RISK FACTORS, SEQUALAE AND INDIRECT EFFECTS of COVID-19
As the number of confirmed cases and deaths from COVID-19 (Coronavirus 2019/SARS-CoV-2) continues to rise, clinicians and pathologists are gradually improving their understanding of the damage it can potentially wreak on the human body. Since the early days of its identification as a novel virus, it has been clear that the infection starts in the lungs, however its reach can extend to many other organs, including the heart and blood vessels, kidneys, gut, and brain.

What we do know is that, of those who become infected and show symptoms, some will require hospitalization and some will develop a “critical” illness that is often fatal. The figures involved are more complex than they seem: certain factors, such as pre-existing conditions linked to lifestyle or genetics, can have an impact on the chances of developing severe forms of the disease.

While COVID-19 is undoubtedly having a strong impact on our lives, it is also having a strong impact on the way we do business. This is particularly true in terms of medical underwriting and how we, as an industry, should adapt our operations, update our guidelines, and protect the lives of our policyholders as best we can.

The objective of this document is to provide an overview of the latest medical studies to keep in mind when adapting medical underwriting to our COVID-19 environment. It brings together the key points, information and knowledge developed so far on potential risk factors linked to COVID-19 infections, severe forms and consequences. However, this document does not provide specific Underwriting and Claims guidelines, on which the SCOR Global Life teams have communicated separately.

This document will focus on providing information to serve as a basis for discussion when laying out the potential operational adjustments that could be needed in the context of COVID-19 (especially with regard to underwriting guidelines). As new studies are published every week, consider this to be a living document that will be continuously updated as the state of our knowledge on COVID-19 evolves.

To maximize its operational usefulness, we will address four areas:

1. Factors increasing or reducing the risk of becoming infected by COVID-19
2. Factors increasing or reducing the risk of developing severe or fatal forms of COVID-19
3. Potential complications and sequelae of COVID-19
4. Indirect effects of COVID-19

Click HERE to access our Underwriting and Claims guidelines

This document will focus on providing information to serve as a basis for discussion when laying out the potential operational adjustments that could be needed in the context of COVID-19 (especially with regard to underwriting guidelines). As new studies are published every week, consider this to be a living document that will be continuously updated as the state of our knowledge on COVID-19 evolves.

To maximize its operational usefulness, we will address four areas:
1. Are there factors which increase or decrease the chances of becoming infected by COVID-19?

Since the beginning of the COVID-19 pandemic, and even more so since the strict measures were taken across the world linked to working from home, social distancing, and lockdowns, we have all become aware of the need to reduce our face-to-face interactions in order to slow the spread of the virus. If we are exposed to the virus, the greater our chance of infection becomes. Reducing ‘exposure’ means reducing the opportunities to encounter droplets, aerosols, or surfaces that might be infected, hence, the need to reduce our interactions with each other. Certain medical factors and other characteristics that might have a protective effect against COVID-19 have made headlines as the pandemic has developed, and they continue to do so today as new studies are released. The aim of this section is to explain if there are indeed factors which either increase or decrease the risk of COVID-19 infection, beyond social distancing.

Some factors have been intentionally excluded from this analysis:

- Socio-economic factors – these factors can have an impact on infection. For example, working from home can be incompatible with some professions and depending on your income or the size of your home, physical distancing measures could be difficult to put in place. The analysis below does not include these factors, which are, more than anything, linked to the difficulties of establishing effective exposure-reduction measures. As a result, the analysis below focuses on medical factors alone.

- Factors linked to an increased likelihood of developing severe or fatal forms of COVID-19 will be discussed in a separate section. The factors below are only a list of medical factors that could have an impact on the probability of catching the disease – not of dying from it.

GENETIC FACTORS

To identify potential genetic factors involved in the development of COVID-19, a genome-wide association study was performed at seven hospitals in Italy and Spain. This study involved a group of patients with severe forms of COVID-19 (defined as respiratory failure) as well as a control group without the disease.

What is a genome-wide association study?

Genome-wide association studies are focused on scanning markers across the complete genome of as many people as possible to find potential genetic variations associated with a particular disease. To carry out a genome-wide association study, researchers use two groups of participants: people with the disease being studied, and similar people (a control group) without the disease. If certain genetic variations are found to be significantly more frequent (allele frequency) in people with the disease compared to people without the disease, the variations are said to be “associated” with the disease.

The study suggested a few potential associations:

- 6 genes at chromosome 3, including genes encoding a protein which functionally interacts with angiotensin-converting enzyme 2, the SARS-CoV-2 cell-surface receptor or controlling lung resident memory CD8 T cells, that play a significant role in immune response.

- Another association was found at chromosome 9, that coincides with the blood group. This could potentially confirm that some blood groups are more likely to develop severe forms of the disease, as previously reported in preprints of certain non-genetic studies.

In conclusion, it seems that genes can have an impact on developing severe forms of COVID-19, but further exploration of these findings, and of their usefulness in clinical risk profiling, is needed.

Specific note on primary immunodeficiency

Scientists have identified rare variants of a gene associated with impaired immunological responses of type I and II interferons in young male patients with severe forms of COVID-19. This gene encodes the Toll-like receptor 7 protein that plays an important role in pathogen recognition and activation of innate immunity.
Some studies have investigated the potential protective effect of O blood types against COVID-19. That said, no study could clearly and unquestionably demonstrate that protective effect, as only a statistical association between blood type and susceptibility could be established. New studies are therefore necessary to draw final conclusions.

- Zhao et al. have looked at blood types of 2,173 COVID-19 patients in three hospitals in Wuhan, China, as well as blood types of more than 23,000 non-COVID-19 individuals in Wuhan and Shenzhen. They found that individuals with O blood types had a lower risk of getting the infection compared with non-O blood types. Conversely, people with A blood types seem to be at a higher risk of contracting the disease.

- Zietz M et al. have looked at 1,559 people tested for SARS-CoV-2 at New York Presbyterian hospital, of which 682 tested positive. Individuals with A blood types were 33% more likely to test positive than other blood types and O blood types were less likely to test positive than other blood groups.

BACILLE CALMETTE-GUÉRIN (BCG) VACCINATION

There is currently no strong evidence that BCG vaccine protects people against infection by the COVID-19 virus. That said, some studies, available as preprints and prone to significant bias from many confounders, suggest a correlation between rates of BCG vaccination and rates of COVID-19 morbidity and mortality. This might mean that BCG could reduce the intensity of SARS-CoV-2 infection by stimulating the memory of innate immunity.

Furthermore, past studies have suggested that BCG vaccination in children contributed to offering a non-specific protective effect against infections, particularly respiratory infections.

In the absence of evidence, the WHO does not recommend BCG vaccination for the specific prevention of COVID-19. Two clinical trials addressing this question are underway, and the WHO will evaluate the evidence when available.

SMOKING

Epidemiological data in different countries shows that the prevalence of current smokers among COVID-19 patients is lower than that of current smokers in the general population. Furthermore, no clear association between current smoking and severe forms of COVID-19 was found. That said, the deleterious effects of tobacco are well known on cardiovascular diseases and cancers, and tobacco favors acute coronary events, especially in the context of a prothrombotic state, frequently observed in infected COVID-19 patients. Therefore, the current position of the CDC in the US is that smokers are at high risk for severe illness from COVID-19, and new studies need to be carried out to properly understand the impact of smoking on COVID-19.

Other risk factors such as diabetes, cardiovascular diseases, obesity, age, and cancer seem to increase the probability of developing severe forms of COVID-19 but don’t seem to have a significant impact on the chances of becoming infected. It is indeed shown across medical studies that the prevalence of these conditions or characteristics among people testing positive for COVID-19 does not seem to be significantly higher than in the general population.

Overall, the likelihood of infection seems mainly linked to exposure to other infected people rather than to genetic characteristics or medical history. Social distancing, wearing masks, hand washing, and generally controlling exposure to the virus, currently remain the primary means of avoiding this disease.

From an underwriting perspective, such factors should also be considered with caution, and a proper understanding of the impact they can have in a different context, not directly linked to COVID-19, is also needed.
2. Factors which increase or reduce the risk of developing severe or fatal forms of COVID-19

Since the beginning of the pandemic, it has been difficult to clearly differentiate between factors which increase the risk of developing severe forms of the disease and factors increasing the risk of death from the disease. The factors set out below correspond to both risks.

An ambitious UK study published as a preprint on May 7, analyzing data from the electronic health records of more than 17 million NHS patients, allowed some factors associated with COVID-19-related hospital deaths to be identified. Among those 17 million people, 5,683 had a COVID-19 hospital death record and some risk factors clearly stood out. The graph below lists those factors and provides a hazard ratio and 95% confidence intervals – this hazard ratio corresponds to the increased risk of death an individual has if they present the factor. On top of providing an overview of the main risk factors linked to dying from COVID-19, the true value of this study resides in its ability to clearly identify the factors and analyze the impact of each individual risk factor once other confounding factors have been removed.

Source: Factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients, May 2020

Estimated Hazard Ratios (shown on a log scale) for each potential risk factor from a multivariable Cox model. Obese class I: 30-34.9kg/m², class II: 35-39.9kg/m², class III: >=40kg/m². OCS= oral corticosteroid. All HRs are adjusted for all other factors listed other than ethnicity. Ethnicity estimates are from a separate model among those with complete ethnicity data, and are fully adjusted for other covariates.

How to read this graph? Let’s take the example of Chronic Liver Disease. The graph explains that people with this condition are approximately 1.6 times more likely to die from COVID-19 than people who don’t have that condition once other comorbidities are removed. Furthermore, the 95% Confidence Interval (CI) spans from ~1.2 to ~2.5, meaning that in 95% of cases, people with this condition are 1.2 to 2.5 times more likely to die from the disease.
Age seems to be the key factor that influences the probability of dying from COVID-19. Once adjusted for all other factors, the UK study which analyzed electronic health records found that the risk of dying from COVID-19 (hazard ratio) is 2.09 times higher for people age 60-70, 4.77 times higher for people age 70-80, and 12.64 times higher for people age 80+. Those results are aligned with what was seen in other countries.

**GENDER**

In some studies which were published across countries, there seems to be a major disbalance between men and women when it comes to the probability of dying from COVID-19. The above UK study which analyzed electronic health records found that men have twice the risk of dying from COVID-19 compared to women once all other factors have been removed. Those results are aligned with what has been seen in public data across most countries, as shown in the table below.

(source: https://globalhealth5050.org/covid19/sex-disaggregated-data-tracker/)

<table>
<thead>
<tr>
<th>Country</th>
<th>Date</th>
<th>Total cases</th>
<th>Total deaths</th>
<th>% males</th>
<th>% females</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>03.06.20</td>
<td>214,191</td>
<td>35,430</td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>Italy</td>
<td>03.06.20</td>
<td>224,086</td>
<td>32,354</td>
<td>46%</td>
<td>54%</td>
</tr>
<tr>
<td>Spain</td>
<td>21.06.20</td>
<td>246,335</td>
<td>20,627</td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>Mexico</td>
<td>08.06.20</td>
<td>126,822</td>
<td>11,008</td>
<td>56%</td>
<td>44%</td>
</tr>
<tr>
<td>Germany</td>
<td>01.06.20</td>
<td>161,457</td>
<td>8,720</td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>Canada</td>
<td>00.06.20</td>
<td>65,814</td>
<td>6,862</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>Belgium</td>
<td>00.06.20</td>
<td>50,110</td>
<td>6,862</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>00.06.20</td>
<td>47,811</td>
<td>6,031</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>Peru</td>
<td>01.06.20</td>
<td>108,695</td>
<td>9,571</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Sweden</td>
<td>03.06.20</td>
<td>45,024</td>
<td>5,471</td>
<td>45%</td>
<td>55%</td>
</tr>
<tr>
<td>Scotland</td>
<td>06.06.20</td>
<td>16,852</td>
<td>4,000</td>
<td>52%</td>
<td>48%</td>
</tr>
<tr>
<td>Ecuador</td>
<td>05.06.20</td>
<td>26,970</td>
<td>3,334</td>
<td>76%</td>
<td>24%</td>
</tr>
<tr>
<td>Pakistan</td>
<td>06.06.20</td>
<td>108,350</td>
<td>2,172</td>
<td>74%</td>
<td>26%</td>
</tr>
<tr>
<td>China</td>
<td>28.06.20</td>
<td>55,924</td>
<td>2,114</td>
<td>51%</td>
<td>49%</td>
</tr>
</tbody>
</table>

This disproportionate death ratio in men may partly be explained by their relatively higher rates of comorbidities (cardiovascular disease, hypertension, diabetes, and chronic lung disease) and higher risk behaviors (i.e., smoking and alcohol use). Behavioral and social differences also favor women, since women are more likely than men to follow hand-hygiene practices and seek preventive care.

That said, a possible link between the presence of active androgens in men’s blood and the severity of COVID-19 disease in men has been suggested. Specifically, the possible interaction between androgens and TMPRSS2 (Transmembrane protease, serine 2) has generated a lot of attention. TMPRSS2 is a membrane-bound enzyme that cleaves the “spike” protein on the coronavirus’ surface, thus allowing the virus to fuse with the host cell’s membrane and get inside the cell. However, although researchers have established that androgens control TMPRSS2 in the prostate, possible actions in the lung are yet to be established.

If women seem to be better protected from severe forms of COVID-19, it is probably because they have generally better health behavior. For the time being, the link between the severity of the disease and androgens remains intuitive, and still lacks solid scientific proof.

**Additional note:** pregnant women do not appear to show an increased risk of severe COVID-19 infection.

**GENETICS**

Across some recently published studies, some genetic causes of severe COVID-19 cases have been suggested:

Zhang et al. sequenced the genomes of 659 severely affected patients and of 534 people with mild infections. They found that many people with severe COVID-19 had mutations in the gene responsible for interferon-I production, which helps regulate the activity of the immune system. **Patients with these mutations produced very low levels of interferon.**

Bastard et al. found that 101 out of 987 patients with severe COVID-19 had **autoantibodies against interferon**, while none were found in people with mild or no COVID-19 symptoms. These antibodies neutralize the interferon produced, thus preventing the development of an adequate immunological response. Researchers believe that the genetic cause of autoantibodies may be mutations on the X chromosome, which could explain the male predominance observed in severe cases.

**DIABETES**

In many studies across the world, it seems that the fatality ratio linked to COVID-19 is higher in patients with diabetes.

That said, as for most COVID-19-related studies, the presence of methodological issues makes both risk quantification and interpretation difficult. Keeping these caveats in mind, here is an update on the findings from the latest studies in China, the US and the UK.

**In China**

Diabetes clearly stands out as one of the most significant comorbidities after hypertension and other cardiovascular diseases:

- **In terms of number of cases**, a first study found that 8% (95% CI: 6%-11%) of the COVID-19 infected population had diabetes. This figure rose to 9.7% in a second study (95% CI: 6.9%-12.5%).

This data needs to be taken with caution, as the observed prevalence of patients with diabetes in COVID-19 cases seems to be near to the estimated prevalence of diabetes for the general Chinese population (prevalence of diabetes in the adult Chinese population, both diagnosed and undiagnosed, is estimated at 10.9%).

Furthermore, it seems that people with type 1 diabetes, who have glucose values close to target, “may not be at greater risk unless their situation is complicated by other concerns and comorbidities”, according to The Juvenile Diabetes Research Foundation (JDRF).
In the US

Diabetes was the most frequently reported comorbidity in terms of its prevalence in total cases. Over the spring, 32% of patients admitted to Intensive Care Units (which is the case for people who have a severe form of the disease) had diabetes, which represents 3 to 4 times the rates that were reported in China. As of today, the American Diabetes Association estimates that ~10.5% of the American population has diabetes.

In conclusion, the risk for diabetic patients seems high, at least in the case of uncontrolled diabetes, so good glycemic control still represents the best prevention strategy.

OBESITY

The Center for Disease Control (CDC) and the European Association for the Study of Obesity (EASO) consider severe obesity (BMI of 40kg/m² or higher) as a medical condition which poses a higher risk for severe forms of COVID-19, though it is not clear if it is obesity itself or the coexistence with diabetes and hypertension (which are highly prevalent in patients with obesity - also known as the metabolic syndrome) that increases mortality rates.

In a cross-sectional analysis of all patients with laboratory-confirmed COVID-19 treated in New York City between March 1, 2020 and April 7, 2020, 39.8% of the hospitalized patients presented obesity. Obesity was the chronic condition with the strongest association for critical forms of COVID-19 compared to any cardiovascular or pulmonary disease. These figures need to be interpreted with caution as the prevalence of obesity in the US is around 40% (which is quite close to the prevalence of obese COVID-19 hospitalized patients in this study).

In the UK

Data from the NHS based on the analysis of electronic health records underscored the risk for patients with type 1 diabetes. After adjusting for age, sex, poverty, ethnicity, and geographical region, people with type 1 and type 2 diabetes had higher odds of dying in hospital with COVID-19 (although further adjustments for existing coronary heart disease, cerebrovascular disease, or heart failure slightly reduced the odds).

Several hypotheses and studies have tried to explain the potential mechanisms that could cause this higher COVID-19 mortality of obese patients:

1. One hypothesis is that adipose tissue can serve as a viral reservoir - the transformation of pulmonary lipofibroblasts into myofibroblasts can contribute to the development of Pulmonary Fibrosis and thus is likely to influence the clinical severity of COVID-19.

2. Another hypothesis is that cells infected with COVID-19 increase the expression of genes associated with lipid metabolism. This is of interest as viruses may “hijack” host lipid metabolism to allow completion of their viral replication cycles.

CARDIOVASCULAR DISEASES (CV)

Cardiovascular diseases (coronary artery disease, stroke, Peripheral Artery Disease (PAD)) have been reported as frequently associated with severe forms of COVID-19.

In China

A study published in February 2020 based on data from 138 COVID-19 patients showed that people with cardiovascular diseases had a significant risk of developing a severe form of the disease. As the prevalence of patients with a cardiovascular disease was 14.5% in the original sample, when looking at the patients admitted to ICUs among them, the prevalence of patients with cardiovascular diseases was 25%.

It seems that the virus (as with influenza) might play a role as a trigger of acute CV events by favoring atherosclerosis plaque rupture, prothrombotic and inflammatory state with microvascular lesions with distal microthrombi, and direct myocardial injury, with an increase of Troponin, an independent marker of mortality of hospitalized patients.

Infected COVID-19 patients with a previous cardiovascular disease condition may develop acute heart failure (HR), acute coronary syndrome (ACS), or lethal dysrhythmia (especially in case of hypokalemia), due to the activation of the renin angiotensin aldosterone system (RAAS) by the virus.

Myocarditis and myopericarditis seem to be less frequent. The occurrence of a left ventricle systolic dysfunction (LV) also seems to be a prognostic marker of infected individuals.

Stroke mortality is also increased by the microthrombi and the hyper-coagulated state.
**CANCER**

The impact of the COVID-19 infection on cancer mortality may result from the direct effects of the virus among the vulnerable population of cancer patients but also from remote effects due to both the disorganization of the healthcare system during remnant phases of the infection and delayed effects relating to the anticipated global economic crisis (please also see below the section on postponement effects).

In China, data from 575 hospitals in 31 provincial regions showed that the prevalence of patients with cancer in the overall patients hospitalized for COVID-19 infection was 1.1%, which is significantly higher than the prevalence of cancer in the general Chinese population (estimated to be at 0.3%). This figure is likely to be underestimated as it does not consider patients with cancer that have not been admitted to hospital for COVID-19. Based on the data in hospitalized patients, 25% had undergone surgery or chemotherapy within the previous month, and 75% had recovered from initial cancer treatments (e.g. surgery or chemotherapy) and had no obvious immunosuppression at the time of infection (note: these numbers are derived from a very limited sample of 20 cancer patients and should therefore be interpreted with caution). It is unlikely that the COVID-19 infection in survivors of previous cancers was related to cancer, being more likely due to regular contamination.

In the Chinese nationwide analysis report, patients with current or a past history of cancer made up 6% of those hospitalized for severe cases of COVID-19 infection. Patients with cancer had worse outcomes from COVID-19 infection (note: these numbers are derived from a very limited sample of 20 cancer patients and should therefore be interpreted with caution). It is unlikely that the COVID-19 infection in survivors of previous cancers was related to cancer, being more likely due to regular contamination.

The impact of the COVID-19 infection on cancer mortality may result from the direct effects of the virus among the vulnerable population of cancer patients but also from remote effects due to both the disorganization of the healthcare system during remnant phases of the infection and delayed effects relating to the anticipated global economic crisis (please also see below the section on postponement effects).

Key Takeaways:
- There is no strong evidence that cancer is a risk factor for COVID-19 infection.
- Cancer appears as a factor that may induce more risks of severe or critical outcome in patients requiring hospitalization.
- Thus far, there is no data gathered from patients with cancer who have not been hospitalized but suffered from a COVID-19 infection at home or in a non/poorly medicalized institution.

**VITAMIN D DEFICIENCY**

Several publications highlighted a possible association between vitamin D levels and severity or mortality from COVID-19.

Vitamin D is produced by the skin when one is exposed to UVB rays. It is metabolized in the liver then in the kidney, where it is transformed into an active hormone which stimulates the intestinal uptake of calcium from food, regulates the calcium level in the blood, and fixes calcium on bones.

Vitamin D also supports the immune system through several immune pathways. Vitamin D has immuno-modulatory properties which limit the pro-inflammatory cytokines and therefore have the potential to prevent cytokine storms. Consequently, some scientists have long claimed that vitamin D has a role to play in modulating the immune system’s response to COVID-19.

Some recent medical studies have brought some more tangible facts on this aspect and seem to show a positive correlation between vitamin D levels and the severity and / or mortality of COVID-19. Some descriptive studies also suggest that vitamin D deficiency has a negative effect on the COVID-19 prognosis of the elderly.

That said, all those studies point to the fact that vitamin D does not have a protective effect against COVID-19 infections, only that the deficiency of vitamin D could have a deleterious effect in people who contract COVID-19.

As an example, Jain et al., in a recently published continuous prospective observational study of 6 weeks, analyzed the vitamin D levels of COVID-19 patients and its potential correlation with disease severity. The study enrolled 154 patients between 30 and 60, split as follows: 91 in Group A (asymptomatic COVID-19 patients) and 63 in Group B (severely ill patients requiring ICU admission).

The mean level of vitamin D (in ng/mL) was 27.89 ± 6.21 in Group A and 14.35 ± 5.79 in Group B (which is a quite significant gap). Furthermore, the serum level of inflammatory markers was found to be higher in vitamin D deficient COVID-19 patients and the fatality rate was much higher in the vitamin D-deficient group (21% vs 3.1%).

As a result of those studies, it can be assumed that: Vitamin D level is markedly low in severe COVID-19 patients. Inflammatory response is high in Vitamin D-deficient COVID-19 patients. This all translates into increased mortality in Vitamin D-deficient COVID-19 patients. These findings confirm that correcting Vitamin D-deficiency could potentially be a medical treatment improving the odds of COVID-19 patients.

**PULMONARY DISEASE**

Although individuals with chronic lung disease are not at higher risk of contracting COVID-19, they seem to be more susceptible to severe forms of the disease.

A meta-analysis demonstrated that patients with Chronic Obstructive Pulmonary Disease have a significantly increased risk, greater than five-fold, of developing a severe form of COVID-19.
GASTRO-INTESTINAL DISEASES

Medical studies currently suggest that patients with severe liver disease, at the cirrhosis stage, present a higher risk of death from COVID-19.

The UK study based on the analysis of electronic health records showed that people with liver disease had a 1.61-fold higher risk of dying from COVID-19 compared to patients with no medical conditions (once adjusted for other factors).

Chronic liver disease, including cirrhosis, currently represents a major disease burden globally. Chronic viral hepatitis B or C, NASH, and alcohol-related liver disease, affect several hundreds of millions of people across the world and it is therefore key to assess the impact of COVID-19 on this population.

KIDNEY FAILURE

An inventory made by the French Biomedicine Agency, from the transplant and dialysis registry, indicates that about 1% of kidney transplant patients and 3% of dialysis patients have been infected with COVID-19.

Among these infected patients, mortality was 14% for transplant patients and 17% for dialysis patients. It should be noted that people aged 65 years or older and diabetic patients were predominant in this population. A Chinese study showed similar results, with a COVID-19 mortality of dialysis patients of 13%.

These studies clearly show that the mortality from COVID-19 in patients with chronic kidney disease, especially dialysis patients and kidney transplant patients, is much higher than in the general population.

INFLUENZA INFECTION

As already seen in China, where influenza was still widely in circulation when COVID-19 broke out, the flu and COVID-19 pandemic can occur simultaneously. As the two viruses have the same transmission modes, coinfection with COVID-19 and Influenza is therefore possible.

At this time though, this phenomenon seems to be quite rare. Physicians from several countries have reported patients who tested positive for both COVID-19 and seasonal influenza, but those patients are only a small minority (making up under 3% in New-York for instance – although COVID-19 broke out at the end of the flu season in the US).

However, coinfection seems to be a significant risk factor for developing a severe form of COVID-19 and therefore for prolonged hospital stay. A study conducted in January and February 2020 at Wuhan’s Tongji Hospital shows that more than 10% of patients with severe COVID-19 were coinfected with influenza. Another study published in the British Medical Journal shows that coinfected people are more at risk of developing severe forms of COVID-19 and also have a risk of dying more than double that of people infected with the COVID-19 virus alone.

To summarize, many factors seem to increase the risk of developing a severe or fatal form of COVID-19. Although some key factors stand out, such as age, it is however sometimes difficult to assess whether the factors mentioned in the various studies previously cited can be clearly differentiated from potential confounding factors.

Again, a cautious approach, therefore, needs to be followed when making operational decisions (for example for underwriting purposes) based on those studies. Furthermore, although most factors can be observed across studies and countries, their importance will vary locally, as the prevalence of pre-existing conditions linked to those factors also varies locally. Obesity is a clear example as it is one of the top COVID-19 comorbidities in the US, but mostly because the prevalence of obesity is high in the US population. It is therefore key to analyze and interpret the figures with rigor, by not only looking at the prevalence of the condition in the general population (not infected by COVID-19), but also by focusing on studies that have made the effort to clearly identify and separate out factors, such as in the UK study, which was only made possible, or at least facilitated, thanks to the very promising use of electronic health records.


The aim of this section is to analyze the direct consequences of COVID-19 for the people infected by the disease. Given the current state of our knowledge on COVID-19, it can be difficult to clearly differentiate between complications of the disease and short- or long-lasting sequelae that might occur when the patient is considered as having recovered (i.e. patients whose PCR tests would be negative). Diseases are a continuum and what begins as complications can last over time. This is why the section below focuses on the complications developed during the disease and formulates reasonable hypotheses on whether those complications will last over time. Please note that only the direct effects of COVID-19 are listed below, as the indirect consequences of the disease will be discussed separately. As previously stated, medical research is only beginning on COVID-19, and many of the studies mentioned in this document are only available as preprints which have not been peer-reviewed and therefore need to be considered with caution. This is all the more true when studying the consequences of COVID-19, as they can be long term.

Post COVID-19 clinical data indicates that some people infected by SARS-COV-2 experience fatigue and pulmonary symptoms after recovery. Most studies that show sequelae of COVID-19 include participants who have had a moderate or severe form, and there is only limited data on sequelae in asymptomatic people or those with mild illness.

A report from the Center for Disease Control and Prevention concluded that COVID-19 “can cause prolonged illness, even in young adults without underlying chronic medical conditions.” A growing number of reports show that some COVID-19 survivors experience symptoms such as fatigue and decreased lung function for months after contracting the disease, even in some cases which are considered as “mild”.

A UK study has shown that approximately 30% of patients with severe COVID-19, at 8-12 weeks after discharge, have abnormal pulmonary images and functional impairment. Similarly, roughly 15% of patients with moderate symptoms have pulmonary abnormalities (radiological or functional).

Summary of symptomatology and clinical results by disease severity.
CARDIAC DISEASE

Cardiac injury is not uncommon in COVID-19. As many as 20 - 30% of patients hospitalized with COVID-19 have evidence of myocardial involvement. There are multiple pathways to myocardial injury: myocardial infarction, myocarditis, vasculitis, or other mechanisms related to inflammation and thrombosis. Recent studies have raised concerns of myocardial inflammation after COVID-19, even in asymptomatic or mildly symptomatic patients. A study reported that in 78% of patients who have recently recovered from COVID-19 (64-92 days after diagnosis), Cardiac Magnetic Resonance Imaging (CMR) shows cardiac involvement, and ongoing inflammation of the myocardium in 60% of patients. These abnormalities were independent of pre-existing conditions, severity level, overall course of acute disease, and time since the initial diagnosis.

Another study, which focused on 26 previously healthy competitive athletes who recovered from COVID-19, shows that 4 (15%) had CMR findings suggestive of myocarditis, and 8 additional athletes (30.8%) exhibited late gadolinium enhancement (LGE) without T2 elevation suggestive of prior myocardial injury. These findings indicate the need to consider the long-term cardiovascular consequences of COVID-19.

Update on athletes:

The American College of Cardiology has recently published a consensus statement on when it is safe to return to play for athletes who have been infected with COVID-19. This statement specifies that some biological tests generally not used in athletes’ check-ups could be performed in some cases. Based on those guidelines, for a safe return to play, former symptomatic (mild or moderate) cases need to:

- Be back to a complete asymptomatic clinical state
- Have normal resting echocardiography
- Have a normal exercise test (valid e.g. Target Heart Rate > 90% of Maximal Heart rate)
- Return to normal biological values for: Troponin (I or T), Dimers D, CRP, White Blood Cells

MULTISYSTEM INFLAMMATORY SYNDROME IN ADULTS

Some cases of Multisystem Inflammatory Syndrome (MIS) associated with SARS-CoV-2 infection in adults have also been reported. MIS differs from typical manifestations of severe COVID-19 in that patients with MIS have minimal respiratory symptoms, hypoxemia, or radiographic abnormalities. Most patients with MIS require intensive care and can have fatal outcomes.

ACUTE KIDNEY INJURY

Acute Kidney Injury (AKI) is a sudden episode of kidney damage that happens within a few hours or a few days. AKI causes a build-up of waste products in your blood and makes it hard for your kidneys to keep the right balance of fluid in your body. It can result in chronic, irreversible end-stage renal insufficiency of both kidneys, necessitating either regular hemodialysis or peritoneal dialysis or a kidney transplant.

AKI seems to be a common severe complication for hospitalized COVID-19 patients. The incidence is variable from one hospital and one country to another, but rough estimates indicate that about 1/3 of hospitalized patients in the US and Europe and less than 1/10 in China have experienced AKI.

According to pool studies, hospitalized patients developing AKI as a result of COVID-19 seem to be more likely to die, with a high death risk ratio of 4.6 (in other words, a patient with AKI is 4 times more likely to die from COVID-19 than a patient without AKI). The death rate seems to be higher if the hospitalized COVID-19 patients need kidney replacement treatment such as hemodialysis.

In case of survival of patients having required kidney replacement treatment, it is crucial to know if the treatment can be stopped at a later stage or if the kidney sequelae brought about by COVID-19 are permanent, requiring hemodialysis for life or possibly kidney transplant in the future.

A recent study published in the American Journal of Kidney Diseases provides information on this important topic. In the study, among 3,854 hospitalized COVID-19 patients with AKI, 638 received kidney replacement treatment during admission. Among survivors, 33 remained on dialysis at discharge. Age > 60, pre-existing cardiovascular disease or chronic kidney disease seem to have stood out as risk factors associated with a higher need for dialysis at discharge.

It is too early to know exactly how many of these patients may subsequently experience kidney recovery. However, from these findings, it can already be supposed that some COVID-19 patients might need hemodialysis or perhaps kidney transplant.

RESPIRATORY DISEASE

COVID-19 survivors are at risk of chronic respiratory complications such as post-viral lung fibrosis, pulmonary thromboembolism, and related functional pulmonary impairment.

Available studies have consistently demonstrated that residual abnormalities on chest CT scans are present in many COVID-19 survivors discharged from hospital 4-6 weeks after the onset of illness. Given that persisting imaging abnormalities correlate with physiological impairment, it is likely that these patients are at a greater risk of long-term parenchymal lung disease (fibrosis and low pulmonary capacity).

In a study on COVID-19 survivors in Italy, while 72.7% of the subjects developed interstitial pneumonia during hospitalization, up to 43.4% reported residual dyspnea at around one-month post-discharge.

COVID-19 infection is also associated with a high prevalence of venous thromboembolic (VTE) disease. Patients remain hypercoagulable during the recovery period.

Cohorts of survivors are being created in several countries to monitor the evolution of residual lung damage, such as pulmonary fibrosis, bronchiectasis or other functional abnormalities and to estimate the impact on subsequent lung function, exercise capacity, and health-related quality of life among the survivors.

RESPIRATORY DISEASE

COVID-19 survivors are at risk of chronic respiratory complications such as post-viral lung fibrosis, pulmonary thromboembolism, and related functional pulmonary impairment.

Available studies have consistently demonstrated that residual abnormalities on chest CT scans are present in many COVID-19 survivors discharged from hospital 4-6 weeks after the onset of illness. Given that persisting imaging abnormalities correlate with physiological impairment, it is likely that these patients are at a greater risk of long-term parenchymal lung disease (fibrosis and low pulmonary capacity).

In a study on COVID-19 survivors in Italy, while 72.7% of the subjects developed interstitial pneumonia during hospitalization, up to 43.4% reported residual dyspnea at around one-month post-discharge.

COVID-19 infection is also associated with a high prevalence of venous thromboembolic (VTE) disease. Patients remain hypercoagulable during the recovery period.

Cohorts of survivors are being created in several countries to monitor the evolution of residual lung damage, such as pulmonary fibrosis, bronchiectasis or other functional abnormalities and to estimate the impact on subsequent lung function, exercise capacity, and health-related quality of life among the survivors.
NEUROLOGICAL DISEASES

Neurologic sequelae seem to be a possible complication of COVID-19, especially for patients who develop a severe form of the disease.

Findings from brain autopsies of patients who died from COVID-19 demonstrate that COVID-19 might be responsible for brain damage such as encephalitis, meningitis, and neuronal cell loss. At present, it’s unclear if the observed brain lesions are a direct consequence of virus infiltration or resulted from an immune response. In some cases, a massive intracranial hemorrhage was also seen, which is consistent with COVID-19-associated coagulopathy.

According to medical literature, the most frequent disorders affecting the central nervous system (CNS) seem to be the following: olfactory and taste disorders, ischemic/hemorrhagic stroke, meningoencephalitis and encephalopathy, including acute necrotizing encephalopathy, a rare type of encephalopathy.

Regarding the peripheral nervous system (PNS), Guillain-Barré and Miller Fisher syndromes are the most frequent manifestations reported in the literature.

Other neurologic manifestations have been observed for COVID-19 patients:
- Central nervous system (CNS) manifestations: dizziness, headache, impaired consciousness, confusion, delirium, somnolence, stupor, coma, acute cerebrovascular disease, ataxia, and seizures.
- Peripheral nervous system (PNS) manifestations (taste impairment, vision impairment, nerve pain).
- Neuromuscular (NM) disorders, skeletal muscular injury manifestations.

Several neurological conditions are likely multifactorial and secondary to hypoxia, metabolic abnormalities, and immunological abnormalities. Although ICU confusion can happen to people receiving treatment for any condition, it seems that some neurological symptoms could be linked to COVID-19 itself. However, the impacts of these symptoms once the patient recovers are unclear, and more data is needed to draw conclusions.

PSYCHIATRIC CONDITIONS

Psychiatric symptoms are a possible complication of COVID-19. Some studies have reported a significant proportion of patients with symptoms of post-traumatic stress disorder (PTSD), depression, anxiety, obsessive-compulsive symptoms, or insomnia.

Maizza et al, in a study including 402 adults having survived COVID-19, show psychiatric symptoms in 28% of cases for PTSD, 31% for depression, 42% for anxiety, 20% for OC symptoms, and 40% for insomnia. Overall, 56% scored in the pathological range in at least one clinical dimension.

Similar results were found in another study by Tomasoni et al. who reported a high prevalence of anxiety/depression among 105 COVID-19 patients at 1 - 3 months from virological clearance. They detected a substantial proportion of patients suffering from anxiety (29%), symptoms of depression (11%), and cognitive disorders (17%).
LONG-COVID AND POST-COVID SYNDROME

Some people seem to be affected with what is called “Post-COVID Syndrome”, having recovered from COVID-19 but still reporting lasting effects of the infection. Other patients have had the usual symptoms for far longer than would be expected (“Long COVID”).

In a study of 143 patients who had been hospitalized for COVID-19 in Italy, only 13% were symptom-free after a mean of 60 days following the onset of the disease. The most common persistent symptoms were fatigue (53%), dyspnea (43%), joint pain (27%), and chest pain (22%). None had fever or any signs or symptoms of acute illness (CARFI).

In the US, another study showed that patients with milder initial infections also frequently have prolonged symptoms [MMWR]. In a survey of 292 patients diagnosed with COVID-19 in the outpatient setting, only 65% reported a return to baseline health by 14 to 21 days after diagnosis. Symptoms that were most likely to persist beyond 14 to 21 days included cough (43%) and fatigue (35%); fever and chills persisted in only 3 and 4%. In this study, it was reported that approximately one in five individuals aged 18 to 34 years, who were previously healthy, did not return to baseline within two to three weeks.

Arnold et al show at 12-week follow-up the most common symptoms were breathlessness, excessive fatigue (39% prevalence each) and insomnia (24%).

Lambert et al show that “long hauler” COVID-19 symptoms are very numerous. These persistent symptoms are associated with many clinically relevant outcomes, including poor health status and impaired functional status.

Source: Arnold et al, Patient outcomes after hospitalization with COVID-19 and implications for follow-up; results from a prospective UK cohort

Cancer

As healthcare providers have been reorganizing to prioritize the management of the COVID-19 pandemic, shortages of both hospital beds and healthcare workforces have resulted in the restriction of cancer patient in-hospital visits. Further, diagnosis and treatment have been postponed as well as many medical appointments during the acute phase of the COVID-19 infection. Cancer patients were instructed early on to comply with stringent prevention measures as they were more likely to develop severe to critical forms of COVID-19. General Practitioners have likewise been reluctant to refer cancer patients for hospital visits during the acute phase of the infection. In many countries, there has been a significant drop in hospital visits for consultations and treatment (70-80%) as well as a significant reduction in urgent referrals in emergency care units (75-80%) since February 2020. Such decreases are frequently observed during seasonal vacation periods such as Christmas but usually do not exceed durations of more than 15-21 days. In the case of COVID-19, hospital lockdowns often lasted a couple of months. In the countries where hospitals reopened after lockdowns, rescheduling patients with cancer proved more challenging than anticipated as hospital facilities taking care of cancer diagnosis and therapy might have found it difficult to reset their prior organizations (possibly even more so in countries where a second wave is currently underway). Patients whose treatment or diagnosis has been delayed are expected to show more advanced diseases and complications requiring more complex medical care, often involving longer hospital stays. As a result, the remnant phase of the COVID-19 infection will have a significant impact in prolonging the healthcare crisis for several months, contributing to the global over-mortality from cancer expected for 2020.
Diabetes

Just as for other diseases, it can be expected that lockdowns and social distancing in general will have a negative impact on glycemic control and the care of diabetes-related complications. This could be due not only to the difficulty involved in visiting a doctor and getting medical guidance, but also to the limitation of exercise, or resources to maintain a healthy lifestyle. No significant shortage of drugs has been seen yet, and if the adherence to treatment remains stable, the variation of HBA1c should not be high and the impact in terms of microvascular complications should be minimal.

OTHER EFFECTS

Impacts linked to the economic crisis

As the COVID-19 crisis is expected to generate an unprecedented recession not seen since WW2 in many countries, some medical impacts linked to difficult economic and social situations might arise. The first impact is linked to the healthcare system itself and to the financial support it can expect to receive in a time of crisis to maintain a good level of care (although some countries, such as France, have announced that they will invest more in their healthcare system going forward, as a consequence of the COVID-19 crisis).

When it comes to the treatment of diabetes for example, the analysis of the consequences of the 2010 financial crisis in Greece showed detrimental effects in terms of poor nutrition, chronic stress, reduced adherence to medication, reduced utilization of laboratory and imaging studies and poor monitoring of vascular complications, all of which could result in poorly controlled diabetes.

A similar type of analysis can be performed for cancer mortality, based on data from the 2008 subprime crisis. On a global level, data from the World Bank and the WHO generated from more than 2 billion people from 1990 to 2010 showed that unemployment rises were significantly associated with an increase in all-cancer mortality, and all specific cancers (except lung cancer in women). This data has also highlighted that the 2008-10 economic crisis was associated with about 260,000 excess cancer-related deaths in OECD countries.

Altogether, an increased mortality rate is expected in cancer patients as a direct consequence of the COVID-19 infection, along with remote aftermath effects of the outbreak on healthcare disorganization and the global economy. Based on data derived from the 2008-10 recession, universal health coverage and public-sector expenditure on healthcare were shown to protect against this increased cancer mortality rate. Patients possessing healthcare insurance protection, or those covered by national healthcare systems which cover expenses for diagnosis and treatment, may not be impacted as much as others by the anticipated post-COVID-19 outbreak economic crisis.

Economic impacts specifically linked to mental health

Projected Increases in Deaths from Suicide

According to data gathered from 1997 to 2010 in the US (which therefore includes the 2008 recession), each percentage point increase in the unemployment rate resulted in a 1.6% increase in the suicide rate. During the COVID-19 pandemic if the unemployment rate were to increase by 20% over a year, Meadows Mental Health Policy Institute (MMHPI) estimates that approximately 18,000 more Americans could commit suicide over that time.

Source: Meadows Mental Health Policy Institute

Suicide experts and prevention groups have deliberately refrained from discussing death projections too widely, since reporting excessively or sensationaly on suicide can lead to increases in suicide attempts, an effect known as "suicide contagion".

Projected Increases in Deaths Due to Overdoses

Based on the same study, one percentage point increase in unemployment per year was associated with an increase of 0.334 overdose deaths per 100,000 people per year, meaning that each 5% increase in yearly unemployment would result in an additional 5,500 overdose-related deaths across the US per year. If the unemployment rate increases by 20%, MMHPI estimates that more than 22,000 Americans could lose their lives from drug overdoses related to unemployment alone.

Source: ibid.
Impact of unemployment and increase in substance use disorders

Illicit Substance Use Disorders (SUD) are also expected to increase with unemployment. A national yearly increase of 5% in the unemployment rate is projected to result in an additional 600,000 cases of SUD per year across the US.

Other indirect effects of COVID-19 on the general population’s mental health

Topping the impacts most linked to the economic crisis are the feeling of uncertainty that the pandemic has provoked, and the measures taken to fight it (social distancing, lockdown etc.), which can have an impact on an individual’s mental health. Please note that although this paragraph also discusses the mental disorders that can affect COVID-19 patients as they fight the disease, or after they recover from it, here we are more focused on the impact of stress and the social aspect of the COVID-19 crisis (especially in terms of the social distancing measures taken to fight it).

According to the Kaiser Family Foundation, nearly 17 million adults (>18 years old) and an additional 3 million adolescents (age 12 to 17) in the US experienced a major depressive disorder in 2019. A recent poll from the same source reported that the coronavirus crisis is harming the mental health of nearly 50% of the US population.

In order to identify the mental health consequences that the COVID-19 context could have on all of us (infected or not), it is interesting to analyze the data collected from 24 studies examining the psychological impact of quarantine during infectious disease outbreaks such as the 2003 severe acute respiratory system epidemic (SARS) and the 2014 Ebola outbreak.

Based on this data, some adverse psychological outcomes linked to this situation of quarantine and isolation included anger, anxiety, boredom, confusion, fear, depression, emotional exhaustion, frustration, irritability, stress, avoidance behaviors (e.g. avoiding crowded or public places), detachment from others, subthreshold symptoms of alcohol use disorder, Posttraumatic stress disorder (PTSD), and excessive preoccupation with distressing somatic symptoms.

Furthermore, suicide has been reported as an adverse effect of quarantine during previous viral epidemics. Historical trends show likely increases in suicidal ideation and behavior, deaths from overdose, substance use disorders and violence (especially domestic violence) as a result of quarantine.

Impact seems more significant for people with pre-existing mental disorders, especially with anxiety and depressive disorders. This population is at risk of developing further symptoms in the context of uncertainty surrounding COVID-19. Quarantine and lockdown can create negative feelings, including anger, confusion, and posttraumatic stress disorder (PTSD) symptoms, that may be long-lasting. Furthermore, cognitive impairment, risk unawareness, difficulty accessing timely health services, and inappropriate emotional responses, are some of the factors that render this population vulnerable to COVID-19.

When looking more specifically at the people infected with COVID-19, past experience from the SRAS pandemic suggests that psychiatric disorders which might have arisen as a result of the anxiety linked to COVID-19 may persist for at least three years. Individuals who were exposed to, or survived, SARS infection presented moderate to severe symptoms of anxiety disorders, depressive disorders, and PTSD in 20 to 30% up to 2.5 to 3 years after the epidemic. The risk for persistent psychiatric symptoms and disorders was especially higher for healthcare workers.

Furthermore, some of the medical treatments currently used or tested to fight COVID-19 can have side effects that influence the mental health of patients. Hydroxychloroquine for example that has been tested on hospitalized COVID-19 patients may cause some people to have suicidal thoughts and tendencies, or to become more depressed or even psychotic in rare cases.
Conclusion

Some risk factors can already be identified when it comes to analyzing the probability of being infected by COVID-19, and of developing a severe or fatal form of the disease. Complications, sequela and indirect effects are already being studied or assessed, based on past data.

As explained frequently in this document, medical research on COVID-19 is not yet mature, as studies often only communicate early findings, and conclusions on the importance of a given factor could be biased by other factors that may not have been considered.

As previously cautioned, it is important to emphasize that “correlation is not causation”. As such, we must be very careful when making operational decisions based on the medical studies mentioned within this document, in order to avoid misinterpretation.