

# Characteristics of a Case Series of Long Covid-19 In General Medicine from March 15, 2020, to October 31, 2022, In Toledo, Spain

Jose Luis Turabian

*Specialist in Family and Community Medicine, Health Center Santa Maria de Benquerencia. Regional Health Service of Castilla la Mancha (SESCAM), Toledo, Spain.*

**\*Corresponding Author:** Jose Luis Turabian, Specialist in Family and Community Medicine, Health Center Santa Maria de Benquerencia. Regional Health Service of Castilla la Mancha (SESCAM), Toledo, Spain.

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## Abstract

Previous epidemiological studies of Long covid-19 have been difficult to interpret given the variety and heterogeneity of methods used, differences in the selection of patient populations and response rates, different follow-up periods and inconsistent terms used to describe symptoms.

To study in general medicine clinical-epidemiological characteristics of patients with Long covid-19 (presence of prolonged symptoms for at least 12 weeks, lasting at least 2 months, after acute covid-19 infection, and that are not explained by an alternative diagnosis).

An observational, longitudinal, and prospective case series study of patients with Long covid-19, based on a prospective cohort of covid-19 patients in a family medicine office in Toledo (Spain) was carried out from March 15, 2020, to October 31, 2022.

During the study period, 27 cases of Long covid-19 were included. The mean age was 48 years, 26% were  $\geq 65$  years, and 4%  $\leq 18$  years; 48% were women; 11% ethnic minority; 30% presented moderate-severe severity of primary infection (pneumonia) and hospitalization in acute phase; 56% had chronic diseases, being more frequent the Nervous and Senses group (20%), Endocrine (17), and Digestive system (14%); 52% presented acute infection during 2021; Only 4% were not vaccinated with any dose. Regarding Long covid-19 symptoms, 27% were respiratory [4 chronic coughs, 7 dyspnea, 1 chest pain], 20% were ENT [5 rhinitis, 2 chronic sore throats, 1 epistaxis, 1 anosmia/ageusia], and 18% were Neurological [5 headaches, 1 dizziness, 2 paresthesias in lower limbs]

In the context of general medicine in Toledo (Spain), patients with Long covid-19 were predominantly middle-aged, had been admitted to the hospital for moderate-severe severity of primary infection, were vaccinated, and had preferably respiratory symptoms. It is estimated that 50% of the cohort had been infected with alpha or delta variants.

**Keywords:** COVID-19; SARS-CoV-2; Long-COVID-19 condition; General Practice; Epidemiology; Case Series

## Introduction

Coronavirus disease (COVID-19) is a highly contagious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its spread was declared a pandemic by the World Health Organization (WHO) in March of 2020 [1]. The clinical symptoms of the disease among covid-19 patients are very different. Covid-19 is a devastating disease that has infected millions of

people since the beginning of 2020, through its multisystemic manifestations that vary widely in severity [2].

Although some people are asymptomatic, common symptoms in the acute phase are generally similar to other viral respiratory illnesses, and include cough, fever, dyspnea, musculoskeletal symptoms (myalgia, joint pain, fatigue), gastrointestinal symptoms, and anosmia/dysgeusia [3-8].

Long covid-19 (post-covid-19 syndrome) was first introduced in early 2020 as part of the evaluation of long-term and persistent symptoms of covid-19 (9). Immediately after the development of the first cases of covid-19, scientists observed that patients had symptoms that lasted for several weeks after acute infection [10].

It has now become apparent that many covid-19 patients may have persistent symptoms even after the acute infection has been treated. These symptoms may be specific to covid-19 or secondary symptoms related to hospitalization. The symptoms of Long covid-19 are both physical and psychological symptoms [11,12]. Symptoms may last for weeks and represent late convalescence or may persist or recur in the post-acute phase and interrupt work activities and quality of life for affected individuals [13-18].

More than two years later from the start of the pandemic there is no consensus on the name, duration or symptoms of this syndrome, alternatively known as "post-acute covid-19", "post-covid syndrome" or "prolonged/long covid" [19,20]. The National Institute for Health and Care Excellence provided a useful outline for definitions of covid-19 [21]:

1. Acute covid-19: signs and symptoms of covid-19:  $\leq 4$  weeks
2. Ongoing symptomatic covid-19: signs and symptoms of covid-19: 4-12 weeks
3. post-covid-19 syndrome or Long covid-19: signs and symptoms that develop during or after covid-19, lasting  $> 12$  weeks and not explained by another diagnosis

Thus, Long covid-19 can be described as a set of persistent physical, cognitive, and/or psychological symptoms that continue for more than 12 weeks after the illness and that are not explained by an alternative diagnosis [22, 23].

In some studies, Long covid-19 complaints and symptoms are self-reported, diverse and nonspecific, and sometimes of unknown severity and functional relevance. In this way, previous epidemiological studies of Long covid-19 have been challenging, with results difficult to interpret given the variety and heterogeneity of the methods used, including differences in the selection of patient populations and response rates, different periods of follow-up, and inconsistent terms used to describe symptoms and adverse health conditions. In addition, any symptom has often been included in interviews and questionnaires, regardless of whether it existed before covid-19 [13].

Consequently, it is important to address the Long covid-19 in practice and research, as quickly as possible, and share findings in a manner that promotes universal awareness of Long covid-19 as a global health crisis [24].

In this context, we present an observational, longitudinal and prospective case series study of patients with Long covid-19, which was carried out from March 15, 2020 to October 31, 2022, in a general medicine office in Toledo (Spain), with the objective of describing the clinical-epidemiological characteristics of the cases of Long covid-19 in the general population  $\geq 14$  years attended in that consultation.

## Material And Methods

### Design and location

An observational, longitudinal, and prospective case series study of patients with Long covid-19 was carried out from March 15, 2020, to October 31, 2022, in a family medicine office in the Health Center Santa Maria de Benquerencia, Toledo (Spain), which has a list of 2,000 patients  $> 14$  years of age (in Spain, the general practitioners [GPs] care for people  $> 14$  years of age, except for exceptions requested by the child's family and accepted by the GP).

### Objective

To describe the clinical-epidemiological characteristics of the cases of Long covid-19 in the general population  $\geq 14$  years attended in a general medicine consultation.

### Inclusion criteria

Basically, Long-covid-19 was diagnosed by the presence of prolonged symptoms for at least 12 weeks, lasting at least 2 months, after acute covid-19 infection that is not explained by an alternative diagnosis (25). The World Health Organization (WHO) defines Long-covid-19 as a post covid-19 condition that occurs among persons with probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, that lasts for at least 2 months and cannot be explained by an alternative diagnosis (24, 26, 27). Criteria inclusions were:

1. Patient with confirmed SARS-Co-2 infection or with high clinical suspicion in the case of patients in the 1st wave (where out-of-hospital diagnostic tests were not performed).
2. Presence of one or more symptoms or signs as more frequent in Long covid-19 (Asthenia, Headache, Arthralgia, Dyspnea, Insomnia, Myalgia, Chest pain, "Brain fog", Rashes, Tachycardia, Anosmia/Dysgeusia, Dysthermia, Cough,

Depression, Erratic pain, Muscle pain, fatigue, anorexia and mood swings), and others associated with acute SARS-Co-2 infection, which persist for more than 12 weeks, and for which there is no alternative explanation. Symptoms may be new onset following recovery from acute COVID-19, or persist from the initial illness. Symptoms can also fluctuate or relapse and remit over time; they may be chronically maintained or progress to complete recovery in subsequent months.

### Exclusion criteria

1.-Patients with specific sequelae of acute infection were not included:

A) Pathologies that are not part of the acute infection, persistent, that appear during the covid-19 infection

B) Pathologies that are not part of the acute infection, persistent, with appearance after the resolution of the initial symptoms (covid-19 post-infection pathologies)

C) Pathologies that are not part of the acute infection but appear as a consequence of the organic damage caused by the severe infection (true sequelae of covid-19).

2. The symptom or symptoms were already present before the infection. This would be a previous pathology aggravated or reactivated by covid-19.

3. The symptom or symptoms were not present in the initial picture; they appear after the resolution of the initial picture; Post-infection COVID-19 symptoms or pathologies.

### Diagnosis of covid-19

The diagnosis was performed with oropharyngeal swab tests for reverse transcriptase polymerase chain reaction (PCR) or antigen testing. Spain had not initially devised an intensive testing strategy for suspected cases of COVID-19 infections (29); since the beginning of the pandemic in mid-March 2020, PCR tests were only performed in the hospital context until mid-May 2020, when they began to be performed in general medicine as well. In mid-December 2020, rapid antigen tests began for symptomatic patients with less than 5 days of evolution. The PCR tests were performed both in symptomatic patients and in asymptomatic contacts. Asymptomatic confirmed case with active infection was considered to be any person with a clinical picture of sudden onset acute respiratory infection of any severity that occurs, among others, with fever, cough or feeling of shortness of breath. Other symptoms such as odynophagia, anosmia, ageusia, muscle pain, diarrhea, chest pain or headache, among others, were also considered symptoms of suspected SARS-CoV-2 infection according to

clinical criteria; and a positive PCR or rapid antigen test positive [30].

### Collected variables

The following variables were collected: age; sex; symptoms; chronic diseases (defined as "any alteration or deviation from normal that has one or more of the following characteristics: is permanent, leaves residual impairment, is caused by a non-reversible pathological alteration, requires special training of the patient for rehabilitation, and / or can be expected to require a long period of control, observation or treatment" [31], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [32], social-occupancy class (according to the Registrar General's classification of occupations and social status code) [33]; If they were Health Care Workers; complex family based on the genogram (It was understood that "complex" genogram identified families with psychosocial problems) [34,35], ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group") [36]; disease severity (classified according to: 1. mild cases: clinical symptoms are mild and no manifestation of pneumonia can be found on images; 2. moderate cases: with symptoms such as fever and respiratory tract symptoms and the manifestation of pneumonia can be seen on the imaging tests; and 3. severe cases: respiratory distress, respiratory rate  $\geq$  30 breaths / min., pulse oxygen saturation  $\leq$  93% with room air at rest, arterial partial pressure of oxygen / oxygen concentration  $\leq$  300 mmHg.) (37); to simplify comparison, moderate and severe cases were counted together; date of acute covid-19 diagnosis; vaccination status against covid-19 at the date of acute infection; and recovery at the study end date.

### Sample

All patients who met the criteria for Long covid-19 from March 15, 2020 to October 31, 2022 and who were treated in the general medicine consultation object of the study, were included.

### Results

During the study period, from March 15, 2020, to October 31, 2022, 27 cases of Long covid-19 were included. The mean age was 48.29+17.98 years, 26% were  $\geq$  65 years and 4%  $\leq$  18 years; 48% were women; 11% ethnic minority; 30% presented moderate-severe severity of primary infection (pneumonia) and hospitalization in the acute phase; 56% had chronic diseases, being more frequent the Nervous and Senses group (20%), Endocrine (17),

and Digestive system (14%); 52% presented acute infection during 2021; Only 4% were not vaccinated with any dose. Regarding Long covid-19 symptoms, 27% were respiratory [4 chronic cough, 7 dyspnea, 1 chest pain], 20% ENT [5 rhinitis, 2 chronic sore throat,

1 epistaxis, 1 anosmia/ageusia], and 18% Neurological [5 headaches, 1 dizziness, 2 paresthesias in the lower limbs] (TABLE 1, TABLE 2, TABLE 3).

TABLE 1: VARIABLES OF LONG COVID-19

VARIABLES	LONG COVID 19N=27
Age in years (Arithmetic mean + - Standard deviation; Range)	48.29+-17.98
> = 65 years	7 (26)
< 45 years	11 (41)
< 18 years	1 (4)
Women	13 (48)
Social-occupancy class of patients (people with some type of labor specialization)	4 (15)
Health Care Workers	1 (4)
Ethnic minority	3 (11)
Complex family	1 (4)
Moderate-severe severity of primary infection	7 (30) [pneumonia]
Hospitalization in the acute phase	7 (30)
Readmission after hospital discharge	3 (11)
Chronic diseases presence	15 (56)
Vaccinated covid-19-1 dose	6 (22)
Vaccinated covid-19- 2 doses	12 (44)
Vaccinated covid-19 with booster (3 doses)	8 (30)
not vaccinated	1 (4)
Recovery at the end date of the study	4 (15)
Covid-19 date in 2020	4 (15)
Covid-19 date in 2021	14 (52)
Covid-19 date in 2022	9 (33)

(): Denotes percentages

TABLE 2: Chronic Diseases in Long Covid-19

CHRONIC DISEASES *	LONG COVID-19N=27
-I Infectious	0
-II Neoplasms	0
-III Diseases of the blood	2 (3)
-IV Endocrine	11 (17)
-V Mental	8 (12)
-VI-VIII Nervous and Senses	13 (20)
-IX Circulatory system	6 (9)
-X Respiratory system	2 (3)
-XI Digestive system	9 (13)
-XII Diseases of the skin	2 (3)
-XIII Musculoskeletal	7 (11)
-XIV Genitourinary	6 (9)
TOTAL, chronic diseases*	66 (100)

(): Denotes percentages; \*Patients could have more than one chronic disease. The percentages of chronic diseases are over the total of chronic diseases of symptomatic and asymptomatic patients

**TABLE 3:** Symptoms in Long Covid-19

<b>SYMPTOMS*</b>	<b>LONG COVID-19N=27</b>
<b>General</b>	6 (14) [2 asthenia, 4 arthralgia, 1 malaise]
<b>Respiratory</b>	12 (27) [4 chronic cough, 7 dyspnea, 1 chest pain]
<b>ENT</b>	9 (20) [5 rhinitis, 2 chronic odynophagia, 1 epistaxis, 1 anosmia/ageusia]
<b>Digestive</b>	2 (5) [1 fecal incontinence, 1 anorexia]
<b>Neurological</b>	8 (18) [5 headaches, 1 dizziness, 2 paresthesias in lower limbs]
<b>Psychiatric</b>	4 (9) [3 anxiety/depression, 1 insomnia]
<b>Circulatory system</b>	2 (5) (peripheral venous [inufficiency, tachycardia on exertion])
<b>Genitourinary</b>	2 (2) [dysuria]
<b>Skin</b>	0
<b>Total, symptoms*</b>	44 (100)

( ): Denotes percentages; \* Patients could have more than one symptom. The percentages are over the total of symptoms

## Discussion

### Main findings

In our study, during the year and a half of the study period, we found that the Long covid-19 cases were predominantly middle-aged, with moderate-severe severity acute infection, preferentially presented respiratory symptoms, especially dyspnea, and it was estimated that 50% of the cohort had been infected with alpha or delta variants.

### Comparison with other studies

One of the problems with Long covid-19 is that it's more difficult to measure than other indicators of covid-19, like hospitalizations or deaths, and there's an absence of biomarkers, there's no imaging test, mechanism, or treatment, and the pathophysiology of many post-acute symptoms remains unresolved [13, 38-42]. Thus, the diagnostic criteria for Long covid-19 are controversial. We use the WHO definition [26].

The prevalence of Long covid-19 symptoms has varied widely between studies also because any symptom has often been included in interviews and questionnaires, regardless of whether it already existed before covid-19 or was considered severe and functionally relevant [13]. The symptoms of Long-covid-19 are very varied. Covid-19 can lead to a wide range of clinical manifestations, ranging from asymptomatic infection to acute respiratory distress syndrome and multi-organ failure with high mortality rates [20, 29, 30, 43].

Persistent symptoms appear to be more likely after severe illness than after non-severe illness, and people treated in the intensive care unit reported the most pronounced symptoms during the convalescent period. Specific symptoms may include extreme tiredness, shortness of breath, chest pain, memory problems, heart palpitations, dizziness, joint pain, cough, loss of taste or smell (or both), myalgia, and gastrointestinal disorders [22, 23]. A review article

found that the prevalence of Long covid-19 symptoms among hospitalized patients was twice that of outpatients [44]. We found results consistent with these data, with 30% of Long covid-19 cases presenting moderate-severe severity of primary infection (pneumonia) and being hospitalized.

What causes the prolonged symptoms of covid-19 and why some people experience them is still being further investigated. However, there are a number of causes suggested in existing studies, including virus dose and host dependency or host resistance [45]. For example, it has been postulated that low-grade muscle damage and inflammation, neuropathy, myopathy after covid-19, and immobility due to disease severity can cause fatigue [45-46]. In addition, pneumonia caused by covid-19 in the acute phase is suggested as another triggering factor for respiratory symptoms and others in Long covid-19 [47].

It has been established that SARS-CoV-2 not only infects the respiratory tract but that subsequent viral replication and immune response also affect multiple organ systems. Throughout the pandemic, numerous variants of SARS-CoV-2 have been described those present genetic differences with the original sequence of the virus [48]. Depending on the variant of the virus, the greater or lesser presence of respiratory pathology has been described. People infected with delta are at risk of developing severe lung disease, infection with omicron often causes milder symptoms, especially in vaccinated people [49].

In Spain, in the period from March to April 2020, the A strain of the coronavirus predominated, especially SEC7 and SEC8, and from summer to December 2020, the 20E (EU1) variant. In the January 2021 period, the alpha variant predominated, and from the summer-autumn of 2021 a very significant increase in the delta variant and a significant decrease in the

alpha variant. In November 2021 there was an almost total hegemony of the circulation of the delta variant with high population vaccination coverage [50-53]. Thus, we estimate that 50% of our study cohort had been infected with alpha or delta variants. There is no data on whether omicron causes Long covid-19. The available findings apply to a pandemic that has changed dramatically. Recent studies on the Long covid-19 incidence with the omicron variant show that, compared to the delta variant, the incidence is lower, between 25 and 50% less [40-42].

Different studies have reported, with some differences, that Fatigue, shortness of breath, and cognitive dysfunction are among the most common symptoms [13-17]. However, clinical presentations are variable. In fact, more than 100 symptoms have been documented; at least a quarter of affected patients report symptoms, including pain, that impact their activities of daily living. In addition, symptoms may be new onset, following recovery from acute covid-19, or persist from the initial illness. Symptoms can also fluctuate or relapse and remit over time [24]. Regarding self-reported symptoms by patients with Long covid-19, these include fatigue, musculoskeletal disorders, sleep problems, headache, cognitive problems, sore throat, lethargy, vertigo, and palpitations after four weeks from onset of the disease [54]. Other authors have reported that the three most common symptoms are intolerance to stress, weakness and fatigue. In addition, symptoms of dyspnea, cardiological symptoms, and dizziness are also common. Symptoms such as hair loss, tinnitus, changes in the sense of taste and smell, skin changes, and sleep disturbances are rarer [55].

Taken together, fatigue and shortness of breath are the predominant symptoms, and the most common symptom reported among prolonged covid cases is "chronic fatigue" [56]. In a systematic review and meta-analysis that analyzed the reported results of 52 studies with a sample size of 127,117 that evaluated the occurrence of chronic fatigue syndrome among patients with covid-19 four weeks after symptom onset, through April 2022, the combined prevalence of chronic fatigue syndrome was 45% [57]. Furthermore, in an international online survey, 78% of covid-19 patients reported chronic fatigue syndrome 7 months after illness onset [58]. However, we found dyspnea as the most frequent symptom (26%; 7/27).

It has been argued that neurological repercussions persistently affect one third of patients [59]. In our study 18% of patients presented neurological symptoms. Regarding cardiac repercussions, it has

been reported that covid-19 causes DNA damage in the heart, affecting the body in a completely different way than influenza does [60,61]. Thus, among other symptoms, postural orthostatic tachycardia syndrome (with palpitations, shortness of breath and weakness) has been identified as a common problem that could affect 1 in 10 patients with persistent symptoms, especially in young people and female [62]. We found 5% of Circulatory system symptoms.

Most symptoms were more common among women than men and Long covid-19 syndrome also affected younger people [13,45]. This women frequency may be due to hormones causing the acute inflammatory phase to continue even after the infection has been treated [11]. It has also been suggested that it may be due to the higher level of IgG antibodies, which helps improve symptoms, but if the presence of this high-level antibody in the body continues, it will cause physical manifestations [63,64]. It is also argued that many women work in health systems, leading to increased contact with covid-19 patients [63]. In our study there were only 4% of socio-sanitary workers, and on the other hand, we found a very similar gender distribution: 48% women; 52% men.

Regarding Long covid-19 and vaccination, at the beginning of 2022, eight studies analyzed in the United Kingdom had established that two doses of a vaccine against Covid-19 reduced the risk of Long Covid-19 by up to 50%; But its biggest limitation is that they still did not collect data on the omicron variant. A large case-control study, with around 13 million people, has shown the effectiveness of vaccination in reducing the symptoms of Long Covid-19 by only 15%, although other observational studies place the effectiveness at 33% [40-42]. In our series, only one case did not have any dose of vaccine. However, the implementation of the vaccination program in Spain, which began in 2021 and was extended sequentially by age groups, makes it difficult to assess its effect in our study [65].

Finally, it has been assessed that taking into account symptoms with at least moderate impairment of daily life,  $\leq 80\%$  recovered general health or work capacity [13]. In our series, 15% of cases were free of symptoms at the end of the study.

### Limitations and strengths of the study

A. Case series studies are studies of "numerators" only. No control group or controlled assignments of patients is involved.

B. The lineages of the infections were not sequenced. Therefore, it cannot be completely ruled out of the causal variant of the acute phase.

- C. The number of cases was relatively small.
- D. Asymptomatic cases of covid-19 in the acute phase may have been missed.
- E. The study has the strength of its longitudinality, characteristic of work in general medicine.

### Conclusions

In the context of general medicine in Toledo (Spain), patients with Long covid-19 were predominantly middle-aged, had been admitted to hospital for moderate-severe severity of primary infection, had previous chronic diseases, were vaccinated, and they had preferably respiratory symptoms. It is estimated that 50% of the cohort had been infected with alpha or delta variants. People living with Long covid-19 showed a complex and multifaceted condition. The relatively small number of cases included (despite the long follow-up time, and the fact that the cases correspond to the unselected general population, with a diagnosis based on recognized criteria) makes many research questions remain.

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