



## Risk Factors Associated with Long Covid Experience of the Virology, Infectious and Tropical Diseases Center

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### Abstract

**Background:** A large number of covid-19 patients experience prolonged symptoms, called long covid. Few systematic national studies have been carried out, especially in outpatient settings. As a result, little is known about the types and severity of symptoms, the clinical course, and the predictive factors linked to this condition.

The aim of this study was to identify the characteristics and predictors of long covid among our patients during the SARS-CoV-2 Omicron wave.

**Methodology:** This was a prospective observational cohort study conducted over 12 months (October 2022 to October 2023). We recruited adult patients (aged 18 years or older) in whom a diagnosis of SARS-CoV-2 infection had been confirmed by Reverse Transcription Polymerase Chain Reaction (RT-PCR) and who had been admitted to the Centre for Virology, Infectious and Tropical Diseases (CVMIT) or were being treated as outpatients. Eligible patients were followed up by telephone four weeks after diagnosis of the infection to collect their sociodemographic and clinical characteristics, as well as their vaccination history.

The characteristics of long covid have been described, and a multivariate logistic regression analysis was performed to determine the predicting factors for long covid.

**Results:** A total of 287 patients participated in this study. Of these, 182 (63.4%) were men with a mean age of 47 years. The mild form of the disease was predominant in our patients (97.5%), and 57 (20.4%) were asymptomatic. The prevalence of long covid was 16% (N=46). Based on the clinical manifestations, the most frequently reported persistent symptoms were asthenia, chronic cough, chest tightness, dyspnea, chronic diarrhea, and headaches.

Statistically significant predictors of long covid at four weeks of follow-up were female sex and the presence of at least one comorbidity, especially chronic pulmonary disease.

**Conclusion:** A significant proportion of long covid cases have been identified among patients with covid-19. Further research is needed in this area to objectively assess symptoms and identify predictors of long covid.

**Keywords:** Long covid; Epidemiology; Risk factors

### Introduction

Covid-19 is an unprecedented pandemic that has affected more than 780 million people worldwide and has resulted in 7.1 million deaths [1]. In the wake of the initial phase of this pandemic, a lot of observational studies, patient groups, and case series have reported persistent symptoms generally aggravated by physical or intellectual effort [2].

As defined by the WHO, the term long covid-19 embraces a group of symptoms that can occur following the acute phase of a SARS-CoV-2 infection and as a consequence thereof. He includes both "ongoing symptomatic Covid-19 that arises from 4 to 12 weeks and "post-Covid-19 syndrome" continuing for more than 12 weeks after an infection, and cannot be explained by another cause [3]. This entity can affect 10% to 20% of individuals who complain of persistent or new-onset symptoms in the longer course [4].

Long Covid affects patients who have asymptomatic, moderate, or severe disease with varying

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percentages. Common symptoms reported in the literature include fatigue, pain, breathlessness, cognitive impairment, anxiety, gastrointestinal symptoms, myalgia, and bone aches [5]. All of these symptoms affect the physical and psychological health of patients [6]. However, six years after the first described cases. The origin of these symptoms remains poorly understood. Several hypotheses have been proposed to explain the various aspects of this complex condition. Direct organ damage, immune system perturbation, autoimmunity, latent virus reactivation or persistent infection, endothelial dysfunction, and microbiome disturbances are among the most relevant avenues for elucidating the mechanisms of long-term Covid [7].

In addition, the risk factors have not yet been clearly defined. This is due to the difficulty of long-term medical follow-up and lack of data, especially for patients who were treated on an outpatient basis. In the literature, most meta-analyses reported that female sex, the severity of covid-19, complications, and dyspnea would increase the risk of developing long covid [8]. However, in developing countries, like Morocco, the characterization and reporting of long covid may be influenced by the predominance of asymptomatic cases [9], the predominantly young population (67,57% younger than 65 years) [10], the high vaccination coverage (9,75 % per 100 residents in 2021) [11], or other sociocultural specificity factors. Therefore, the present study aims to determine the potential risk factors for post-covid-19 syndrome in patients with covid-19 confirmed by SARS-CoV-2 PCR.

## Materials and Methods

### Participants

In this prospective cohort study conducted on a sample of adult patients aged 18 and over who were treated at the Centre for Virology, Infectious Diseases and Tropical Diseases (CVMIT -HMIMV) from November 01, 2022, to November 31, 2023.

All patients had a confirmed covid-19 diagnosis with a positive result on real-time Polymerase Chain Reaction (PCR) testing of the nasopharyngeal and oropharyngeal samples.

### Data collection

For each patient admitted with a diagnosis of covid-19, the following data were collected by the physician and recorded on standardized paper forms (on admission): age, sex, underlying chronic health problems, vaccination status, presence of symptoms, results of clinical- paraclinical evaluation, and established therapeutic protocol.

The patients participated in a maximum of two follow-up consultations, as recommended by the clinicians. These consultations were conducted by telephone seven days and four weeks later. All participants provided oral consent (We are conducting a study on the symptoms of long covid. Do you agree to participate in this study?)

Participants were free to answer questions during the interview, which lasted 5 to 10 minutes. Their accounts were classified according to recent recommendations from the WHO and NICE (National Institute for Health and Clinical Excellence) [3], that long covid-19 correlated with persistent symptoms after the acute phase of SARS-CoV-2 infection.

### Statistical analyses

Data were collected using a paper-based questionnaire and were subsequently entered and analysed using the statistical software

JAMOVI (version 2.6.44). The incidence of long covid was determined by the number of patients who self-reported one of the symptoms of long covid during the 4-week follow-up period.

Qualitative variables were described using absolute numbers and proportions, whereas quantitative variables were described using means and standard deviations if the distribution was normal; otherwise, they were described using the median and the interquartile range.

Univariate analysis was carried out using statistical tests appropriate to the nature of the variables; thus, the chi-square test or Fisher's exact test was used to compare categorical variables, and the t-test was used to compare quantitative variables. Logistic regression was used to identify predictors of long Covid at the four-week follow-up. Demographic variables, medical history (including variables related to acute covid-19), and covid-19 vaccination status were included in the logistic regression model based on previous literature.

Statistical significance for the univariate analysis was set at a p-value of less than 0.05. A multivariate logistic regression was performed to obtain an adjusted odds ratio with a 95% confidence interval. Clinically significant variables were added to the multivariate model.

## Results

In total, 318 people met the inclusion criteria for the study. Thirty-one participants declined to give their consent; as a result, 287 telephone interviews were successfully conducted after four weeks of follow-up.

The mean age was  $47.0 \pm 16.4$  (21-92) years, and 79.9% were less than 60 years old. Of the participants, 63.3% were male, and 32.3% had at least one comorbidity. The most common comorbidities were hypertension (12.9%), chronic pulmonary disease (9.3%), and diabetes (7.5%).

A total of 20.6% of patients were infected multiple times with Covid-19, and 92.7% were fully vaccinated against SARS-CoV-2. Half of the patients (39.1%) fall into the high-risk group for developing severe Covid, and the majority of the patients (95.1%) had a mild Covid-19 in the acute stage of the disease. The baseline demographics and characteristics of the patients are presented in Table 1.

In the acute phase of the disease, 79.6% of the patients were symptomatic and presented with sore throat (43.6%), fever (41.1%), cough (37.9%), and arthralgia (32.1%). After four weeks of symptom onset, 46 patients had persistent symptoms, and more than half had three or more symptoms that could not be explained by another cause. General systemic symptoms were the most frequent persistent symptoms, and at least one was present in 58.7% of the patients. Respiratory symptoms (34.7%) were the second most persistent symptom, and one-third of the patients complained of intermittent dry cough. Among the patients, 32.6% had persistent symptoms associated with neurological disorders. Headache (13.4%) and dizziness (10.8%) were the most common neurological symptoms. Some patients reported the appearance of other subjective symptoms such as psychological disturbances, decreased libido, and skin lesions (Table 2).

The mean duration of symptoms was 114 days among patients classified as having long covid, whereas it was 3.79 days among patients without long Covid.

**Table 1:** Demographic and clinical characteristics of patients infected with SARS-CoV-2 (n=287).

| Variables                                        | Total population |      | Group not long covid (n=241) |     | Group long covid (n=46) |    | p-value |
|--------------------------------------------------|------------------|------|------------------------------|-----|-------------------------|----|---------|
|                                                  | n                | %    | n                            | %   | n                       | %  |         |
| Female sex, n (%)                                | 105              | 36.6 | 81                           | 34  | 24                      | 52 | 0.017   |
| Age >60 years, mean (SD)                         | 56               | 19.9 | 48                           | 20  | 8                       | 17 | 0.604   |
| Presence of chronic diseases.                    | 97               | 35.5 | 73                           | 30  | 26                      | 57 | 0.005   |
| number of comorbidities                          |                  |      |                              |     |                         |    |         |
| None                                             | 182              | 65.2 | 161                          | 67  | 21                      | 46 |         |
| On comorbidity                                   | 68               | 24.4 | 47                           | 20  | 21                      | 46 |         |
| At least two comorbidities                       | 29               | 10.4 | 1                            | 0.1 | 4                       | 9  |         |
| Past medical history                             |                  |      |                              |     |                         |    |         |
| Diabetes                                         | 21               | 7.5  | 40                           | 17  | 6                       | 13 | 0.139   |
| Hypertension                                     | 36               | 12.9 | 30                           | 12  | 6                       | 13 | 0.984   |
| Cardiovascular diseases (excluding hypertension) | 15               | 5.4  | 10                           | 4   | 5                       | 11 | 0.101   |
| Chronic pulmonary disease                        | 26               | 9.3  | 15                           | 6   | 11                      | 24 | <0.001  |
| Neurological diseases                            | 4                | 1.4  | 4                            | 2   | 0                       |    |         |
| Kidney failure,                                  | 1                | 0.4  | 1                            | 0.1 | 0                       |    |         |
| autoimmune diseases                              | 11               | 3.9  | 11                           | 5   | 0                       |    |         |
| Malignity                                        | 10               | 3.6  | 8                            | 3   | 2                       | 4  | 0.64    |
| immunosuppression                                | 10               | 3.6  | 9                            | 4   | 1                       | 2  | 0.487   |
| Obesity (BMI>30)                                 | 22               | 11.4 | 16                           | 7   | 6                       | 13 | 0.436   |
| History of COVID-19 infection                    | 51               | 23.9 | 41                           | 17  | 10                      | 22 | 0.759   |
| Sars-Cov2 vaccinated                             | 262              | 94.9 | 220                          | 91  | 42                      | 91 | 0.344   |
| Tobacco smoking                                  | 56               | 22.9 | 47                           | 20  | 9                       | 20 | 0.851   |
| Severity of acute illness                        |                  |      |                              |     |                         |    |         |
| Mild                                             | 272              | 97.5 | 229                          | 95  | 43                      | 93 |         |
| moderate                                         | 7                | 2.5  | 4                            | 2   | 3                       | 7  | 0.121   |

**Table 2:** Symptoms reported by COVID-19 patients and their characteristics at the four-week follow-up (n=287).

| Symptoms                  | Group not long covid (n=241) |      | Group long covid (n=46) |      |
|---------------------------|------------------------------|------|-------------------------|------|
|                           | n                            | %    | n                       | %    |
| General Symptoms          | 193                          | 80   | 27                      | 58.7 |
| Fever                     | 115                          | 41.1 | 3                       | 6.5  |
| Lethargy                  | 83                           | 29.6 | 22                      | 47.8 |
| Anorexia                  | -                            | -    | 7                       | 15.2 |
| Respiratory Symptoms      | 228                          | 94.6 | 16                      | 34.8 |
| Cough                     | 106                          | 37.9 | 14                      | 30.4 |
| Dyspnea                   | -                            | -    | 6                       | 13   |
| Sore throat               | 122                          | 43.6 | -                       | -    |
| Neurological Symptoms     | 85                           | 35.2 | 15                      | 32.6 |
| Headache                  | 75                           | 26.8 | 6                       | 13   |
| Tinnitus                  | -                            | -    | 2                       | 4.3  |
| Anosmia                   | 8                            | 2.9  | 2                       | 4.3  |
| Ageusia                   | 2                            | 0.7  | 3                       | 6.5  |
| Dizziness                 | -                            | -    | 5                       | 10.9 |
| Difficulty concentrating  | -                            | -    | 1                       | 2.2  |
| Memory difficulties       | -                            | -    | 1                       | 2.2  |
| Gastrointestinal Symptoms | 16                           | 5.7  | 11                      | 23.9 |
| Vomiting                  | 3                            | 1.3  | 3                       | 6.5  |

|                                |    |      |    |      |
|--------------------------------|----|------|----|------|
| Diarrhea                       | 7  | 2.9  | 7  | 15.2 |
| Abdominal pain                 | 6  | 2.5  | 5  | 10.9 |
| <b>Cardiovascular Symptoms</b> | -  | -    | 10 | 21.7 |
| Chest tightness                | -  | -    | 9  | 19.6 |
| Chest pain                     | -  | -    | 1  | 2.2  |
| Palpitation                    | -  | -    | 4  | 8.7  |
| <b>Psychiatric Symptoms</b>    | -  | -    | 12 | 26.1 |
| Sleep disorder                 | -  | -    | 11 | 23.9 |
| Anxiety                        | -  | -    | 4  | 8.7  |
| <b>General Symptoms</b>        |    |      |    |      |
| Arthralgia/Myalgia             | 90 | 32.1 | 5  | 10.9 |

**Table 3:** Predictors of self-reported Long COVID symptoms at four weeks follow-up.

| Variables                                     |                                                  | Univariate logistic regression |         |            | Multivariate logistic regression |         |             |
|-----------------------------------------------|--------------------------------------------------|--------------------------------|---------|------------|----------------------------------|---------|-------------|
|                                               |                                                  | Crude Odds Ratio               | p-value | 95% IC     | Adjusted Odds Ratio              | p-value | 95% IC      |
| Female Gender                                 |                                                  | 2.20                           | 0.017   | 1.14-4.20  | 2.02                             | 0.050   | 1.000-4.061 |
| Age >60 years                                 |                                                  | 0.80                           | 0.604   | 0.348-1.8  | 0.58                             | 0.265   | 0.218-1.520 |
| Comorbidities (at least one comorbid disease) |                                                  | 2.54                           | 0.005   | 1.32-4.89  | 2.11                             | 0.105   | 0.852-5.221 |
| Comorbidities                                 |                                                  |                                |         |            |                                  |         |             |
| No comorbidities                              |                                                  | 1                              |         |            |                                  |         |             |
|                                               | Diabetes                                         | 2.17                           | 0.139   | 0.78-6.05  | 2.60                             | 0.133   | 0.746-9.064 |
|                                               | Hypertension                                     | 1.01                           | 0.984   | 0.39-2.61  | 0.41                             | 0.135   | 0.129-1.317 |
|                                               | Cardiovascular diseases (excluding hypertension) | 2.60                           | 0.101   | 0.83-8.17  |                                  |         |             |
|                                               | Chronic pulmonary disease                        | 4.57                           | <0.001  | 1.89-11.02 | 3.02                             | 0.042   | 1.041-8.746 |
|                                               | Malignity                                        | 1.48                           | 0.640   | 0.29-7.56  |                                  |         |             |
|                                               | Immunosuppression                                | 0.48                           | 0.487   | 0.06-3.86  |                                  |         |             |
| Obesity: BMI >30                              |                                                  | 1.51                           | 0.436   | 0.54-4.25  |                                  |         |             |
| History of COVID-19 infection                 |                                                  | 0.88                           | 0.759   | 0.40-1.96  |                                  |         |             |
| Sars-Cov2 vaccinated                          |                                                  | 0.56                           | 0.344   | 0.17-1.87  |                                  |         |             |
| Tobacco use                                   |                                                  | 0.92                           | 0.851   | 0.41-2.09  |                                  |         |             |
| Disease severity                              |                                                  |                                |         |            |                                  |         |             |
|                                               | Mild                                             | 1                              |         |            |                                  |         |             |
|                                               | Moderate                                         | 3.37                           | 0.121   | 0.73-15.60 |                                  |         |             |

To determine the predictive factors associated with long covid in our series, we performed a univariate analysis that demonstrated that female sex (2.19,  $p=0.017$  [1.14-4.20]) and the presence of comorbidities (2.544,  $p=0.05$  [1.32-4.89]), particularly chronic pulmonary disease (4.56,  $p<0.001$  [1.895-11.018]), were associated with a high risk of persistence of symptoms after the acute phase of the disease.

The multivariate regression study, involving several factors, concluded that female sex and people with chronic pulmonary disease were independent risk factors for developing long Covid in this Moroccan cohort (Table 3).

## Discussion

The long-term effects of the documented coronaviruses relate to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [12]. However, in the context of the recent epidemic of the SARS-CoV-2 virus, long-term effects of the

disease have been recognized as a public health issue and a cause of concern for the general population. Although several studies have reported on this condition, many questions remain unanswered.

This study addresses the problem of long Covid, not only in hospitalized patients, but also in young patients and patients with a mild form of the disease.

Our main finding was that symptoms persisted four weeks after infection in 16% of individuals. This result is consistent with findings reported in the literature for non-hospitalised individuals, which vary between 10 and 30% [13].

The most common symptom in our study was asthenia, affecting 47.8% of patients. This finding is consistent with a recent meta-analysis by Alkodaymi, et al. [14], which included 257,348 patients with at least 12 weeks of follow-up. In that meta-analysis, asthenia was the most prevalent symptom at all time points, even more than a year after contracting SARS-CoV-2. Prevalence rates were 32%, 36%, 37%

and 41% at 3, 6, 9 and 12 months, respectively. Other notable findings were respiratory distress in 34.8% of our patients and gastrointestinal distress in 23.9%.

The persistence of these multiple symptoms is consistent with that reported in a recent meta-analysis of 15 studies involving 47,910 patients. This analysis documented 50 long-term symptoms of post-viral infection, with the most frequent being asthenia (58%), headaches (44%), attention deficit (27%), hair loss (25%), and dyspnoea (24%) [15].

Unexpectedly, most of these studies found an association between ageing and the persistence of symptoms of COVID-19 [16,17], our study did not reveal any statistically significant differences related to age when the 18-60 age group was used as the reference point (OR = 0.802, CI = [0.348, 1.8],  $p = 0.604$ ). This could be due to selection bias, meaning that only certain healthy elderly patients participated in the study, or it could be due to other unidentified factors.

Female sex was associated with a high prevalence of long covid at an OR of 2.54 (CI = [1.322-4.893],  $p = 0.05$ ). This finding has been documented in multiple studies [18,19] concluding that women have a higher risk of developing long COVID compared to men.

Our study showed that the presence of at least one comorbidity was associated with long Covid. This finding is similar to that of an earlier study by Blomberg et al., in which a higher frequency of persistent symptoms was reported in hospitalised patients, and asthma was found to be linked to an increased risk of developing long-term symptoms [20]. Similarly, another study in South Africa involving 845 patients identified hypertension, dyslipidaemia and type II diabetes as comorbidities that play a significant role in the development of long Covid [21].

In the literature, smoking, being overweight or obese, and vaccination were identified as risk factors for developing long Covid [22], which could not be proven in our study. This finding agrees with that of Blomberg, et al. [20], which can be explained by the limited number of patients included in both studies.

In summary, our results are consistent with those reported in previous studies, which support the idea that long-term symptoms are more likely to persist if they have at least one chronic disease.

In summary, our results are consistent with those in the literature, which reinforce the relationship between the persistence of long Covid symptoms and the presence of at least one chronic disease.

While this study provides valuable insights into the clinical presentation and risk factors influencing Long-Covid in a developing country such as Morocco, it does have some limitations. The population studied was mostly healthcare workers who did not present with severe forms of the disease, and all symptoms of this condition are subjective and not confirmed by any objective test.

## Conclusion

Owing to its frequency and severity, long Covid is increasingly posing a public health problem. Therefore, systematic, consensus-based monitoring of patients with long-term effects of the virus is necessary to improve the diagnostic, prognostic and therapeutic evaluation of this new condition.

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