

The evolving picture of long COVID

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Much is still unknown about long COVID, but some pieces of the puzzle are starting to fall into place.

A systematic review by Canadian researchers identified more than 100 symptoms associated with long COVID. Some of the most common include fatigue, general pain, sleep disturbances, shortness of breath, cognitive impairment, and mental health symptoms. Researchers also found that 9% of people were unable to return to work after three months.

Meanwhile, a work-in-progress report of a longitudinal cohort study (CANCOV) found that 53% of nonhospitalized patients still experienced symptoms three months after infection. That decreased to 37% at 12 months postinfection. At three months postinfection, fatigue was the most common symptom (22%), followed by cognitive changes (16%), headaches (11%), dyspnea (9%), and chest heaviness or pain and tightness (8.5%).

The World Health Organization (WHO) estimates that 10%–20% of people who have COVID will develop post-COVID conditions, which would mean that upwards of 388 000 people in Canada have developed long COVID (to date, 3.8 million people in Canada have had COVID-19).

Women most at risk of long COVID

Outside of Canada, research from China, Italy and Spain shows women to have a higher risk of developing long COVID. In the Spanish study, women were also more likely to experience a higher number of long COVID symptoms than men (2.25 for women, compared with 1.5 for men). Another study found women younger than 50 were twice as likely to report fatigue and seven times as likely to report

dyspnea than men of the same age seven months after hospital discharge.

A UK preprint study also found that older people, women, and people who already had poor physical or mental health had an increased risk of long COVID.

The number of symptoms patients have during acute infection appears to be correlated with the risk of developing long COVID. A study published in *Nature* found that people who had more than five symptoms during the first week of illness were significantly more likely to go on to experience long COVID than those with fewer symptoms.

It's not clear why long COVID seems to affect women more frequently than men, but this wouldn't be the first time an acute infection has been associated with unexplained chronic disability.

Long COVID shares “many similarities” with other “enigmatic chronic illnesses,” write scientists in *Nature Medicine*. Post-acute infection syndromes represent “a substantial health care burden, but there is a lack of understanding of the underlying mechanisms, representing a significant blind spot in the field of medicine,” the authors write.

“This is not a pattern that we’re used to seeing”

Long COVID is still largely diagnosed by ruling other disorders out.

The WHO defines long COVID as a post-COVID condition that occurs “three months from the onset of COVID-19 with symptoms and that last for at least two months and cannot be explained by an alternative diagnosis.”

This definition is a diagnosis of exclusion, says Adeera Levin, a professor of medicine at the University of British

Columbia. It's difficult to study or establish consistency internationally, especially when different investigators use different tools to identify or describe the symptomatology.

“No one's defined how you would rule out other causes,” says Levin. She says not every country has access to diagnostic tests that can rule out underlying heart or lung disease, for example. “Also, what if they have underlying kidney disease—does that make it not long COVID?”

Diagnosing long COVID remains a big challenge, says Angela Cheung, co-lead investigator of the CANCOV study looking at the outcomes of COVID-19 in Canadian patients and their caregivers. Cheung is also leading the RECLAIM trial (REcovering from COVID-19 Lingering symptoms Adaptive Integrative Medicine), which not only looks at management of symptoms of long COVID, but also its root causes.

Some clinicians have not seen a lot of long COVID, she says, and because patients are often anxious, some physicians may also misinterpret patients' worry about their symptoms. “It's easy to chalk it up to anxiety and mental health issues and it's very hard to tease out how much mood and anxiety plays into all of this,” Cheung says.

While patients often feel like they're not able to get a diagnosis, physicians struggle with how to diagnose.

“It's so vague, and all the tests seem normal. It's one thing if you do a CT scan, and you actually see lung changes, but I would say for most of our patients, it's not like that,” says Cheung. “It's a bit of an issue because fatigue, dizziness, a lot of the symptoms are fairly nonspecific.” Chest pain, for example, can be caused by problems with the heart, lungs, muscles, or joints.

“As health practitioners, we do a lot of pattern recognition. And this is not a pattern that we’re used to seeing,” says Cheung.

Some big remaining questions

Researchers have to account for a large number of factors as both COVID-19 and the global pandemic response evolves. People exposed to SARS-CoV-2 in the spring of 2020 — before vaccines, variants, and new therapeutics — may not experience the same long-haul symptoms as those exposed during the later Delta and Omicron waves.

There also needs to be more understanding of the mechanism of the disease, which could open a door to potential treatment, says Alain Piché, a microbiologist, infectious disease physician, and director of a post-COVID clinic in Sherbrooke.

“At this point, we really need new drugs or known drugs that will be effective against long COVID, because I’m seeing so many patients that have a huge impairment on their daily lives,” he says.

“They cannot work, they cannot take care of themselves, they need somebody around, they forget things, they cannot concentrate, they cannot live a normal life anymore. Unfortunately, these patients are severely impaired and this is too common. I’ve seen so many of these patients and there are few things that we can do to help them besides trying to ease some of the symptoms.”

Piché hopes that studies like Cheung’s RECLAIM study as well as several others around the world — which hopefully will be available within the next year to 18 months — will provide much-needed answers.

Diana Duong, *CMAJ*

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