

# The Effects of Gender on Frequency, Severity, and Long-term Prognosis of Patients with Long-term COVID-19

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The coronavirus disease of 2019 (COVID-19,) caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread around the world since the first reported case in December of 2019. With this virus came a condition referred to as ‘Long-COVID,’ where the symptoms of COVID-19 persist in patients for much longer than what is expected of a usual diagnosis. Recovery from typical COVID-19 usually takes 7-10 days after the initial diagnosis, or up to 3-6 weeks in extreme cases. However, for those with Long-COVID, symptoms can persist for months. Through analyzing the risk factors of Long COVID, it was found that Long-COVID disproportionately affected females, older individuals, and people with underlying medical conditions. Patients of Long-COVID are often unable to return to work due to their persisting symptoms, causing a loss of income; these unequal Long-COVID incidences will cause thousands to be out of work indefinitely, especially women. This paper aims to explore to causes behind the unequal incidences of Long COVID, and it was discovered that it could be caused by several reasons relating to the immune system, hormones of the different sexes, or a number of other reasons, all of which will be explored in depth within this paper.

## Introduction

In December 2019, the first case of SARS-CoV-2 was reported in Wuhan, Hubei Province<sup>1</sup>.

The virus was a novel coronavirus related to SARS-CoV, so, it was named Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2.) The respiratory disease caused by this virus was deemed COVID-19, as it is a coronavirus that first occurred in 2019. Since then, COVID-19 has spread rapidly around the globe, with the World Health Organization declaring a pandemic on 12 March 2022<sup>2</sup>. As of 24 August 2022, there are 595,219,966 confirmed cases and 6,453,458 deaths from COVID-19 worldwide<sup>3</sup>.

A coronavirus is any virus that belongs to the family Coronaviridae, the name coming from the club-shaped glycoprotein spikes in their enveloped virions (virus particles) that give the virus a crown-like appearance<sup>4</sup>. Its genome comprises a single strand of positive-sense RNA (ribonucleic acid.) COVID-19’s primary mode of transmission is direct person-to-person respiratory spread<sup>5</sup>. It occurs through close-ranged contact, within approximately six feet or two meters, and through respiratory particles that can be released when an infected person talks, sneezes, or coughs. It can also be transmitted through a person’s hands being contaminated by touching a contaminated surface and then touching their nose, mouth, or eyes. Only a fraction of COVID-19 cases have actually been diagnosed and reported, as such, the reported number of patients doesn’t fully account for the overall burden of COVID-19.

Of all of the COVID-19 cases, there are some patients who have never recover and continue to develop persistent or new symptoms that can last from weeks to months<sup>6</sup>. This condition is commonly referred to as ‘Long-COVID syndrome,’ ‘post-COVID syndrome,’ or ‘Long Haulers’, and most commonly ‘Long-COVID.’ Recovery from typical COVID-19 usually takes 7-10 days after the onset of symptoms, occasionally taking up to 3-6 weeks in severe cases. However, for those with Long-COVID, symptoms can persist months after the onset of symptoms. Patients suffering from COVID-19 who continue to exhibit the presence of one or more symptoms of COVID-19 long after the expected period of recovery can be defined as having Long-COVID.

A report from Italy through April and May of 2020, found that in patients with COVID-19, 87.4% still showed the presence of at least one symptom even 60 days after the initial onset, and 44.1% reported a worse quality of life<sup>7</sup>. Another study shows that some COVID-19 patients still show breathlessness and fatigue 3 months after the initial onset<sup>8</sup>.

Patients of Long-COVID are often unable to return to work due to their persisting symptoms, causing a loss of income, especially when combined with the cost of visiting doctors, buying medications, and attending physical and mental therapy. For people working in physical labor jobs, especially women, who are more likely to have Long-COVID and experience fatigue, according to Raveendran et al., 2021, the effects of Long-COVID could be a death sentence to them and their families<sup>6</sup>. One study finds that 7% of the U.S. adult

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population is suffering from Long-COVID, and as of January 2022, the total losses from Long-COVID are around \$386 billion when counting lost wages, lost savings and medical expenses<sup>9</sup>.

Long-COVID is the term used for a constellation of disease symptoms experienced by many millions of people in the wake of COVID-19. However, as I stated before, new evidence suggests that the disease burden of Long-COVID disproportionately affects women more than men<sup>10</sup>. This literature review will discuss the role that sex plays in frequency, severity, and long-term prognosis of patients suffering from Long-COVID.

## Possible Causes of Long-COVID

There are many possible reasons for the persistence of COVID-19 symptoms long after the expected recovery period such as chronic inflammation, a rare persistence of the virus in the body, or post-intensive care syndrome. According to research Lan et al., 2020, who observed multiple patients exposed to COVID-19 and tested positive in RT-PCR tests that were released from quarantine after two negative RT-PCR tests, tested positive again 5 to 13 days after the release<sup>11</sup>. This may be why some patients still show symptoms long after the initial onset.

Another theory by Colafrancesco et al., 2020 is that Long-COVID qualifies to be a new hyperferritinemia syndrome<sup>12</sup>. This is because when compared to the other four known hyperferritinemia syndromes (Septic shock, Adult-onset Still's disease (AOSD), Macrophage activation syndrome (MAS), and Cryopyrin-Associated Autoinflammatory Syndromes (CAPS)) they have similar characteristics such as high ferritin rang ( $>300$ ), cytokine release, infection as a trigger, and multi-organ involvement. The inflammation caused by the cytokine releases may be the cause of the persistence of COVID-19 symptoms.

Another possible cause is post-intensive care syndrome (PICS)<sup>13</sup>. Patients with PICS have new or worsened impairments in cognitive, physical, or mental capabilities after intensive care for critical illness. As researcher Biehl and Sese, 2020, finds, PICS itself can cause a higher prevalence of physical impairments (up to 80%), mental health impairments such as PTSD, anxiety, and depression also occurred in 8% to 57% of patients with PICS. Additionally, cognitive impairments such as memory loss and difficulty in comprehension were found in 30% to 80% of PICS patients in a study of over 800 patients. Many patients with COVID-19 are at higher risk of developing PICS, which may be a cause of persistent symptoms such as shortness of breath due to the other systems and impairments attributed to it. However, it is important to keep in mind that in patients younger than 40, the ratio that needed

to be hospitalized was only 0.4%, while in those older than 60, it was 9.2%<sup>14</sup>.

There are not enough studies on Long-COVID to make a conclusive decision on what the cause of it may be, with studies speculating on the inflammation caused by Long-COVID, or the PICS which may be a side effect of short term COVID-19 as the most likely causes.

## Risk Factors of Long-COVID

The risk factors of Long-COVID are similar to those of COVID-19, disproportionately affecting females, older individuals, and people with underlying medical conditions<sup>15</sup>. In a study performed on 201 individuals between April and September of 2020, 70% of the Long-COVID patients were female, and obesity was the most common pre-existing medical condition in patients with an incidence of 20%. The British Medical Journal's (BMJ) expert panel, 2020, shares that their data shows that women were twice as likely to get Long-COVID than men, while the average age of those with Long-COVID is about 4 years older than those who did not develop Long-COVID<sup>16</sup>. From these studies, it appears that female gender, underlying medical conditions such as obesity, and old age are the most common risk factors for Long-COVID.

## What Role Does Gender Play?

As stated in the earlier section, females are more likely to develop Long-COVID than males<sup>10</sup>. More specifically, a literature review by Sylvester et al., 2022 in Long-COVID found that females were more likely to contract it compared to males with an odds ratio of 1.22. They found that females were more likely to suffer symptoms in the categories of psychiatric and mood (i.e., depression), ear, nose or throat, musculoskeletal, and respiratory. On the other hand, male patients were more likely to have sequelae in the category of renal disorders (i.e., acute kidney injury). However, another review by Stewart et al., 2021 found that while Long-COVID is more common in females, vulnerability to and mortality from acute COVID-19 is higher in males<sup>17</sup>.

The studies by Sylvester et al., 2022 and Stewart et al., 2021 hypothesizes that difference in immune system function or hormone differences between the sexes may be one of the causes of the differences between incidences in Long-COVID patients<sup>10,17</sup>. Females often have more rapid and robust innate immune systems, which can protect them from the initial infection but may leave them more vulnerable against prolonged autoimmune-related diseases. This may also be why mortality from COVID-19 is more common in males. Another possible cause is the hormone differences, based on the overlapping

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symptoms of Long-COVID with those in menopause and perimenopause.

## Possible Causes of the Gender Discrepancies

Some researchers theorize that Long-COVID could be an autoimmune disease, which shines some light on its unequal incidences<sup>18</sup>. Studies have noted many shared symptoms between Long-COVID and other suspected autoimmune diseases, such as chronic fatigue syndrome, fibromyalgia, mood disorders, memory difficulties, and muscle pain. Autoantibodies, another distinctive feature of autoimmune diseases, have also been detected in a large portion of acute COVID-19 cases. In other studies, a specific autoantibody against angiotensin-converting enzyme 2 (ACE2) was discovered in COVID-19 patients. ACE2 is an enzyme that controls inflammation, another central factor in many autoimmune diseases, and a possible cause of Long-COVID. ACE2 is also X-linked, meaning it's expressed more in females<sup>19</sup>. Another study in patients with COVID-19 found that autoantibody levels in the body rose over time as the infection progressed, which suggests that, in some ways, COVID-19 can stimulate autoantibody production<sup>18</sup>. In any case, evidence indicates that COVID-19 and autoimmune diseases are highly correlated.

Biological sex had long been known to influence risk and vulnerability to diseases and their consequences<sup>20</sup>. Ngo et al., 2014 compiled data on adults who suffered from autoimmune diseases from across the world and found a very high gender bias towards females in most analyzed studies. For example, systemic diseases such as systemic lupus erythematosus and Sjögren's syndrome show a very clear bias towards females. Many other cases are also more prevalent in females, for instance, multiple sclerosis, many endocrine-related diseases such as Grave's Disease, Hashimoto's thyroiditis, and rheumatoid arthritis. Some cases vary regionally, but in most cases, they are consistent around the world. However, neurological diseases such as myasthenia gravis and Guillain-Barré syndrome have a nearly equal distribution between males and females.

Biological sex does not just affect prevalence; however, it can also have an effect on the severity of the autoimmune disease<sup>20</sup>. For example, psoriasis is more severe in males and males are also more likely to develop and relapse into autoimmune hepatitis, but often have a better prognosis than females. A study on systemic lupus erythematosus by Crosslin et al., 2011 found that female patients were more likely to suffer from urinary tract infections, hypothyroidism, depression, esophageal reflux, asthma, and fibromyalgia, while males were more likely to suffer renal and cardiovascular comorbidities<sup>21</sup>.

The research by Ngo et al., 2014 found that commonly, autoimmune disease in males have a young onset, with au-

toantibodies and acute inflammation<sup>20</sup>. While in females the disease is either acute onset and non-inflammatory, or associated with chronic pathology. As the Guardian, 1999, puts it, women get sick and men die<sup>22</sup>. While women lives longer than their male younger parts, they spent it wracked with the symptoms of their disease.

Ngo et al., 2014 also expand on the idea that the differences in the immune system and hormones are the main causes of the gender discrepancies<sup>20</sup>. They also found that females have a higher immune reactivity, with a difference in the number of responsive cells that constitute the immune response and a differential resistance to organ damage. Hormonal changes, such as stated above, during menopause, pubertal maturation, and pregnancy, as well as the difference in hormones females exert (estrogen, progesterone, and prolactin) and male hormones (androgens) could be another cause. The paper also suggests that exposure to different environmental factors and other genetic factors may also be causes. However, it seems that the most supported theory so far for the cause of unequal Long-COVID incidences is that it is due to hormonal changes and differences between the sexes. As the Guardian, 1999 reports, some studies show that women with MS often get worsened symptoms just before their period, but with pregnancy (when estrogen levels are higher,) the disease goes into remission<sup>22</sup>. Another study by Klein, 2016 found that women had a higher inflammatory response to pathogens, one which decreased over time<sup>23</sup>. However, men's inflammatory response seemed to increase with age, which Klein, 2016 speculates is due to the different levels of testosterone, which is anti-inflammatory. The study also suggests that certain estrogen-based compounds help the immune system fight against flu cells. Through these studies, it is clear that while hormone differences and changes may not be the main cause of gender discrepancies in diseases and viruses, it does have some effect on the symptoms and prognosis of the patients.

## Consequences of unequal Long COVID incidence

Increasing our knowledge on the gender discrepancy in Long COVID is crucial for the identification and design of effective treatment and therapies. Such knowledge can optimize a successful outcome for both genders, and allows future researches to anticipate sex as a variable in infectious outbreaks.

Those infected with COVID-19 already commonly suffer from symptoms that prevent them from returning to work, with Long COVID, these symptoms are stretched out over months. Many will be unable to work, much less provide for themselves and their family, especially women, who are already commonly underrepresented and underpaid in work fields such as manual labor. Essential workers such as doctors

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and nurses are also more likely to be exposed to COVID-19 and contract Long COVID, with these workers being unable to do their jobs for an indefinite amount of time, the shortage of healthcare workers will be even more exacerbated.

## Conclusion

This paper has analyzed other reports and papers on Long COVID incidence and the unequal sex distribution. It was found that females are much more likely to be diagnosed with Long COVID, and, possibly due to immune system or hormonal differences in the two sexes. This unequal incidence between the genders should be further examined, as it affects people all around the globe, and will leave thousands, especially woman, out of work for an indefinite amount of time.

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