhao, Yi Hu, Li Zhang, et al. "Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China." *The Lancet* 395, no. 10223 (February 15, 2020): 497–506.
8. Tu, Huilan, Sheng Tu, Shiqi Gao, Anwen Shao, and Jifang Sheng. "The Epidemiological and Clinical Features of COVID-19 and Lessons from This Global Infectious Public Health Event." *Journal of Infection*, April 18, 2020. https://doi.org/10.1016/j.jinf.2020.04.011.
9. Wu, Zunyou, and Jennifer M. McGoogan. "Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention." *JAMA* 323, no. 13 (April 7, 2020): 1239–42. https://doi.org/10.1001/jama.2020.2648.
10. Zheng, Zhaohai, Fang Peng, Buyun Xu, Jingjing Zhao, Huahua Liu, Jiahao Peng, Qingsong Li, et al. "Risk Factors of Critical & Mortal COVID-19 Cases: A Systematic Literature Review and Meta-Analysis." *Journal of Infection*, April 23, 2020. https://doi.org/10.1016/j.jinf.2020.04.021.
11. Petrilli, Christopher M., Simon A. Jones, Jie Yang, Harish Rajagopalan, Luke F. O'Donnell, Yelena Chernyak, Katie Tobin, Robert J. Cerfolio, Fritz Francois, and Leora I. Horwitz. "Factors Associated with Hospitalization and Critical Illness among 4,103 Patients with COVID-19 Disease in New York City." Preprint. Intensive Care and Critical Care Medicine, April 11, 2020. https://doi.org/10.1101/2020.04.08.20057794.

12. Luks, Andrew M, and Erik R Swenson. "COVID-19 Lung Injury and High Altitude Pulmonary Edema: A False Equation with Dangerous Implications." *Annals of the American Thoracic Society*, April 24, 2020, AnnalsATS.202004-327FR. https://doi.org/10.1513/AnnalsATS.202004-327FR.

13. Matthay, Michael A., Rachel L. Zemans, Guy A. Zimmerman, Yaseen M. Arabi, Jeremy R. Beitler, Alain Mercat, Margaret Herridge, Adrienne G. Randolph, and Carolyn S. Calfee. "Acute Respiratory Distress Syndrome." *Nature Reviews Disease Primers* 5, no. 1 (December 2019): 18. https://doi.org/10.1038/s41572-019-0069-0.

14. Gattinoni, Luciano, Silvia Coppola, Massimo Cressoni, Mattia Busana, Sandra Rossi, and Davide Chiumello. "Covid-19 Does Not Lead to a 'Typical' Acute Respiratory Distress Syndrome." *American Journal of Respiratory and Critical Care Medicine*, March 30, 2020, rccm.202003-0817LE. https://doi.org/10.1164/rccm.202003-0817LE.

15. Ziehr, David R., Jehan Alladina, Camille R Petri, Jason H. Maley, Ari Moskowitz, Benjamin D Medoff, Kathryn A Hibbert, B. Taylor Thompson, and C. Corey Hardin. "Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study." *American Journal of Respiratory and Critical Care Medicine*, April 29, 2020, rccm.202004-1163LE. https://doi.org/10.1164/rccm.202004-1163LE.

16. DiSilvio, Briana, Meilin Young, Ayla Gordon, Khalid Malik, Ashley Singh, and Tariq Cheema. "Complications and Outcomes of Acute Respiratory Distress Syndrome." *Critical Care Nursing Quarterly* 42, no. 4 (December 2019): 349–361. https://doi.org/10.1097/CNQ.0000000000000275.

17. Chiumello, Davide, Silvia Coppola, Sara Froio, and Miriam Gotti. "What's Next After ARDS: Long-Term Outcomes." *Respiratory Care* 61, no. 5 (May 1, 2016): 689. https://doi.org/10.4187/respcare.04644.

COVID-19 and the Heart

Valerie Kaufman, MD, FACC, DBIM
Vice President and Medical Director
RGA U.S. Mortality Markets
vkaufman@rgare.com

Pre-existing cardiovascular conditions are common in hospitalized COVID-19 patients and convey risk for a severe course. A study of 1,591 patients admitted to ICUs in the Lombardy region of Italy[1] noted 49% had hypertension (HTN) and an additional 21% had other cardiovascular diseases (CVD). In the US, the COVID-19 Associated Hospitalization Surveillance Network (COVID-NET) reported similar findings in 1,482 patients admitted to hospital in March 2020 – 49.7% with HTN and 27.8% with CVD.[2]

Case Fatality Rate and Pre-existing Conditions

Pre-existing Condition	Case Fatality Rate
Cardiovascular disease	10.5%
Diabetes	7.3%
Chronic respiratory disease	6.3%
Hypertension	6.0%
Cancer	5.6%
No pre-existing condition	0.9%

Table adapted from Liu et al.

In addition, the case fatality rate for those with underlying CVD is much higher than for other pre-existing conditions. In a series of 44,672 confirmed cases from China, only 4.2% had underlying cardiovascular disease, however this group accounted for 22.7% of deaths. The case fatality rate in those with CVD is 10.5%, much higher than for other common comorbidities, including lung disease.

With or without pre-existing conditions, COVID-19 has many effects on the cardiovascular system. Elevated troponin indicating acute myocardial injury is a strong predictor of adverse outcome. This acute myocarditis-

like syndrome, often accompanied by left ventricular systolic dysfunction and arrhythmias, has been called Acute COVID-19 Cardiovascular Syndrome (ACovCS). ACovCS often occurs as a late complication, after recovery from fever and pulmonary manifestations has begun. As many as 28% of hospitalized COVID-19 patients have elevated troponin, which confers up to five times the mortality risk.[5] Other biomarkers including NTproBNP also predict unfavorable outcome.

The pathophysiology of cardiac injury is complex and not completely understood. COVID-19 can cause myocarditis through direct infection of myocardial cells or through immune processes. Stress cardiomyopathy is another proposed mechanism of cardiac dysfunction. Down-regulation of angiotensin converting enzyme2 (ACE2) results in unopposed angiotensin II effects – pro-inflammatory, pro-thrombotic, pro-oxidant – and an increased susceptibility to heart failure. Given the role of ACE2 in COVID infections, there has been considerable speculation that the use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) could be harmful in those being treated or at risk for COVID-19. Three observational studies [9, 10, 11] published May 1, 2020 in the New England Journal of Medicine refuted this, showing no evidence of harm with continued use of ACEIs and ARBs.

There is also increasing evidence of involvement of the vasculature with vasculitis, microangiopathy, and thrombosis, which can lead to myocardial ischemia, contractile dysfunction, and arrhythmias. The intense systemic inflammatory response may also contribute to destabilization of atherosclerotic plaque and acute coronary syndrome/myocardial infarction.

Compromised cardiac function is often amplified by increased metabolic demand due to sepsis, hypoxia due to pulmonary impairment, and failure of other organs. Heart failure may ensue.

Cardiac arrhythmias, including atrial fibrillation and ventricular arrhythmias, are common, occurring in 6.9% of hospitalized patients and 44.4% of ICU patients in a Chinese cohort.[8] Fever is a well-known trigger for polymorphic ventricular tachycardia in Brugada syndrome and other inherited arrhythmia syndromes. QT prolongation, which can also lead to polymorphic ventricular tachycardia and ventricular fibrillation, may occur due to the high levels of cytokines often seen in severe COVID-19 cases. Many medications used to combat the illness also have QT-lengthening effects. These medications include chloroquine, hydroxychloroquine, azithromycin, and the antiretroviral agents remdesivir and lopinavir/ritonavir. Electrolyte disturbances, hypoxia, and myocardial damage are also factors that predispose to serious arrhythmias.

Underwriting Takeaways

- Underlying CVD of many types is clearly associated with higher risks of severe disease, hospitalization, and death related to COVID-19.
- The name Acute COVID-19 Cardiovascular Syndrome (ACovCS) has been coined to describe the combinations of acute myocarditis, left ventricular dysfunction, and arrhythmias that can be seen, often as a late complication.
- Elevated troponin indicating acute myocardial injury is a strong predictor of an adverse outcome. Survivors of severe infections will need to be monitored carefully for possible long-term sequelae, such as cardiomyopathy, chronic heart failure, and ongoing arrhythmia risk.

References

1. Grasselli G, Zangrillo A et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* 2020;323(16):1574-1581.
2. Garg S, Kim L et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 – COVID-NET, 14 states, March 1-30, 2020. MMWR;69(15):458-464.
3. Liu PP, Blet A et al. The science underlying COVID-19: Implications for the cardiovascular system. *Circulation* 2020. Originally published 15 Apr 2020
4. Madjid M, Safavi-Naeni P et al. Potential effects of coronaviruses on the cardiovascular system – a review. *JAMA Cardiol*. doi:10.1001/jamacardio.2020.1286. Published online March 27, 2020.
5. Hendren NS, Drazner MH et al. Description and proposed management of the acute COVID-19 cardiovascular syndrome. *Circulation* 2020. Originally published16 Apr 2020.
6. Gupta AK, Jneid H et al. Current perspectives on coronavirus 2019 (COVID-19) and cardiovascular disease: A white paper by the JAHA editors. *Journal of the American Heart Association* 2020. Originally published 29 Apr 2020 *Journal of the American Heart Association*.
7. Lazzerini PE, Boutjdir M and Capecchi PL. COVID-19, arrhythmia risk and inflammation: *Mind the gap!* Circulation 2020. Originally published 14 Apr 2020
8. Driggin E, Madhavan MV et al. Cardiovascular considerations for patients, health care workers, and health systems during the Coronavirus Disease 2019 (COVID-19) pandemic. *Journal of the American College of Cardiology* 2020.
9. Mehra MR, Desai SS et al. Cardiovascular disease, drug therapy, and mortality in Covid-19. *NEJM* 2020. Published May 1, 2020. DOI: 10.1056/NEJMoa2007621
10. Mancia G, Rea F et al. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *NEJM* 2020. Published May 1, 2020. DOI: 10.1056/NEJMoa2006923
11. Reynolds HR, Adhikari S, et al. Renin-angiotensin-aldosterone system inhibitors and the risk of Covid-19. *NEJM* 2020. Published May 1, 2020. DOI: 10.1056/NEJMoa2008975
12. Jarcho JA, Ingelfinger JR, et al. Inhibitors of the renin-angiotensin-aldosterone system and Covid-19. *NEJM* 2020. Published May 1, 2020. DOI: 10.1056/NEJMe201292

COVID-19, Obesity and Diabetes

Maryam Shapland, MD, DBIM
Vice President and Medical Director
RGA U.S. Mortality Markets
maryam.shapland@rgare.com

As COVID-19 continues to spread worldwide, characteristics of a country's population may be associated with clinical features and outcomes of the disease. The higher case-fatality rate in Italy compared to China, for example, has been attributed to its older population[8]. However, some authors have argued that the increased prevalence of obesity in older adults in Italy may also account for the differences in mortality between the two countries.[2]

Obesity has also been linked to severe coronavirus disease in Americans. According to the CDC[1], in 2017-2018, the prevalence of obesity in the United States was 42.4%. Americans have a high burden of severe obesity, as 9.2% of the population have a BMI>40 kg/m^2. Findings from recent studies have shed some light on the intersection of COVID-19 and obesity:

- Per the March MMWR[11], 48.3% of adults hospitalized with COVID-19 were obese. Remarkably, of the admitted patients aged 18-49, 59% were obese. In older patients, 49% of those aged 50-64 and 41% of those aged 65 years and older were obese.
- A retrospective analysis[7] of BMI stratified by age was performed in 3,615 COVID-19-positive patients presenting to a large academic hospital system in New York City. This study showed that compared to patients in the same age category with a BMI <30:
    - Patients aged <60 years with a BMI of 30-34 were two times more likely to be admitted to acute care and 1.8 times more likely to be admitted to critical care.
    - Patients aged <60 years with a BMI ≥35 were 2.2 times more likely to be admitted to acute care and 3.6 times more likely to be admitted to critical care.
- A retrospective case series[5] of 393 adults admitted to a community hospital in New York City with confirmed COVID-19 infection found that 35.8% of admitted patients were obese. Of the patients who required invasive mechanical ventilation, 43.4% were obese.

Obesity was recognized as an independent risk factor for complications from H1N1 infection during the 2009 pandemic.[4] Although it remains to be seen whether obesity is an independent risk factor for severe COVID-19 illness, anatomy and pathophysiology indicate this may be the case. Obesity exerts a mechanical effect on lung physiology, and adipose tissue can function as an endocrine organ producing systemic inflammation and effecting central respiratory control.[12] This can then lead to diseases such as obstructive sleep apnea, restrictive lung disease, obesity hypoventilation syndrome, and airway inflammation, which subsequently exacerbates underlying asthma and COPD. Intubation and ventilation of obese patients are often complicated by unaccommodating anatomy, poor lung function, and smaller lung volumes. An increased work of breathing places additional strain on already impaired cardiac and pulmonary functions.[12]

Persons with obesity are also at high risk by virtue of the chronic diseases that obesity drives[4]. Not only does chronic hyperglycemia lead to an immunodeficient state and increased pulmonary infection risk, but patients with diabetes exhibit more severe disease when infected with respiratory viruses. In fact, during the 2009 H1N1 pandemic, the presence of diabetes tripled the risk of hospitalization and quadrupled the risk of ICU admission once hospitalized.[9]

Researchers have hypothesized[3] that diabetic patients are at increased risk for COVID-19 infection as human pathogenic coronaviruses bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels. The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes, facilitating infection with COVID-19. Once infected, it has been shown[6] that patients with diabetes and no other comorbidities were at higher risk of severe pneumonia, excessive uncontrolled inflammatory response, and hypercoagulable state, which are all associated with dysregulation of glucose metabolism. In a recent study[10], the authors noted that among 1,382 COVID-19 patients, diabetes was the second most frequent comorbidity found. Diabetic patients had an increased risk of ICU admission (OR 2.79); and in 471 patients analyzed for secondary outcome, those with diabetes had a higher mortality risk (OR 3.21). In the March MMWR[11], diabetes was present in 28.3% of adults hospitalized with COVID-19 in the US.

Given the complex interplay, much of which is still unclear, between SARS-CoV-2 and obesity, and its associated conditions such as diabetes and pulmonary disease, it is evident that the management of obese patients with COVID-19 will continue to be a challenge as this pandemic develops.

Underwriting Takeaways

- In the US, obese adults of all ages are at higher risk for severe and critical COVID-19 disease.
- It appears that the effect of obesity on the severity of COVID-19 disease skews towards a younger population, with disease severity worsening as BMI increases.
- It is still undetermined to what extent obesity is an independent risk factor or a confounding variable for severe COVID-19 disease. However, the metabolic and pulmonary sequelae of morbid obesity have been shown to increase the risk and complications of respiratory infections.
- Diabetic patients appear to be at increased risk for infection and worse prognosis from COVID-19 via ACE2 expression and an excessive inflammatory response.

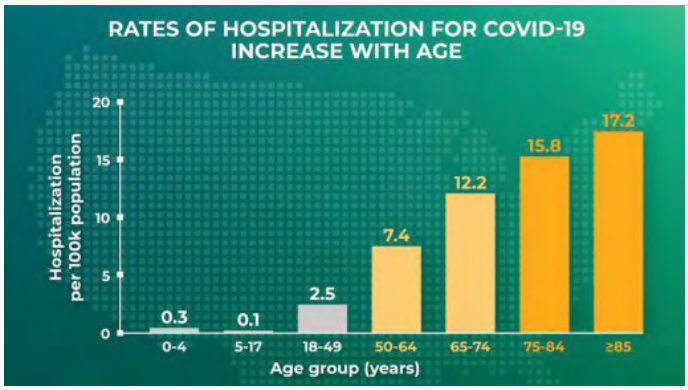
References

1. Centers for Disease Control and Prevention: Adult Obesity Facts. https://www.cdc.gov/obesity/data/adult.html
2. Dietz, W. and Santos-Burgoa, C. (2020), Obesity and its Implications for COVID-19 Mortality. Obesity. doi:10.1002/oby.22818
3. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21. doi:10.1016/S2213-2600(20)30116-8
4. Finer N, Garnett SP, Bruun JM, COVID-19 and obesity, *Clinical Obesity,* (2020). Wiley Online Library
5. Goyal P, Choi J, Pinheiro L et al. Clinical Characteristics of Covid-19 in New York City. *NEJM.* April 17, 2020. DOI: 10.1056/NEJMc2010419
6. Guo, W, Li, M, Dong, Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020; e3319. https://doi.org/10.1002/dmrr.3319
7. Lighter J, Phillips, M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission, *Clinical Infectious Diseases,* ciaa415, https://doi.org/10.1093/cid/ciaa415
8. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA*. Published online March 23, 2020. doi:10.1001/jama.2020.4683
9. Puig-Domingo, M., Marazuela, M. & Giustina, A. COVID-19 and endocrine diseases. A statement from the European Society of Endocrinology. *Endocrine* 68, 2–5 (2020). https://doi.org/10.1007/s12020-020-02294-5
10. Roncon L, Zuin M, Rigatelli G et al. Diabetic Patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. *Journal of Clinical Virology*. Available online April 9, 2020. https://doi.org/10.1016/j.jcv.2020.104354
11. US Department of Health and Human Services/Centers for Disease Control and Prevention. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019-COVID-NET, 14 States, March 1-3, 2020. MMWR/April 17, 2020/Vol 68/No 15
12. Zammit C, Liddicoat H, Moonsie I, Makker H. Obesity and respiratory diseases. *Int J Gen Med*. 2010; 3:335–343. Published 2010 Oct 20. doi:10.2147/IJGM.S11926

Impact on the Older Age Population
(Defined as over the age of 65)

Lisa Duckett, MD, DBIM
Vice President and Medical Director
RGA U.S. Mortality Markets
lduckett@rgare.com

Individuals of any age can contract COVID-19 with variability in symptoms and, more importantly, severity of disease. However, older individuals infected with COVID-19 experience more severe symptoms, higher mortality, and prolonged recovery when compared to younger age cohorts. Studies of hospitalized patients from both China and the US identified factors that correlate with increased risk for death: age has been a consistent factor.[1]



https://www.cdc.gov/mmwr/volumes/69/wr/mm6915e3.htm?s_cid=mm6915e3_w

Why has this disease hit the elderly so hard? One of the reasons was shared earlier by my colleague and is intuitive: mortality related to COVID-19 is clearly impacted by comorbidities, which are more common in the elderly. From a statistical standpoint, it can be challenging then to disentangle the relative contribution of age and comorbidity in this cohort.

There are, however, several other factors which predispose the elderly to worse outcomes from COVID-19. First, the presence of atypical symptoms has been reported in geriatric populations infected with the coronavirus from Europe and the US. Observed signs and symptoms include delirium, falls, low blood pressure, painful swallowing, abdominal pain, and loss of smell and taste. Any unusual signs or symptoms in a geriatric population may signal COVID-19 infection.[2] Delayed recognition further compounds the local spread of disease as virus is shed in the days prior to diagnosis.

Second, the general decline in immune function with aging (immunosenescence) is well established. This is due to reduction of both B and T cells in the bone marrow and thymus, neither of which function as well in the older adult.[3] A particular challenge in older adults is the loss of naïve-T cells, which are normally activate upon presentation of unfamiliar pathogens and develop into effector T cells responsible for clearing the virus. This leads not only to a diminished ability to fight novel infections like COVID-19 but also raises concerns regarding the efficacy of potential vaccines in older adults. For example, a recent analysis estimated influenza vaccine effectiveness at 30-50% in adults older than 65 as compared to 70-90% for children and younger adults.[4] While several techniques are being studied in COVID-19 vaccine research[5], such as the use of adjuvants, the effectiveness of any potential vaccines in this vulnerable group will need to be closely followed.

Finally, there are large subsets of older individuals for whom physical and social distancing is not feasible. This is nowhere more evident than in the nursing home and long-term care facility setting. As of May 1, there have been 97,000 positive tests and 16,000 deaths among residents and staff of these facilities, which represents over a quarter of the overall deaths in the US.[6] While the precise risk is unclear due to inconsistent reporting, there are clear and increasing cases of "wildfire" transmission and very high rates of mortality. Another study found that the 101 residents of facilities associated with the Washington state outbreak, who had an average age of 83 and the majority had at least one comorbid condition, the case fatality rate was 34%.[7] It should be noted that the inability to adequately socially and physically distance is not limited to nursing home patients and likely extends to those at-home residents with more moderate degrees of dementia and chronic medical illness.

Underwriting Takeaways

- Atypical symptoms may be present in the older-age cohort (over 65 years of age) in relation to COVID-19 infection. These may include unexplained falls, confusion, trauma, and abdominal pain.
- Elderly individuals who have already developed diseases related to immune compromise or are on immunosuppressant medications represent further elevated risk given the baseline contribution of diminished immune function to COVID-19-related older-age mortality.

References

1. McIntosh K, Corona disease 2019 (COVID-19) : Epidemiology, virology, clinical features, diagnosis and prevention. Accessed April 30.2020. *UpToDate*.
2. Graham J, Seniors With COVID-19 Show Unusual Symptoms, Doctors Say. Medscape- April 27, 2020.
3. Montecino-Rodriguez, Encarnacion, Beata Berent-Maoz, and Kenneth Dorshkind. "Causes, Consequences, and Reversal of Immune System Aging." *The Journal of Clinical Investigation* 123, no. 3 (March 1, 2013): 958–65.
4. Ciabattini, Annalisa, Christine Nardini, Francesco Santoro, Paolo Garagnani, Claudio Franceschi, and Donata Medaglini. "Vaccination in the Elderly: The Challenge of Immune Changes with Aging." Seminars in Immunology, Inflammaging, 40 (December 1, 2018): 83–94. https://doi.org/10.1016/j.smim.2018.10.010.
5. Weintraub, Karen. "Coronavirus Vaccines May Not Work for the Elderly and This Lab Aims to Change That." Scientific American. Accessed May 4, 2020. https://www.scientificamerican.com/article/coronavirus-vaccines-may-not-work-for-the-elderly-and-this-lab-aims-to-change-that/.
6. Kwiatkowski, Tricia L. Nadolny and Marisa. "'Our Patients Are Dropping like Flies': 16,000 Dead from COVID-19 in U.S. Nursing Homes." USA TODAY. Accessed May 4, 2020. https://www.usatoday.com/story/news/investigations/2020/05/01/coronavirus-nursing-homes-more-states-pressured-name-facilities/3062537001/.
7. McMichael TM, Currie DW, Clark S, et al. Epidemiology of Covid-19 in a Long-Term Care Facility in King County, Washington. *N Engl J Med*; 2020 Mar 27. doi: 10.1056/NEJMoa2005412.

Neurologic Complications of COVID-19

Dave Rengachary, MD, DBIM, FALU, FLMI
Senior Vice President and Chief Medical Director
RGA U.S. Mortality Markets
drengachary@rgare.com

There are no neurologic conditions specifically included on the CDC list of those at higher risk for severe illness[1], though it is certainly reasonable to raise concerns about those individuals whose neurologic disease places them at higher risk due to immune, respiratory, swallowing compromise, or those at greater risk of care in a hospital or long-term-care facility.

Not surprisingly, the first reports of neurologic complications arose from a case series of patients from the Wuhan, China outbreak.[2] In a series of 214 individuals, 78 patients (36.4%) had some sort of neurologic manifestation of disease. The most common symptoms affected the central nervous system (24.8%), were nonspecific, and included dizziness and headache. However, six patients (2.8%) presented with acute cerebrovascular disease. Interestingly, two of the six stroke patients presented to the hospital with typical stroke symptoms and were only later found to have lung lesions characteristic of COVID-19. The other strokes occurred later in the disease cycle and in more severely affected individuals, which is a finding that is difficult to interpret given the known, higher level of cardiovascular comorbidities. Impaired taste and smell emerged as the most common symptoms attributed to the peripheral nervous system. This finding has since been replicated in several other publications[3,4], and the symptoms are now recognized by the CDC as indicative of the disease. Though certain olfactory cells have been identified as more susceptible to the virus, the etiology of these symptoms remains unclear. An axonal neuropathy has been described in SARS, which raises the specter of a similar process for COVID-19, but EMG/NCS was not performed in patients with sensory symptoms.[5]

Table 1. Neurologic Complications in Wuhan, China COVID-19 series			
Nervous System Symptoms	**All Cases (%)**	**Severe Cases (%)**	**Non-severe Cases (%)**
Any	36.4	45.5	30.2
CNS	24.8	30.7	20.6
Dizziness	16.8	19.3	15.1
Headache	13.1	17.0	10.3
Impaired Consciousness	7.5	14.8	3
Stroke	2.8	5.7	0.8
Visual	1.4	2.3	0.8
Ataxia	0.5	1.1	2.4
Seizure	0.5	1.1	0
PNS	8.9	8.0	9.5
Loss of Taste	5.6	3.4	7.1
Loss of Smell	5.1	3.4	6.3
Nerve Pain	2.3	4.5	0.8
Skeletal Muscle Injury	10.7	19.3	4.8

Table adapted from Mao et al.[2]

A second case series has since been reported in the New England Journal of Medicine[6] examining 58 COVID-19 patients admitted to the intensive care unit in Strasbourg, France in March and April of 2020. A high proportion of these patients (69%) showed evidence of agitation and confusion even as sedation was discontinued. While ICU-related delirium is a very common phenomenon, there were also relatively high rates of meningeal enhancement, corticospinal tract signs, and stroke, which suggest at least a reasonable possibility of specific neurologic COVID-19 sequelae.

Perhaps of greatest concern is a series of strokes in individuals affected by COVID-19 as reported by New York City physicians in a letter also to the New England Journal of Medicine. While the number of individuals is quite small (five), it raises concern for several reasons: 1) all the patients were under 50 years old, 2) the COVID-19 symptoms were otherwise mild or non-existent, and 3) the large cerebral vessels were disproportionately affected. This may provide support to reports from the Netherlands[8] of a very overall high rate of thrombotic complications (31%) in severely affected individuals. A series[9] of five patients has also been reported out of northern Italy. The patients developed Guillain-Barre syndrome (GBS) with a typical latency of 5-10 days after the onset of COVID-19 symptoms. This is not unexpected given the association of the disease with other coronavirus infections.

At the time of publication, there are no studies available on the long-term cognitive outcomes from the disease. It is worth noting, however, that at least mild cognitive impairment is felt to be quite common after prolonged intensive care hospitalization.[10]

Underwriting Takeaways

- Neurologic symptoms are very common in COVID-19, especially early in the disease. The greatest mortality concern relates to stroke, which tends to occur in more severely affected individuals and may be a manifestation of overall elevated thrombotic risk.
- Anosmia (loss of smell) and ageusia (loss of taste) are uniquely associated with the disease, and particular caution is recommended if these symptoms are encountered near the time of application.
- Long-term cognitive outcomes related to the disease are unclear at this time, but prolonged intensive care hospitalization of any type often results in some degree of cognitive impairment.

References

1. CDC. "Coronavirus Disease 2019 (COVID-19)." Centers for Disease Control and Prevention, February 11, 2020. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html.
2. Mao, Ling, Huijuan Jin, Mengdie Wang, Yu Hu, Shengcai Chen, Quanwei He, Jiang Chang, et al. "Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China." *JAMA Neurology*, April 10, 2020.
3. Yan, Carol H., Farhoud Faraji, Divya P. Prajapati, Christine E. Boone, and Adam S. DeConde. "Association of Chemosensory Dysfunction and Covid-19 in Patients Presenting with Influenza-like Symptoms." *International Forum of Allergy & Rhinology* n/a, no. n/a. Accessed April 27, 2020.
4. "Loss of Smell and Taste in Combination with Other Symptoms Is a Strong Predictor of COVID-19 Infection | MedRxiv." Accessed April 27, 2020. https://www.medrxiv.org/content/10.1101/2020.04.05.20048421v1.
5. Pleasure, Samuel J., Ari J. Green, and S. Andrew Josephson. "The Spectrum of Neurologic Disease in the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic Infection: Neurologists Move to the Frontlines." *JAMA Neurology*, April 10, 2020.
6. Pleasure, Samuel J., Ari J. Green, and S. Andrew Josephson. "The Spectrum of Neurologic Disease in the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic Infection: Neurologists Move to the Frontlines." *JAMA Neurology*, April 10, 2020.
7. Placeholder for NEJM article
8. Klok, F.A., M.J.H.A. Kruip, N.J.M. van der Meer, M.S. Arbous, D.A.M.P.J. Gommers, K.M. Kant, F.H.J. Kaptein, et al. "Incidence of Thrombotic Complications in Critically Ill ICU Patients with COVID-19." *Thrombosis Research*, April 2020.
9. Toscano, Gianpaolo, Francesco Palmerini, Sabrina Ravaglia, Luigi Ruiz, Paolo Invernizzi, M. Giovanna Cuzzoni, Diego Franciotta, et al. "Guillain–Barré Syndrome Associated with SARS-CoV-2." *New England Journal of Medicine*, April 17, 2020. https://doi.org/10.1056/NEJMc2009191.
10. Prevligliano, I. et al. "Long-Term Cognitive Impairment after Critical Illness – Definition, Incidence, Pathophysiology and Hypothesis of Neurotrophic Treatment," September 10, 2015.