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Research Article

Long Covid-19 Clinical and Epidemiological Characteristics Variation from 2022 to 2025 in a General Medicine Clinic in Toledo, Spain

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Abstract

Background

Five years after the start of the COVID-19 pandemic, the evolution of the clinical-epidemiological characteristics of Long COVID-19 is unknown.

Objective

To analyze the variation in the clinical-epidemiological characteristics of patients with Long COVID-19 in 2025 compared to those in 2022.

Methodology

Comparison of data among two cross-sectional descriptive studies: patients with Long COVID-19 (symptoms prolonged beyond 12 weeks) on October 31, 2022, versus patients with Long COVID-19 on May 31, 2025, in the same population in general medicine in Toledo (Spain).

Results

27 cases of Long COVID-19 on October 31, 2022, and 3 on May 31, 2025 were included. When comparing Long COVID-19 in May 2025 vs. In October 2022, the only statistically significant differences were in the presence of more cases in middle age (> 45 and < 65 years), with complex families, more chronic musculoskeletal diseases, and fewer vaccinated with 1, 2, or 3 doses. There were no statistically significant differences in symptoms, although in 2025 there were more general symptoms and fewer respiratory and ENT symptoms.

Conclusion

Current cases of Long COVID-19 did not clearly differ in clinical variables from those of 2022, although general symptoms predominated over respiratory and ENT symptoms. Current versus 2022 Long COVID-19 occur in middle-aged people with social problems, chronic musculoskeletal diseases, and fewer vaccinated with 1, 2, or 3 doses.

Key words: COVID-19; SARS-CoV-2; Post-COVID-19 condition; General Practice; Epidemiology

Introduction

It has been five years since coronavirus disease 2019 (COVID-19) spread rapidly across the globe, causing the largest public health crisis of the 21st century (1 , 2). While the acute and severe damage caused by the SARS-CoV-2 COVID-19 virus was eventually controlled with vaccines, public health measures, and surveillance systems, the long-term effects of the infection are still not fully understood (1).

Beyond the acute phase of COVID-19 symptoms, a wide spectrum of persistent or new-onset symptoms has been observed after recovery from the initial infection, termed Long COVID-19. This condition presents with a complex array of symptoms,

including fatigue, cognitive and psychiatric difficulties, dyspnea, myalgia, and other persistent manifestations, totaling more than 200 reported symptoms (2 , 3). Long-term COVID-19 is a debilitating and persistent illness that affects people in multiple and dynamic ways, resulting in significant physical, emotional, and economic impacts on individuals, their families, and society at large (4).

Although the risk of developing long-term COVID-19 has been reported to have decreased significantly since the start of the pandemic (5, 6), the initial virus infection caused quite severe cardiorespiratory or primarily respiratory symptoms in the acute phase, along with other symptoms such as mental confusion. The alpha variant was associated with an increased risk of muscle pain, insomnia, mental confusion, and anxiety/depression. When the alpha variant was dominant, the prevalence of myalgia, dyspnea, mental confusion, and anxiety/depression increased significantly relative to the original variant, while anosmia, dysgeusia, and hearing impairment were less common. Runny nose had become more common during the delta wave. The Omicron subvariants BA.1 and BA.2 primarily cause upper respiratory symptoms, fever, myalgia, fatigue, sneezing, sore throat, and cough. The BA.4 and BA.5 subvariants are more likely to cause sore throat and hoarseness of voice; night sweats and insomnia are also symptoms that have emerged more frequently in the recent BA.5 era. Skin involvement during the Omicron wave was less common than during the Delta wave. More neurological and psychiatric disorders have been observed with the Delta variant than with the Alpha variant, and the Omicron variant was associated with similar neurological and psychiatric risks. Neurological symptoms after acute COVID-19 appear to be a fairly predominant feature in patients with the older variants: the wild-type variant, the Alpha variant, and the Delta variant (7).

After 2020, the risk of post-COVID symptoms may have decreased with the availability of anti-SARS-Cov-2 vaccines and evolved with the emergence of new SARS-Cov-2 variants. This risk likely also varied depending on the timing of the subject's initial acute COVID episode, even before the spread of variants or the availability of anti-SARS-Cov-2 vaccines. Evidence of temporal changes in the risk of post-COVID-19 symptoms could therefore provide insight into the possible underlying mechanisms of these symptoms, as it would suggest that their persistence may depend on the context of the acute COVID-19 episode. These changes could also partly explain the heterogeneous estimates of the risk of post-COVID-19 symptoms across studies conducted in diverse temporal settings (8).

Por lo tanto, it must be borne in mind that the symptoms of covid-19 have changed throughout the pandemic. Different variants could also generate different symptoms of Long covid-19. In addition, the implementation of vaccination has changed the intensity of symptoms. That is, the new variants could show changing clinical pictures, not only with respect to the severity and symptoms of the acute disease, but possibly also with respect to the sequelae (9).

However, it is unknown whether there has been any variation in the clinical-epidemiological presentation of Long COVID-19 during this period, from the pre-Delta to the Omicron eras, and in populations with high vaccination rates.

The primary care physician is the patient's first point of contact with the healthcare system and provides curative, rehabilitative, and palliative services throughout the patient's lifespan. Therefore, general practitioners (GPs) can provide tailored and targeted interventions to people recovering from COVID-19. However, data from general practice are scarce, and only a few studies have been conducted using self-reported data from unselected cohorts, estimating the prevalence and predisposition for Long COVID-19 in real-world settings (10).

In this context, we present a work based on the comparison of two transversal studies, to try to clarify the clinical-epidemiological differences between Long COVID-19 (presence of prolonged symptoms for at least 12 weeks) in 2022 and 2025, in a population of a general medicine outpatient clinic.

Material and Methods

Design and Emplacement

Comparison of data between two cross-sectional descriptive studies: 1) patients with long-term COVID-19 as of October 31,2022, previously published (11). 2) patients with long-term COVID-19 as of May 31, 2025.

Both studies were carried out in the same population of patients treated in a general 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 analyze the variation in the clinical and epidemiological characteristics of patients with long-term COVID-19 in 2025 compared to those in 2022.

Criteria of Long-covid-19

The diagnostic criteria for Long covid-19 have already been published (11). 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 are not explained by an alternative diagnosis).

Collected variables

The definitions of the variables collected have been previously published (11), but are repeated here for better understanding of the present study.The following variables were collected:

-Age and sex.

-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" (12), classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 (13)

-Social-occupancy class of patients (according to the Registrar General's classification of occupations and social status code) (14, 15).

-Socio-Health Care Workers

-Problems in the family context based on the genogram (genogram is a schematic model of the structure and processes of a family, which included the family structure, life cycle and family relational patterns. It was understood that "complex" genograms present families with psychosocial problems) (16, 17)

-Ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group") (18)

-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 ≥ 30 breaths / min., pulse oxygen saturation ≤ 93% with room air at rest, arterial partial pressure of oxygen / oxygen concentration ≤ 300 mmHg.) (19); to simplify comparison, moderate and severe cases were counted together

-Hospitalization in acute phase and readmission after hospital discharge

-Covid-19 Reinfection (defined as a documented infection occurring at least 90 days after a previous infection) (20-22)

-Vaccination status against covid-19 at the date of reinfection: vaccinated with 2 doses of vaccine (23), vaccinated with first booster for fall-winter 2021 (24), vaccinated with fourth dose (second booster) for fall-winter 2022 (25), and vaccinated with fifth dose (third booster) for fall-winter 2023 (26, 27). In our study, only Pizfer / BioNTech, Spikevax (mRNA-1273- Moderna), Vaxzevria, Oxford / AstraZeneca and Janssen (Johnson & Johnson) vaccines were used for the first and second doses. For the first booster, only messenger RNA (mRNA) was used. And

only Moderna and Pfizer-BioNTech's bivalent covid-19 vaccines were used for the second booster. The vaccines adapted to omicron XBB.1.5 Pfizer / BioNTech and Spikevax (Moderna) were used for the third booster in autumn-winter 2023-2024.

Statistic analysis

The bivariate comparisons were performed using the Chi Square test (X2) with Yates correction or Fisher Exact Test when necessary (according to the number the expected cell totals).

Ethical issues

No personal data of the patients were used, but only group results, which were taken from the clinical record

Results

27 cases of Long COVID-19 in October 31, 2022, and 3 in May 31, 2025 were included. Long COVID-19 in May 2025 vs. in October 2022 were only statistically significantly different because there was more cases in middle age (> 45 and < 65 years), more with complex families, more chronic musculoskeletal diseases, and fewer vaccinated with 1, 2, or 3 doses. There were no statistically significant differences in symptoms, although more general symptoms and fewer respiratory and ENT symptoms were found in Long COVID-19 in May 2025.

Table 1: Comparison of Selected Variables of Long Covid-19 in October 2022 and May 2025

VARIABLES	LONG COVID-19 IN OCTOBER 2022 N=27	LONG COVID-19 IN MAY 2025 N=3	STATISTICAL SIGNIFICANCE
TOTAL	27 (100)	3(100) [62, 54, 61]	
>= 65 years	7 (26)	0	Fisher exact test=1. NS
>45 and <65 years	9 (33)	3(100)	Fisher exact test=0.0542. NS
= <45 years	11 (41)	0	Fisher exact test=0.2793. NS
<18 years	1 (4)	0	Fisher exact test=1. NS
Women	13 (48)	3(100)	Fisher exact test=0.2276. NS
Men	14 (52)	0	Fisher exact test=0.2276. NS
Social-occupancy class of patients (people with some type of labor specialization)	4 (15)	1	Fisher exact test statistic value is 0.5249. NS
Socio-Health Care Workers	1 (4)	1	Fisher exact test statistic value is 0.1931.NS
Ethnic minority	3 (11)	0	Fisher exact test=1. NS
Complex family	1 (4)	2 (67)	Fisher exact test=0.0202. Significant at p <.05.
Moderate-severe severity of primary infection	7 (26) [pneumonias]	0	Fisher exact test=1. NS
Hospitalization in acute phase	7 (26)	0	Fisher exact test=1. NS
Readmission after hospital discharge	3 (11)	0	Fisher exact test=1. NS
Chronic diseases	15 (56)	3(100)	Fisher exact test=0.2552. NS
Vaccinated with 1, 2 or 3 doses	26 (96)	1 (33)	Fisher exact test=0.0202. Significant at p <.05.
not vaccinated	1 (4)	0	Fisher exact test=1. NS
Covid-19 date in 2020	4 (15)	0	Fisher exact test=1. NS
Covid-19 date in 2021	14 (52)	1	Fisher exact test=1. NS
Covid-19 date in 2022	9 (33)	2 (100)	Fisher exact test=0.5367. NS
Covid-19 date in 2025	-	0	-
Covid-19 Reinfection	0	1 (33)	Fisher exact test=0.1. NS

( ): Denotes percentages; NS: Not significant at p< .05.

Table 2: Comparison of Chronic Diseases De Long Covid-19 in October 2022 and May 2025

CHRONIC DISEASES*	LONG COVID-19 IN OCTOBER 2022 N=27	LONG COVID-19 IN MAY 2025 N=3	STATISTICAL SIGNIFICANCE
-I Infectious	0	1 (6) [recurrent herpes simplex]	Fisher exact test=0.2143. NS
-II Neoplasms	0	0	Fisher exact test=1. NS
-III Diseases of the blood	2 (3)	0	Fisher exact test=1. NS
-IV Endocrine	11 (17)	0	Fisher exact test=0.11. NS
-V Mental	8 (12)	1 (6) [dysthymia]	Fisher exact test=0.6763. NS
-VI-VIII Nervous and Senses	13 (20)	3 (17) [Hearing loss, Arnold's occipital headache, vascular tension headache]	X2with Yates correction= 0.0023. *p*-value=.961422.
-IX Circulatory system	6 (9)	0	Fisher exact test=0.333.NS
-X Respiratory system	2 (3)	1 (6) [Allergic rhinitis]	Fisher exact test= 0.5198. NS
-XI Digestive system	9 (13)	1 (6) [Dyspepsia]	Fisher exact test=0.6817. NS
-XII Diseases of the skin	2 (3)	0	Fisher exact test=1. NS
-XIII Musculo-skeletal	7 (11)	7(39) [Rheumatoid arthritis on immunosuppressive treatment, osteoarthritis (2), cervical arthrodesis, chondromalacia (2), painful shoulder]	X2with Yates correction=6.2364. *p*-value= .012515. Significant at $p < .05$.
-XIV Genitourinary	6 (9)	4 (22) [Ovarian cyst, myoma, metrorrhagia, hysterectomy with oophorectomy]	Fisher exact test=0.2103. NS
TOTAL chronic diseases*	66 (100)	18(100)	---

*( ): Denotes percentages; *Patients could have more than one chronic disease. The percentages of chronic diseases are over the total of chronic diseases; NS: Not significant at p< .05.*

Table 3: Comparison of Symptoms De Long Covid-19 in October 2022 and May 2025

SYMPTOMS**	LONG COVID-19 INOCTOBER 2022 N=27	LONG COVID-19 IN MAY 2025 N=3	STATISTICAL SIGNIFICANCE
General	6 (14) [2 asthenia, 4 arthralgia, 1 malaise]	3 (23) [Her body feels strange, she's lost about 6 kg of weight, asthenia]	X2 with Yates correction is 0.15. *p*-value is .698541.NS
Respiratory	12 (27) [4 chronic cough, 7 dyspnea, 1 chest pain]	2 (15)[Dyspnea, cough]	X2 with Yates correction is 0.2583. *p*-value is .61131.NS
ENT	9 (20) [5 rhinitis, 2 chronic odynophagia, 1 epistaxis, 1 anosmia/ ageusia]	1 (8)[Ageusia]	Fisher exact test=0.4261 NS
Digestive	2 (4) [1 fecal incontinence, 1 anorexia]	0	Fisher exact test=1. NS
Neurological	8 (18) [5 headaches, 1 dizziness, 2 paresthesias in lower limbs]	2 (15) [paresthesia of the tongue and pharynx, headache]	Fisher exact test=1. NS
Psychiatric	4 (9) [3 anxiety/depression, 1 insomnia]	2 (15)[anxiety]	Fisher exact test statistic value is 0.6109.NS

Circulatory system	2 (4) [peripheral venous inufficiency, tachycardia on exertion]	1 (8) [hypotensión]	Fisher exact test statistic value is 0.5474.NS
Genitourinary	2 (4) [dysuria]	1 (8) [Metrorrhagia]	Fisher exact test statistic value is 0.5474.NS
Skin	0	1 (8) [Alopecia]	Fisher exact test statistic value is 0.2281. NS
Total symptoms**	44 (100)	13(100)	

*( ): Denotes percentages; ** Patients could have more than one symptom. The percentages are over the total of symptoms; NS: Not significant at p< .05.*

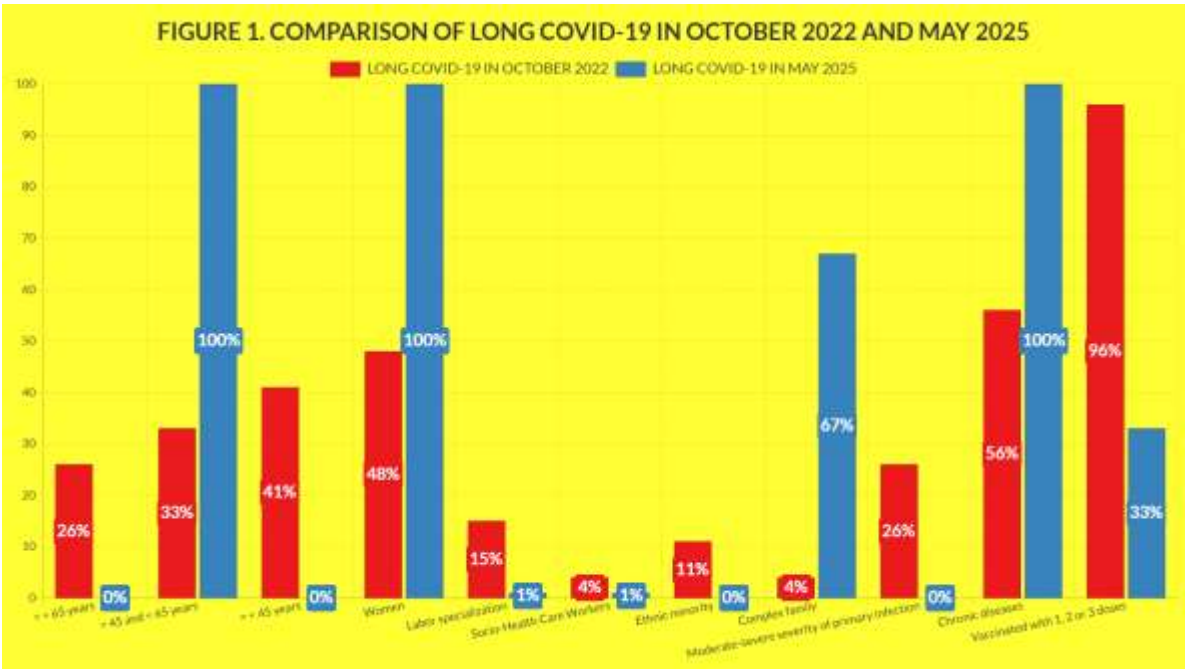

Figure1. Comparison of Long Covid-19 in October 2022 and May 2025

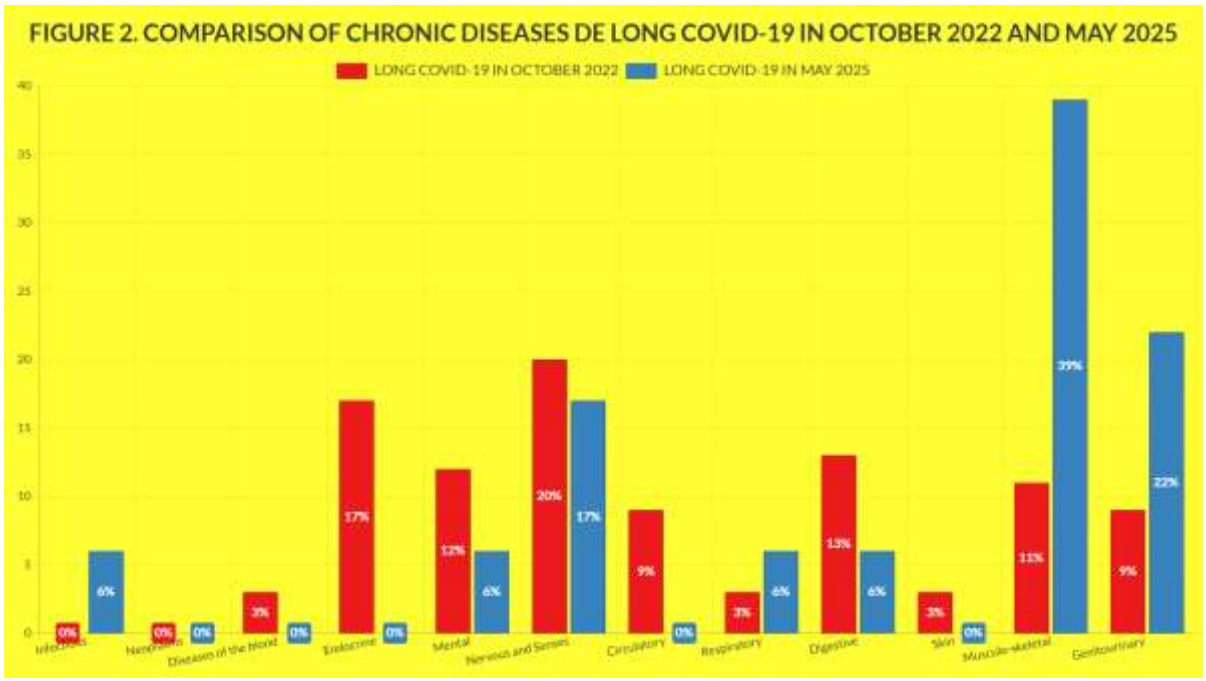

Figure2. Comparison of Chronic Diseases De Long Covid-19 in October 2022 and May 2025

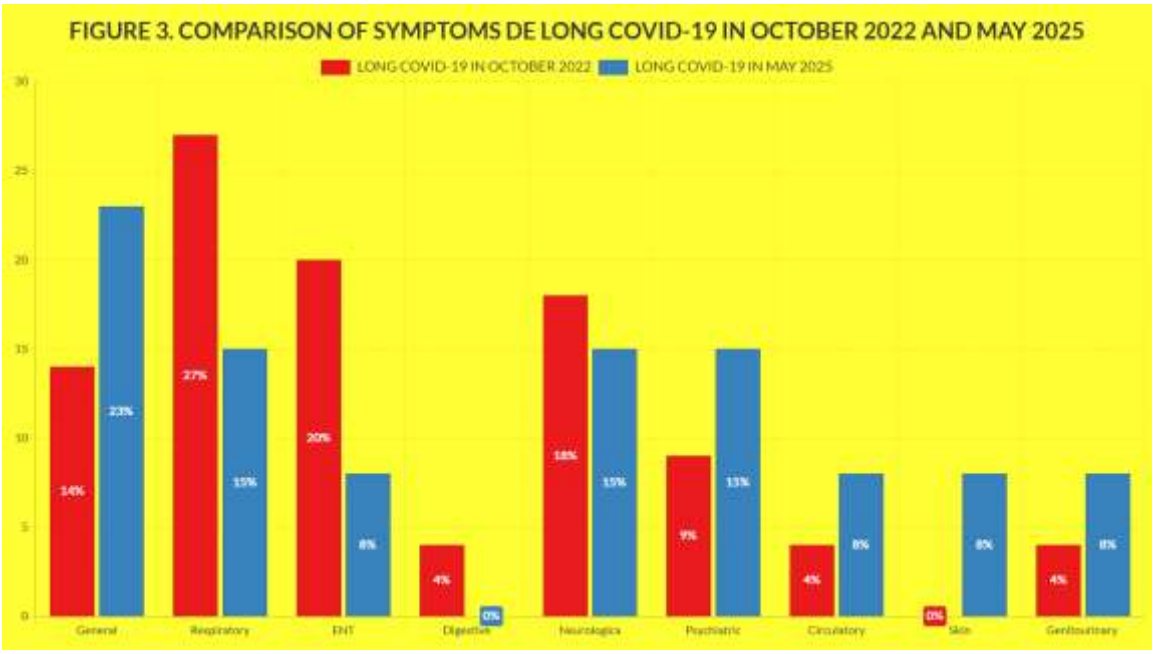

Figure3. Comparison of Symptoms De Long Covid-19 in October 2022 and May 2025

Discussion

1. Main Findings

Our main results in 2025 vs. 2022 were:

1. The only statistically significant differences were in having more cases in middle age (> 45 and < 65 years), more with complex families, more chronic musculoskeletal diseases, and fewer vaccinated with 1, 2, or 3 doses.

2. There were no statistically significant differences in symptoms, although more general symptoms and fewer respiratory and ENT symptoms were found in Long COVID-19 in May 2025.

Since 2020 SARS-CoV variants spectrum covers alpha, beta, gamma, delta and omicron. In Spain, the Alpha variant was dominant during 2020. By June 2021, only sporadic cases and outbreaks in various communities of the beta and gamma variants were detected in Spain. In Aug. 2021, the Delta variant accounted for 90% of total cases in Spain. In May 2022, the Omicron variant was the dominant one in Spain after having displaced the Delta variant. The omicron variant was the dominant one in Spain November, 2022. The predominant variants in Spain during 2023 were those of the XBB family. In January 2024 in Spain, XBB.1.5-like + F456L accounted for 42% and BA.2.86 for 44% of positive cases. In July and August 2024, the KP.3 lineage was detected in 84% of cases. In September 2024, the incidence of the XEC variant, a new Omicron subvariant was increasing markedly in Spain. At that time, it was the second most common strain in cases recorded in September, although still far behind the main KP.3.3, with an incidence of 13% (28, 29).

On the other hand, in Spain, in November 2022, more than 60% of people over 80 years of age, and 37% of people over 60 years of age, already had the second booster dose of the COVID-19 vaccine (30, 31). And 60% of the population over 80 years of age has already received the vaccine adapted against the COVID-19 subvariants of the 2023/2024 campaign (32).

In any case, the results must be evaluated with caution. In Spain, since April 28, 2022 there was a new "Surveillance and Control Strategy Against COVID-19" that included the non-performance of diagnostic tests, which were focused only on those over 60 years of age (33). This means that positive cases have been counted with tests carried out in health services and with tests carried out at home and later reported to the GP. Thus, there is probably an underreporting.

2. Comparison with Other Studies

From a clinical perspective, Long COVID-19 is not a homogeneous disease. It

must be considered a multisystem syndrome, making its differentiation from other conditions very difficult. The clinical picture is as markedly heterogeneous and multisystemic as in the acute phase. Furthermore, its onset is not related to the severity of the initial infection, so it can affect both mild, even asymptomatic, patients and severely ill patients who have required hospitalization. Although it can affect people of any age, it is more common in middle-aged women (34).

Although coordinated efforts seek to refine the definitions of Long COVID-19, due to the novelty and diversity of its manifestations, various terms and definitions have been proposed, although none have gained widespread acceptance and support from patients, physicians, researchers, or government agencies (35).

Despite advances in helping clinicians recognize symptoms associated with Long COVID-19, no standard diagnostic tests have been identified (36). Since the disease is undetectable by biological tests, there is a pressing need to develop and evaluate biomarkers (e.g., blood tests) to diagnose and monitor Long COVID-19 (37). Many studies assess Long COVID-19 symptoms through self-report/questionnaires, and self-reported results do not necessarily match clinical reports, but despite these complexities and variability, asthenia (22%), dyspnea (15%), insomnia (13%), and arthralgia/myalgia (11%) were the most common symptoms estimated by a systematic review that included 120 studies of the general population (38). Another study showed that the most persistent symptom in the post-acute phase was fatigue (10). Another systematic review showed that asthenia, insomnia, and dyspnea are the most prevalent symptoms of Long COVID-19 among both hospitalized, non-hospitalized, and mixed cohorts (39). Similarly, asthenia, myalgia, cough, and dyspnea were also the most frequent general symptoms (persistent or new) after the first episode of COVID-19 in another study (34).

Similarly, in another study of 679 healthcare workers in India, the most common symptom was asthenia (11.5%), followed by insomnia (8.5%), dyspnea on exertion (6%), and arthralgia (5%) (40). A meta-analysis of studies reported an overall prevalence of asthenia during the acute phase of COVID-19 of 23% (41). A review of the epidemiological and clinical aspects of the disease published in 2023 reported common symptoms including fatigue, dyspnea, chest pain, cough, depression, anxiety, post-traumatic stress disorder, memory loss, and difficulty concentrating (42). A 2023 population-based cross-sectional study in Iran found that prevalent manifestations included fatigue, upper respiratory tract symptoms such as sinonasal complaints and altered sense of smell or taste, concerns about sexual well-being, gastrointestinal disturbances, and musculoskeletal symptoms (2). A prospective cohort study focused on non-hospitalized individuals (healthcare personnel) aged 18–59 years, diagnosed with COVID-19, and collecting data between December 2022 and August 2023, in Beijing, China, following Omicron infection, found that patients with Long COVID-19 were predominantly female and had comorbidities. The most prevalent persistent symptoms were cough (46%), fatigue (38%), and dyspnea (34%). The authors note that this implies that, regardless of virus mutation or hospitalization status, chronic fatigue and shortness of breath persist as significant detriments affecting individuals' quality of life. They further note that their findings also suggest a correlation between Long COVID-19 and osteoarthritis, implying potential musculoskeletal involvement. This knowledge could help formulate rehabilitation strategies for managing post-COVID-19 fatigue (43).

Women aged 41 to 60 years constituted the largest proportion of subjects in our post-acute COVID-19 group. This is consistent with a cross-sectional study (10). The hypothetical explanation given by researchers for the majority of patients being women is that immune-mediated diseases are much more common in them. It is also related to hormones, as symptoms have been shown to vary during different ovulation phases (44).

In a systematic review of Long COVID-19 using a secondary analysis of data collected from anti-coronavirus therapy trials in a considerable number of

countries around the world (Argentina, Brazil, Canada, Colombia, Ecuador, Egypt, India, Nepal, Pakistan, the Philippines, Russia, Saudi Arabia, South Africa, and the United Arab Emirates), the most frequently reported symptoms were sleep disturbances (13%), joint pain (10%), fatigue (9%), and headaches (8%) (45).

The rate of Long COVID-19 in the most deprived quintile of the UK population (3.2%) is more than double that in the least deprived quintile (1.5%) (37). Some socioeconomic or environmental factors, such as deprivation, isolation, or air pollution exposure, were also recently documented as risk factors for post-COVID symptoms. In addition, there is inconsistent evidence on the role of ethnicity in the risk of post-COVID symptoms (8).

In summary, our study shows that from 2022 to 2025, cases of Long COVID-19 varied, becoming more frequent in middle-aged people (>45 and <65 years), women, with complex families, with more chronic musculoskeletal diseases, and fewer vaccinated with 1, 2, or 3 doses. There were no statistically significant differences in symptoms, although more general symptoms and fewer respiratory and ENT symptoms were found in Long COVID-19 patients in May 2025.

Limitations and Strengths of the Study

1. The population and investigator were the same in both studies, which could allow for reliable results that couldbe generalized to similar populations.

2. The number of cases was small, which may hide differences between the groups.

3. There is likely underreporting of Long COVID-19, especially in the 2025 cross-sectional study, as neither diagnostic testing was systematically performed for acute cases nor screening for asymptomatic patients.

4. Our study did not include a control group (comparing symptom frequency with uninfected populations).

Conclusions

In the context of general medicine in Toledo (Spain), the clinical-epidemiological characteristics of Long covid-19 from 2022 to 2025 varied in the sense of affecting the disease more frequently in middle-aged people (> 45 and < 65 years), women, with complex families, with more chronic musculoskeletal diseases, and less vaccinated with 1, 2 or 3 doses. There were no statistically significant differences in symptoms, although more general symptoms and fewer respiratory and ENT symptoms were found in Long COVID-19 patients in May 2025.

These results suggest that there has been a change in our context and currently in Long COVID-19 versus 2022, with general symptoms (rather than respiratory and ENT symptoms) affecting middle-aged individuals (> 45 and < 65 years; rather than older and younger individuals), women, those with complex families (indicating social problems), more chronic musculoskeletal diseases (osteoarthritis and arthritis on immunosuppressive therapy), and fewer vaccinated individuals with 1, 2, or 3 doses.

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