

Risk Factors and Management of Long COVID

Xiangmin Dong

Sichuan University, Chengdu, Sichuan 610044, China

Abstract. The COVID-19 pandemic has been spreading around the world and cause serious harm to individual health and social development. Although we have established a comparatively perfect epidemic prevention system and medical system against SARS-CoV-2. Recent research suggests the emergence of a novel syndrome known as 'long COVID', a term used to describe a diverse set of symptoms that persist after a minimum of 4 weeks from the onset of a diagnosed SARS-CoV-2 infection. Like COVID-19, long COVID affect multiple organs and many systems including, but not limited to, the neurological, respiratory, gastrointestinal, cardiovascular and musculoskeletal systems. However, the exact factors leading to the long COVID-19 are not clear at present. This review summarizes many potential risk factors linked long COVID found in some papers, including age, gender, symptom experienced and comorbidity. Preliminary evidences also suggest physical therapy (respiratory support in the ICU, evaluation and dietary approaches), protect mental health (government and social help) and gain social support can help mitigate long COVID.

Keywords: Long COVID; Risk Factors; Managements.

1. Background

Globally, SARS-CoV-2 infection (COVID-19) has caused earth-shattering mortality and morbidity. Even if the symptoms in most people are mild and flu-like, some patients, especially those with underlying diseases, may develop respiratory failure, cardiac and cardiovascular complications, thromboembolic complications, neurologic complications and inflammatory complications.[2] Meanwhile, evidences show that 35% to 60% people who recovered from COVID-19 still suffer ongoing symptoms for months.[3] Currently, there is no universally accepted definition of "long COVID." As defined by the British National Institute for Health and Care Excellence (NICE), post-COVID-19 syndrome is defined by more than 12 weeks' persistent symptoms after onset. [1] The most prevalent symptoms included in a meta-analysis is dysgeusia/anosmia, and many COVID-19 survivors experienced co-prevalence based on the follow-up. Other persistent symptoms include cough (20–25%), anosmia (10–20%), ageusia (15–20%) or joint pain (15–20%).[3] It is noted that some papers reviewed that some patients may experience some mental problems, like concentration difficulties, anxiety, memory loss, depression.[4]

2. Risk Factors

Risk factors are agents that increase the risk of disease or infection. The most common factors associated with the prevalence of the long COVID include age, gender, symptoms experienced and comorbidity.

2.1 Age

Among long COVID patients, there is a significant association between developing persistent symptoms and older age. Several cohorts reported that hospitalization rates for COVID - 19 increased with age, ranging from 4 % in subjects aged 50 - 59 years to 18 % in subjects aged 80 years and older. These patients were more likely to develop in these patients over time.[4] Also, a study performed descriptive clinical follow-up found Persistent symptoms were significantly associated with age 40 to 60 years old.[6] When grouping for age, a prospective cohort study reported that younger patients (<60 years) reported significantly higher rates of breathing difficulties, sleep problems and concentration problems than patients 60 years and older.[7] This may be due to their reduced organ function and weak recovery ability.

2.2 Gender

The incidence of post-COVID symptoms was higher in females than in males eight months after hospital discharge.[8] Additionally, three multicenter studies also reported that Women are at higher risk for some symptoms after COVID, such as fatigue, dyspnea, and skin problems.[9][10][11] A study showed that the proportion of long-COVID-19 (15%) among middle-aged women was slightly higher than among men (10 %). However, this gender-related difference was not observed in subjects aged over 70.[12] According to these results, female gender is potential risk of COVID sequelae and they are vulnerable to long COVID. Therefore, sex differences should be considered when managing people who have recovered from COVID-19 and develop COVID sequelae. In addition, it is important to note that a meta-analysis found that males are easier to be infected and stand a higher possibility to become severe,[13] which makes the influence of sex confused. A hypothesis is that woman's hormones and a stronger IgG production may result in this contrasting phenomenon.[14]

2.3 Symptoms Experienced

A multicenter study found that persistent symptoms are associated with higher number of symptoms on admission.[15] This study randomly selected 400 individuals from each hospital. According to its results, the number of symptoms experienced in patients with long COVID increased with the number of co-morbidities or COVID-19 onset symptoms. In the study of COVID, a greater number of symptoms was not relevant with co-morbid conditions (e.g., obesity, hypertension). COVID-related acute symptoms were also independently associated with longer-term symptoms (all, $p < 0.01$). More than 1250 general practices in Germany took part in another study of nearly 31,000 patients with COVID-19 found obvious associations between sequelae and clinical characteristics (non-infectious enterocolitis and colitis, impaired response and adaptation to severe stress, atopic dermatitis, mononeuropathy, reflux disease, diabetes mellitus and hypertension). [16]

The number (more than five) of initial presenting symptoms was also a risk factor for long COVID. A report analyzed 32 self-reported short and long-term symptoms in a general adult population and observed that those with a high number of initial symptoms were more likely to experience long-term COVID. [17] Similarly, a 4-month follow-up study including 434 samples indicate that the presentation of more than 10 symptoms was also linked with long COVID.[18]

2.4 Comorbidity

Many studies have reported that the comorbidity is highly associated with long COVID. patients with heart failure (HR, 2.12 [CI, 1.41 to 3.19]), diabetes with complications (HR, 1.71 [CI, 1.17 to 2.52]) stand a higher possibility to be rehospitalized.[19] Another report investigated 538 COVID survivors in Wuhan and found a history of pulse ≥ 90 bpm during hospitalization and asthma is associated with Clinical sequelae.[20] It is plausible to figure out the relationship between comorbidity and long COVID. Abnormal blood glucose levels will result in dysregulation of immune components and reduced response. In addition, problems of cardiovascular may lead to heart failure and organ dysfunction. Therefore, they become vulnerable to long COVID.

3. Management

People with long-term COVID appear to experience a significant decline in quality of life. A total of 12 studies were selected to calculate in a systematic review and meta-analysis to calculate the pooled prevalence of poor quality of life. The pooled prevalence of poor quality of life (EQ-VAS) was (59%, 95% CI: 42%–75%, $p < 0.0001$) amongst patients experiencing long COVID.[19] Therefore managements for people with persistent symptoms to rehabilitate are essential.

3.1 Physical Therapists

Long COVID may lead to severe physical dysfunction. acquired muscle weakness, decreased physical function, and myopathy and neuropathy in the ICU are also known as the physical areas of

post-intensive care syndrome.[22] A paper advises people with long covid to start with breathing practices and some light muscle activity. After the patient has tolerated light stretching and strengthening, aerobic training will be introduced.[24] Even if data of this approach about the outcome is poor, a paper recruited 72 participants who were just discharged from hospital to assess the effect of respiratory rehabilitation, and they found that the respiratory function of an individual who underwent six-week respiratory rehabilitation improved.[25] As for Post-COVID-19 acute sarcopenia, a paper addresses the importance of proper evaluation of the patient, the introduction of tailored rehabilitation and dietary approaches.[23]

3.2 Mental Health

Mental issues such as anxiety, depression, PTSD and suicidal attempt have been found to be potential symptoms of long COVID.[26] Therefore, there is an urgent need for proper managements. A paper recommended a kind of behavioral psychotherapy called cognitive behavioral therapy (CBT) for chronic fatigue syndrome.[27] However, it is easy to understand that face to face CBT is almost impossible in today's world since government requires us to keep social distance to avoid infection. Fortunately, we can build a public psychological crisis management platform to solve this problem. The advantage of CBT through internet is that we can decrease the risk of virus transmission, save time spent on travel or schedule appointment and reduce potential nervousness since you can stay where you are comfortable.

3.3 Social Services

Due to persistent symptoms, many people find it difficult to go back to work or school.[28] Government and companies are supposed to aid them to identify and manage the both physical and mental crisis after COVID-19 infection. They need understand their situation, support them to work online and give them enough time to adapt.

4. Conclusion

The wide range of potential symptoms patients with long COVID may experience stress the importance of risk factors and management for long COVID. Elder age, female gender, symptoms experienced and more than five initial presenting symptoms are regarded as the prevalent risk factors for long COVID. In fact, the most effective approaches to prevent long COVID is to prevent COVID-19. (vaccination, masks, isolation and washing hands). An interesting discovery is that vaccination can lower our rates of long COVID. Considering people with long COVID are expected to experience reduction in life quality, managements including mental health, physical health and social supports are put forward to help patients rehabilitate and back to work.

References

- [1] World Health Organization (2021) A clinical case definition of post COVID-19 condition by Delphi consensus, 6 October 2021. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.
- [2] McIntosh K, Hirsch M S, Bloom A. COVID-19: Clinical features[J]. UpToDate. Post TW (ed): UpToDate, Waltham, MA, 2021.
- [3] César Fernández-de-las-Peñas, Domingo Palacios-Ceña, Víctor Gómez-Mayordomo, Lidiane L Florencio, María L. Cuadrado, Gustavo Plaza-Manzano, Marcos Navarro-Santana, Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis, *European Journal of Internal Medicine*, Volume 92, 2021, Pages 55-70, ISSN 0953-6205.
- [4] Han Q, Zheng B, Daines L, Sheikh A. Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. *Pathogens*. 2022; 11(2):269. <https://doi.org/10.3390/pathogens11020269>.

- [5] Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis.* 2020;20(6):669–677. Doi: 10.1016/S1473-3099(20)30243-7.
- [6] Carvalho-Schneider C, Laurent E, Lemaigen A, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect.* DOI: 10.1016/j.cmi.2020.09.052.
- [7] Jessica Seeßle, Tim Waterboer, Theresa Hippchen, Julia Simon, Marietta Kirchner, Adeline Lim, Barbara Müller, Uta Merle, Persistent Symptoms in Adult Patients 1 Year After Coronavirus Disease 2019 (COVID-19): A Prospective Cohort Study, *Clinical Infectious Diseases*, Volume 74, Issue 7, 1 April 2022, Pages 1191–1198, <https://doi.org/10.1093/cid/ciab611>.
- [8] Fernández-de-las-Peñas, C.; Martín-Guerrero, J.D.; Pellicer-Valero, Ó.J.; Navarro-Pardo, E.; Gómez-Mayordomo, V.; Cuadrado, M.L.; Arias-Navalón, J.A.; Cigarán-Méndez, M.; Hernández-Barrera, V.; Arendt-Nielsen, L. Female Sex Is a Risk Factor Associated with Long-Term Post-COVID Related-Symptoms but Not with COVID-19 Symptoms: The LONG-COVID-EXP-CM Multicenter Study. *J. Clin. Med.* 2022, 11, 413. <https://doi.org/10.3390/jcm11020413>.
- [9] Zhang, X.; Wang, F.; Shen, Y.; Zhang, Z.; Cen, Y.; Wang, B.; Zhao, S.; Zhou, Y.; Hu, B.; Wang, M.; et al. Symptoms and health outcomes among survivors of COVID-19 infection 1 year after discharge from hospitals in Wuhan, China. *JAMA Netw. Open* 2021, 4, e2127403.
- [10] Munblit, D.; Bobkova, P.; Spiridonova, E.; Shikhaleva, A.; Gamirova, A.; Blyuss, O.; Nikita Nekliudov, N.; Bugaeva, P.; Andreeva, M.; DunnGalvin, A.; et al. Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19. *Clin. Exp. Allergy* 2021, 51, 1107–1120.
- [11] Sigfrid, L.; Drake, T.M.; Pauley, E.; Jesudason, E.C.; Olliaro, P.; Lim, W.S.; Gillesen, A.; Berry, C.; Lowe, D.J.; McPeake, J.; et al. Long COVID in adults discharged from UK hospitals after COVID-19: A prospective, multicentre cohort study using the ISARIC WHO Clinical Characterisation Protocol. *Lancet Reg. Health Eur.* 2021, 8, 100186.
- [12] Sudre CH, Murray B, Varsaysky T, et al. Attributes and predictors of Long-COVID: analysis of COVID cases and their symptoms collected by the COVID symptoms study app. medRxiv. 2020.
- [13] Md. Abdul Barek, Md. Abdul Aziz, Mohammad Safiqul Islam, Impact of age, sex, comorbidities and clinical symptoms on the severity of COVID-19 cases: A meta-analysis with 55 studies and 10014 cases, *Heliyon*, Volume 6, Issue 12, 2020, e05684, ISSN 2405-8440, <https://doi.org/10.1016/j.heliyon.2020.e05684>. (<https://www.sciencedirect.com/science/article/pii/S2405844020325275>).
- [14] Francesca Bai, Daniele Tomasoni, Camilla Falcinella, Diletta Barbanotti, Roberto Castoldi, Giovanni Mulè, Matteo Augello, Debora Mondatore, Marina Allegrini, Andrea Cona, Daniele Tesoro, Gianmarco Tagliaferri, Ottavia Viganò, Elisa Suardi, Camilla Tincati, Tomaso Beringheli, Benedetta Varisco, Chiara Luridiana Battistini, Kyrie Piscopo, Elena Vegni, Alessandro Tavelli, Stefano Terzoni, Giulia Marchetti, Antonella d'Arminio Monforte, Female gender is associated with long COVID syndrome: a prospective cohort study, *Clinical Microbiology and Infection*, Volume 28, Issue 4, 2022, Pages 611.e9-611.e16, ISSN 1198-743X, <https://doi.org/10.1016/j.cmi.2021.11.002>.
- [15] César Fernández-de-las-Peñas, Oscar J. Pellicer-Valero, Esperanza Navarro-Pardo, Domingo Palacios-Ceña, Lidiane L. Florencio, Carlos Guijarro, José D. Martín-Guerrero, Symptoms Experienced at the Acute Phase of SARS-CoV-2 Infection as Risk Factor of Long-term Post-COVID Symptoms: The LONG-COVID-EXP-CM Multicenter Study, *International Journal of Infectious Diseases*, Volume 116, 2022, Pages 241-244, ISSN 1201-9712, <https://doi.org/10.1016/j.ijid.2022.01.007>. (<https://www.sciencedirect.com/science/article/pii/S1201971222000078>).
- [16] Louis Jacob, Ai Koyanagi, Lee Smith, Christian Tanislav, Marcel Konrad, Susanne van der Beck, Karel Kostev, Prevalence of, and factors associated with, long-term COVID-19 sick leave in working-age patients followed in general practices in Germany, *International Journal of Infectious Diseases*, Volume 109, 2021, Pages 203-208, ISSN 1201-9712, <https://doi.org/10.1016/j.ijid.2021.06.063>. (<https://www.sciencedirect.com/science/article/pii/S120197122100552X>).
- [17] Long-term COVID-19 symptoms in a large unselected population Elizabeth T. Cirulli, Kelly M. Schiabor Barrett, Stephen Riffle, Alexandre Bolze, Iva Neveux, Shaun Dabe, Joseph J. Grzymski, James T. Lu, Nicole L. Washington medRxiv 2020.10.07.20208702; doi: <https://doi.org/10.1101/2020.10.07.20208702>.
- [18] Stavem K, Ghanima W, Olsen MK, et al. 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. *Thorax.* 2021;76(4):405.

- [19] Bowles KH, McDonald M, Barrón Y, Kennedy E, O'Connor M, Mikkelsen M. Surviving COVID-19 After Hospital Discharge: Symptom, Functional, and Adverse Outcomes of Home Health Recipients. *Ann Intern Med.* 2021 Mar;174(3):316-325. Doi: 10.7326/M20-5206. Epub 2020 Nov 24. PMID: 33226861; PMCID: PMC7707212. Malik, P, Patel, K, Pinto, C, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)--A systematic review and meta-analysis. *J Med Virol.* 2021; 94: 253- 262.
- [20] Qiutang Xiong, Ming Xu, Jiao Li, Yinghui Liu, Jixiang Zhang, Yu Xu, Weiguo Dong, Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study, *Clinical Microbiology and Infection*, Volume 27, Issue 1, 2021, Pages 89-95, ISSN 1198-743X.
- [21] Malik, P, Patel, K, Pinto, C, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)--A systematic review and meta-analysis. *J Med Virol.* 2021; 94: 253- 262. [https:// doi.org/ 10.1002/ jmv.27309](https://doi.org/10.1002/jmv.27309).
- [22] Candan, SA, Elibol, N, Abdullahi, A. Consideration of prevention and management of long-term consequences of post-acute respiratory distress syndrome in patients with COVID-19. *Physiother Theory Pract* 2020; 36: 663–668.
- [23] Piotrowicz, K., Gąsowski, J., Michel, JP. et al. post-COVID-19 acute sarcopenia: physiopathology and management. *Aging Clin Exp Res* 33, 2887–2898 (2021). <https://doi.org/10.1007/s40520-021-01942-8>.
- [24] Mikkelsen, M. E., & Abramoff, B. COVID-19: evaluation and management of adults with persistent symptoms following acute illness (“Long COVID”). UpToDate. Updated July 19, 2022.
- [25] Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. *Complement Ther Clin Pract.* 2020 May; 39:101166. doi: 10.1016/j.ctcp.2020.101166. Epub 2020 Apr 1. PMID: 32379637; PMCID: PMC7118596.
- [26] Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long COVID: a review. *Journal of the Royal Society of Medicine.* 2021;114(9):428-442.
- [27] Sanaz Shanbehzadeh, Mahnaz Tavahomi, Nasibeh Zanjari, Ismail Ebrahimi-Takamjani, Somayeh Amiri-arimi, Physical and mental health complications post-COVID-19: Scoping review, *Journal of Psychosomatic Research*, Volume 147, 2021, 110525, ISSN 0022-3999, [https:// doi.org/ 10. 1016/j. jpsychores. 2021.110525](https://doi.org/10.1016/j.jpsychores.2021.110525).
- [28] Garrigues, E, Janvier, P, Kherabi, Y, et al. post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect* 2020; 81: e4–e6.
- [29] Azzolini E, Levi R, Sarti R, Pozzi C, Mollura M, Mantovani A, Rescigno M. Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers. *JAMA.* 2022 Aug 16;328(7):676-678. Doi: 10.1001/jama.2022.11691. PMID: 35796131; PMCID: PMC9250078.