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# Risk factors and incidence rate of long covid-19. A longitudinal study in general medicine from March 15, 2020 to October 31, 2022, in Toledo, Spain

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***Abstract***

***Background:*** *Long covid-19 is a recognizable health problem, but its precise clinical-epidemiological contours remain the subject of debate.*

***Objectives:*** *To estimate the incidence rate and the risk and protective factors of Long covid-19 in general practitioner consultation.*

***Methodology:*** *An observational, longitudinal and prospective study of patients with Long covid-19 in a general practice setting in Toledo, Spain, from March 15, 2020 to October 31, 2022.*

***Results:*** *687 positive cases of acute covid-19 were diagnosed in the general medicine consultation under study. Of these, 27 cases (48% were women and 26% were >=65 years old) evolved into Long covid-19, which represents a gross incidence rate of 4%. The incidence rate of Long covid-19 in the general practitioner consultation with respect to the total population attended in that consultation (N= 2,000) from March 15, 2020 to October 31, 2022 was 1.35%. The only statistically significant risk factors for Long covid-19 were having presented moderate-severe severity of primary infection (RR= 4.67 (95% CI: 2.08, 10.5); Strong risk; Fisher exact test= 0.0007) and present chronic diseases of the Nervous and Senses groups (RR= 1.89 (1.04, 3.44); Moderate risk; X2= 5.2542. p= .021894).*

***Conclusion:*** *The incidence rate of Long covid-19 is moderately high (4% of acute covid-19 cases and 1.35% of the general population) and having presented moderate-severe severity of primary infection is the main risk factor for developing it, and to a lesser degree the comorbidity of the Nervous and Senses groups. Although incidence figure found can be considered moderate, it is higher than the prevalence of other important chronic diseases in community. This knowledge should alert the general practitioner to manage comorbidities and risk factors in acute covid-19, and can serve to outline future health policy strategies.*

**Keywords:** COVID-19; SARS-CoV-2; Long-COVID; Long-term complications after COVID-19; General Practice; Longitudinal Studies; Risk Factors

## Introduction

Global deaths due to coronavirus disease 2019 (covid-19) are decreasing globally, however, during the week of November 4 to 10, 2022, when this text is written, there were more than 2.1 million in the world of new cases reported, a falsely low figure due to the absence of tests and underreporting of positives [1].

People who have had the virus that causes covid-19 infection (SARS-CoV-2) and experience symptoms that continue beyond the acute phase have been referred as "Long covid-19." The World Health Organization estimates that 10% of covid-19 survivors, including hospitalized and non-hospitalized individuals, have persistent problems 12 weeks after infection [2]. In addition, the risk of suffering from Long covid-19 or of being reinfected again and thus accumulating more risks for the long-term effects of SARS-CoV-2 infection remains [3].

Since the beginning of the covid-19 pandemic, scientific interest has focused on acute disease, but little by little the concern for Long covid-19 is emerging [4]. The global burden of Long covid-19 has highlighted the long-neglected mystery of post-viral syndromes. After recovery from acute covid-19, a substantial proportion of patients continue to experience symptoms of a physical, psychological, or cognitive nature [5]. Long covid-19 is not just a problem for public health. The Long covid-19 will entail a great economic cost due to the number of people who see or will see their ability to work limited [6.] In this way, it is so critical to understanding and treating Long covid-19 [7-9].

However, Long covid-19 has been difficult to study, among other things because the variety of symptoms makes it difficult to define. Long covid-19 is a multisystemic condition with more than 200 reported symptoms in most organ systems, often with a chronic fluctuating pattern of presentation [10]. This is related to the fact that experts do not agree on a name for prolonged symptoms after the acute phase of covid-19: "persistent covid-19", "prolonged covid-19", "post-covid-19 syndrome" or "post-acute sequelae of covid-19" are some of the terms used, and there are no specific symptoms or biomarkers, no imaging tests, no known pathophysiological mechanism, and no effective treatment. In addition, there is evidence that suggests large variations in estimates of the prevalence and incidence of Long covid-19 syndrome due to differences in study populations, recruitment methods, follow-up periods, and sample sizes [11, 12]. However, having good data on Long covid-19 will be crucial to investigate the prevalence, its causes and consequences, and to plan services effectively [13].

In this context, the objectives of this study were: 1. Estimate the incidence rate (IR) of Long covid-19; and 2. Assess the risk and protective factors to present in Long covid-19, all based on the follow-up of a cohort of patients diagnosed with acute covid-19 in a general medicine consultation.

## Material and Methods

### Design and location

An observational, longitudinal and prospective 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). The dependent neighborhood of the Health Center has a population of 20,000 inhabitants. Toledo (one of the provinces of Castilla La Mancha) has a population of 700.000 inhabitants.

## Objectives

1. Estimate the incidence rate (IR) of Long covid-19 in GP consultation. IR was calculated by dividing the number of cases of Long covid-19 by the primoinfections of covid-19 in the follow-up time (from March 15, 2020 to October 31, 2022) (14). Likewise, the data on the incidence of Long covid-19 were extrapolated to the entire population attended in the consultation (N=2,000 people), to the community that depended on the health center where the study was carried out (N= 20,000 people), and to Toledo province (N=700,000 people) [15].

2. Assess the risk and protective factors to present Long covid-19. In this sense, the variables collected were compared by calculating the relative risk (RR) as the incidence of risk factors in those exposed to Long covid-19 / incidence of risk factors in those not exposed to Long covid -19. The RR was interpreted as follows: From 0 to 0.5: protection factor effectively; from 0.6 to 0.8: true benefits; from 0.9 to 1.1: not significant; from 1.2 to 1.6: weak risk; from 1.7 to 2.5: moderate risk; more than 2.5: strong risk [16].

## Inclusion and exclusion criteria

The inclusion and exclusion criteria have been previously published [17]. 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 [4, 18-21].

## Diagnosis of covid-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction (PCR) oropharyngeal swab tests or antigen testing. Spain had not initially devised an intensive testing strategy for suspected cases of COVID-19 infections; 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 [22]. 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. A symptomatic 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 [23].

## Definition of cases and controls

Patients with Long covid-19 were considered "cases." "Control" patients were considered cases of acute covid-19 without Long covid-19. Control data were obtained from previous studies in the same consultation, with the same population attended, and carried out by the same researcher [24-28].

## Collected variables

The variables collected and their definitions and criteria have been previously published [17]. The following variables were collected: age; sex; chronic diseases; disease; vaccination status against covid-19 at the date of acute infection in the controls and at the study end date in the cases.

## 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) for percentages.

## Results

From March 15, 2020 to October 31, 2022 (31 and a half months, the development time of the entire covid-19 pandemic to date) in the general medicine consultation (N=2,000 people) object of the study, 687 were diagnosed cases of acute covid-19. Of these, 27 evolved to Long covid-19 (48% were women and 26% were >=65 years old), which represents a gross RI of 4%. The RI regarding cases of acute covid-19 for >=65 years was 12%, for =< 45 years 3%, and for both women and men it was 4% (TABLE 1). The IR of Long covid-19 in the GP consultation regarding the total population attended in that consultation (N= 2,000) from

March 15, 2020 to October 31, 2022 was 1.35%; Extrapolating this figure, it would be 270 cases/20,000 people (population treated at the health center under study), 1,350/100,000 people, and in Toledo province (Spain) it would be 9,450/700,000 people.

**Table 1: Incidence Rates of Long Covid-19 In General Medicine (Toledo, Spain) Regarding Acute Covid-19 Cases from March 15, 2020 to October 31, 2022**

| Variables | Long Covid-19 N=27 | Acute Covid-19 Without Long Covid-19 N= 687 | Incidence Rates Of Long Covid-19 In General Medicine (Toledo, Spain) Regarding Acute Covid-19 Cases From March 15, 2020 To October 31, 2022 |
|---|---|---|---|
| TOTAL | 27 (100) | 687 (100) | 4 % cases x March 15, 2020 to October 31, 2022 |
| > = 65 years | 7 (26) | 60 (9) | 12% cases x March 15, 2020 to October 31, 2022 |
| = < 45 years | 11 (41) | 425 (62) | 3% cases x March 15, 2020 to October 31, 2022 |
| Women | 13 (48) | 332 (48) | 4% cases x March 15, 2020 to October 31, 2022 |
| Men | 14 (52) | 355 (52) | 4% cases x March 15, 2020 to October 31, 2022 |

( ): Denotes percentages

The only statistically significant risk factors for Long covid-19 were having presented moderate-severe severity of primary infection [RR= 4.67 (95% CI: 2.08, 10.5); Strong risk; Fisher exact test= 0.0007. The result is significant at p < .05] and to present chronic diseases of the Nervous and Senses groups [RR= 1.89 (1.04, 3.44); Moderate risk; X2= 5.2542. p= .021894. The result is significant p < .05]. There were more cases of Long covid-19 vaccinated vs. controls, but this comparison is not pertinent, since the vaccination data in controls refers to the date of acute covid-19, and that of Long covid-19 to October 2022 at the end of follow-up (TABLE 2, TABLE 3). 52% of our Long covid-19 cohort had acute infection during 2021. Patients in the acute period of covid-19 were treated, according to clinical needs, with a wide variety of drugs: NSAIDs, analgesics, antitussives, mucolytics, antihistamines, inhaled and systemic corticosteroids, beta2-adrenergic agonists, and antibiotics. No patient was treated with antivirals.

**Table 2: Risk Factors of Long Covid-19**

| Risk Factors | Long Covid-19 N=27 | Acute Covid-19 Without Long Covid-19* N=188 | Statistical Significance | Relative Risk (Ci 95%) |
|---|---|---|---|---|
| > = 65 years | 7 (26) | 32 (17) | X2= 1.2607. p= .261516.NS | RR= 1.58 (0.56, 4.48). Weak risk |
| Women | 13 (48) | 101 (54) | X2= 0.2946. p= .587274. NS | X2= 0.82 (2.57, 0.26). True benefits |
| Health Care Workers | 1 (4) | 31 (16) | X2= with Yates correction= 2.1209. p= .145305. NS | RR= 0.22 (1.68, 0.03). Protection factor effectively |
| Moderate-severe severity of primary infection | 7 (30) [pneumonias] | 8 (pneumoniae) (4) | Fisher exact test= 0.0007. The result is significant at p < .05. | RR= 4.67 (2.08, 10.5). Strong risk |
| Chronic diseases presence | 15 (56) | 108 (57) | X2= 0.0345. p= .852656. NS | RR= 0.54 (1.23, 0.24). Protection factor effectively |
| Vaccinated with 1, 2 or 3 doses | 26 (96) | 88 (88) | NR | |
| not vaccinated | 1 (4) | 100 (53) | NR | |

*Taken from a covid-19 sample in the same general medicine consultation object of the current study, from previous studies (References 24-28); ( ): Denotes percentages; RR: Relative risk; NS: Not significant; NR: Not relevant

**Table 3: Chronic Diseases Risk Factors in Long Covid-19**

| Chronic Diseases | Long Covid-19 N=27 | Acute Covid-19 Without Long Covid-19* N=188 | Statistical Significance | Relative Risk (Ci 95%) |
|---|---|---|---|---|
| -I Infectious | 0 | 0 | Fisher exact test= 1. NS | RR= NaN |
| -II Neoplasms | 0 | 9 (3) | Fisher exact test= 0.3656. NS | RR= 0 (Infinity, 0). Protection factor effectively |
| -III Diseases of the blood | 2 (3) | 5 (1) | Fisher exact test= 0.3141. NS | RR= 1.8 (0.09, 34.53). Moderate risk |
| -IV Endocrine | 11 (17) | 65 (19) | X2= 0.1821. p= .669534. NS | RR= 0.88 (2.4, 0.32). Not significant |
| -V Mental | 8 (12) | 24 (7) | X2= 2.0367. p= .153543. NS | RR= 1.63 (0.72, 3.67). Weak risk |
| -VI-VIII Nervous and Senses | 13 (20) | 34 (10) | X2= 5.2542 . p= .021894. Significant at p < .05. | RR= 1.89 (1.04, 3.44). Moderate risk |
| -IX Circulatory system | 6 (9) | 44 (13) | X2= 0.7079. p= .400144. NS | RR= 0.72 (1.97, 0.26). True benefits |
| -X Respiratory system | 2 (3) | 23 (7) | X2 with Yates correction= 0.7329. p= .391947. NS | RR= 0.48 (2.56, 0.09). Protection factor effectively |
| -XI Digestive system | 9 (13) | 43 (12) | X2= 0.0646. p= .799413. NS | RR= 1.09 (0.04, 31.96). Not significant |
| -XII Diseases of the skin | 2 (3) | 11 (3) | Fisher exact test= 1. NS | RR= 0.9 (2.41, 0.34). Not significant |
| -XIII Musculo-skeletal | 7 (11) | 46 (13) | X2= 0.3764. p= .539533. NS | RR= 0.8 (2.32, 0.28). True benefits |
| -XIV Genitourinary | 6 (9) | 40 (12) | X2= 0.3578. p= .549718. NS | RR= 0.79 (2.58, 0.24). True benefits |
| TOTAL chronic diseases** | 66 (100) | 344 (100) | --- | --- |

## Discussion

### Main findings

The two main results of our study are:

1. Having presented moderate-severe severity of primary infection was the main risk factor for developing Long covid-19, which is consistent with what has been reported by other authors. The incidence of post-Covid-19 symptoms is higher among hospitalized than outpatients and in those who had more severe acute illness [29-35,18,36]. Patients with severe covid-19 pneumonia were more likely to have persistent respiratory abnormalities 10 months after diagnosis than those with moderate disease [37]. Likewise, it has communicated that burden of symptoms was correlated with the severity of the initial infection [30].

2. Gross IR in the GP consultation was moderately high, of 4% of acute covid-19 cases, and 1.35% of the general population. As has been correctly pointed out, with millions of people affected by covid-19, even a small percentage who develop Long-term covid-19 will have a detrimental effect on public health, and many people will need long-term follow-up and care [38]. The different studies on the frequency of Long covid-19 give conflicting results. The reasons are the differences in how the syndrome is defined or diagnosed and the population from which those cases are studied [39, 40]. Our study was carried out in the population seen in a GP consultation. Other studies in this same type of population have described IR of 8.5% of Long covid-19 [32]. Although, it should be noted that it has been suggested that cases of Long covid-19 are not reported in GP records, and a wide variation has been found in reports of Long covid-19 prolonged by GP practice. In addition to issues related to underreporting of diagnoses, there is a strong possibility that physicians are currently underdiagnosing their patients with Long covid-19. This could be because patients do not present to their GP or because doctors do not know the diagnosis [13].

## Comparison with other studies

Contrary to the observed variability in reported disease prevalence/incidence, Long covid-19 risk factors tend to be fairly consistent: female gender, mean age (35 to 65 years), obesity, smoking, asthma, general health poor, poor pre-pandemic mental health, and poor sociodemographic factors (socioeconomic deprivation, ethnicity) [41-44].

Four other factors have been reported that could correlate with an increased risk of having Long covid-19: the level of SARS-

CoV-2 RNA in the blood early in the infection (an indicator of viral load), the presence of certain autoantibodies, reactivation of the Epstein-Barr virus, and having type 2 diabetes [45, 46]. Likewise, it has been published that low levels of IgM and IgG3 before infection can means a higher risk of Long covid-19 [47-49].

A wide range of comorbidities have also been associated with an increased risk of Long covid-19 symptoms, including chronic obstructive pulmonary disease, benign prostatic hyperplasia, fibromyalgia, anxiety, and depression [44]. In our study, the only statistically significant comorbidity detected was the diseases of the Nervous and Senses group.

Data have been published suggesting that the proportion of infected people who develop Long covid-19 is reduced in those who received the vaccine prior to SARS-CoV-2 infection [50, 51]. In our study, there were more patients vaccinated with Long covid-19 than in the control group (without Long covid-19), which could be erroneously interpreted as that vaccination is a risk factor, and non-vaccination a protective factor. But this data cannot be interpreted because they are dynamic figures and not comparable over time (obviously there are more vaccinated as the vaccination campaign progresses). As the vaccination data of the controls refers to the moment of acute covid-19, and that of Long covid-19 refers to the final closing date of the study follow-up time, the comparisons in our study are not relevant.

It has been hypothesized that the frequency of Long covid-19 could be lower in people infected with the omicron variant than in those infected with earlier variants [52]. In our study, 52% of our Long covid-19 cohort presented acute infection during 2021. In the January 2021 period, the alpha variant predominated, and from the summer-autumn of 2021 there was 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. Thus, we estimated that 50% of our study cohort had been infected with alpha or delta variants [17].

Lastly, it is clearly unknown whether acute treatments for covid-19 affect the probability of developing Long covid-19 (5). Nirmatrelvir/rinonavir has been suggested that reduce probability of developing long covid-19 (53). In any case, in our study, no patient was treated with antivirals.

## Study Strengths and Weaknesses

1. Although registries in general practice are key sources for morbidity estimates (especially if all people are registered in a general practice and if the GP is the gatekeeper of health care and diagnoses from medical specialists and other health care providers they are also known by the GP), the results presented probably indicate a “minimal incidence”, and there is the possibility of underestimating the real incidence, since there are many reasons why patients with persistent symptoms may not attend the public health service, such as mild symptoms or private medical care.
2.-The variants of SARS-CoV-2 associated with Long covid-19 were not determined. Therefore, presence of Long covid-19 cannot be accurately associated with virus variety of acute onfection.
3. The number of Long covid-19 cases was relatively small.
4. Asymptomatic cases of covid-19 in the acute phase may have been missed.
5. The study does not include children.
6. The study has the strength of its longitudinality, characteristic of work of the GP.

## Conclusion

In our context of population attended in a GP consultation in Toledo (Spain), from March 15, 2020 to October 31, 2022, the incidence of Long covid-19 was moderately high (4% of acute cases and 1.35% of the general population), and the having presented moderate-severe severity of primary infection is the main risk factor for developing it, and to a lesser degree the comorbidity of the Nervous and Senses groups. It must be taken into account that even a moderately high incidence of 4% of Long covid-19 with respect to large number of patients who have presented acute covid-19, can represent a significant public health problem: Extrapolating this figure, it would be 270 cases/20,000 people (population treated at the health center under study), 1,350/100,000 people, and in Toledo province (Spain) it would be 9,450/700,000 people. This figure is higher than prevalence of many major chronic diseases in community. This knowledge should alert the GP to manage comorbidities and risk factors in acute covid-19, and can serve to outline future health policy strategies.

## References


1. Croft J (2022) World COVID-19 Death Rate Down 90%, WHO Chief Says. Medscape; Nov 09. https://www.medscape.com/viewarticle/983810
2. Mullard A (2021) Long COVID’s long R&D agenda. Nat Rev Drug Discov. https://www.nature.com/articles/d41573-021-00069-9?utm_source=Nature+Briefing&utm_campaign=81889634d4-briefing-dy-20210420&utm_medium=email&utm_term=0_c9dfd39373-81889634d4-42937943
3. Looi M, Mahase E (2022) Has covid-19 become milder? BMJ;379: o2516. https://www.bmj.com/content/379/bmj.o2516
4. Pinto MD, Chakraborty R, Lambert N (2022) The Elephant in the Waiting Room: An Urgent Call for Papers to Address the Public Health Crisis of Long COVID. Clinical Nursing Research; 0(0). 10.1177/10547738221132603
5. Brightling CE, Evans RA (2022) Long COVID: which symptoms can be attributed to SARS-CoV-2 infection? Lancet; 400(10350): 411-3. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)01385-X/fulltext?dgcid=raven_jbs_etoc_email
6. Ho S (2022) Long COVID Could Cost the Economy Trillions, Experts Predict. Medscape; Sep 28. https://www.medscape.com/viewarticle/981583
7. WHO (2021) In the wake of the pandemic: preparing for Long COVID. https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2021/in-the-wake-of-the-pandemic-preparing-for-long-covid-2021

8. Alger HM, Williams IV JH, Walchok JG, Bolles M, Fonarow GC, Rutan C (2020) Role of data registries in the time of COVID-19. Circ Cardiovasc Qual Outcomes; 13: e006766. https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.120.006766
9. Nanda S, Toussaint L, Vincent A, et al. (2021) A Midwest COVID-19 Cohort for the Evaluation of Multimorbidity and Adverse Outcomes from COVID-19. J Prim Care Community Health. https://journals.sagepub.com/doi/10.1177/21501327211010991
10. Brown DA, O'Brien KK (2021) Conceptualising Long COVID as an episodic health conditionBMJ Global Health; 6: e007004. http://dx.doi.org/10.1136/bmjgh-2021-007004
11. Peter RS, Nieters A, KrÃ¤usslich H, et al. (2022) Post-acute sequelae of covid-19 six to 12 months after infection: population based study. BMJ; 379: e071050. https://www.bmj.com/content/379/bmj-2022-071050?utm_source=etoc&utm_medium=email&utm_campaign=tbmj&utm_content=weekly&utm_term=20221014
12. Ayoubkhani D, Khunti K, Nafilyan V, et al. (2021) Epidemiology of post-COVID syndrome following hospitalisation with coronavirus: a retrospective cohort study. BMJ; 372: n693. https://www.bmj.com/content/372/bmj.n693?
13. Wise J (2021) Covid-19: Long covid cases are underreported in GP records, research suggests. BMJ; 374: n1685. https://www.bmj.com/content/374/bmj.n1685?utm_source=etoc&utm_medium=email&utm_campaign=tbmj&utm_content=weekly&utm_term=20210709
14. Nandí-Lozano E, Espinosa LE, Viñas-Flores L, Avila-Figueroa C (2002) [Acute respiratory infection in children who go to a child development center]. Salud Publica Mex; 44:201-6. https://www.scielosp.org/article/spm/2002.v44n3/201-206/es/
15. Cauthen DB (1994) Family practice incidence rates. JABFP; 7: 303-9. https://www.ncbi.nlm.nih.gov/pubmed/7942099
16. Rey Calero J (1989) [Epidemiological method and community health]. Madrid: Interamericana. McGraw-Hill.
17. Turabian JL (2022) Characteristics of a case series of Long covid-19 in general medicine from March 15, 2020 to October 31, 2022, in Toledo, Spain. Journal of Virology and Vaccination. In Press.
18. Greenhalgh T, Sivan M, Delaney B, Evans R, Milne R (2022) Long covid—an update for primary care. BMJ; 378: e072117. https://www.bmj.com/content/378/bmj-2022-072117?utm_source=etoc&utm_medium=email&utm_campaign=tbmj&utm_content=weekly&utm_term=20220930
19. WHO (2021) A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.
20. Frellick (2022) [When is COVID-19 not persistent, but intermediate?]. Medscape; 3 de mayo. https://espanol.medscape.com/verarticulo/5908984
21. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, on behalf of theWHO Clinical Case Definition Working Group on Post-COVID-19 Condition (2021) A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis. https://doi.org/10.1016/S1473-3099(21)00703-9
22. Montenegro P, Brotons C, Serrano J, et al. (2021) Community seroprevalence of COVID-19 in probable and possible cases at primary health care centres in Spain. Family Practice; 38(2): 154–9. https://doi.org/10.1093/fampra/cmaa096
23. Instituto de Salud Carlos III (2020) [Strategy for early detection, surveillance and control of COVID-19. Updated December 18, 2020]. Ministerio de Sanidad. España. https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Estrategia_vigilancia_y_control_e_indicadores.pdf
24. Turabian JL (2022). Covid-19 Breakthrough Infections In Vaccinated People With Vaccine Booster In 2022 Versus Covid-19 Cases In Unvaccinated People In 2020: A New Disease Whose Clinic We Should Know Or Another Cause Of The Old Symptoms Of The Common Cold? J General medicine and Clinical Practice; 5(2). https://www.auctoresonline.org/uploads/articles/1655371786Covid__1_.pdf
25. Turabian JL (2022) Secondary infections in the family from primary cases of covid-19 breakthrough infections in fully vaccinated or not fully vaccinated people. Two doses modestly reduce family transmission but does not eliminate it. Journal of SARS-CoV-2 Research; 2, 12-24. https://doi.org/10.36013/sarc-cov-2.v2i.85
26. Turabian JL (2022) Risk Factors and Incidence Rates of Covid-19 Breakthrough Infections in Vaccinated People in General Medicine Practice in Toledo (Spain). Arch Fam Med Gen Pract; 7(1): 183-92. https://scholars.direct/Articles/family-medicine/afmgp-7-033.pdf?jid=family-medicine
27. Turabian JL (2022). Covid-19 Breakthrough Infections In Vaccinated People With Vaccine Booster In 2022 Versus Covid-19 Cases In Unvaccinated People In 2020: A New Disease Whose Clinic We Should Know Or Another Cause Of The Old Symptoms Of The Common Cold? J General medicine and Clinical Practice; 5(2). https://www.auctoresonline.org/uploads/articles/1655371786Covid__1_.pdf
28. Turabian JL (2022) Incidence Rates and Risk Factors of Covid-19 Reinfections from March 1, 2020 To July 1, 2022 in A General Medicine office in Toledo, Spain. Ann Community Med Prim Health Care; 1(1): 1006. https://meddocsonline.org/annals-of-community-medicine-and-primary-health-care/incidence-rates-and-risk-factors-of-covid-19-reinfections-from-March-1-2020-to-july-1-2022-in-a-general-medicine-office-in-toledo-spain.pdf
29. Xie Y, Xu E, Al-Aly Z (2022) Risks of mental health outcomes in people with covid-19: Cohort study. BMJ; 376: e068993. https://doi.org/10.1136/bmj-2021-068993
30. Cohen K, Ren S, Heath K, et al. (2022) Risk of persistent and new clinical sequelae among adults aged 65 years and older during the post-acute phase of SARS-CoV-2 infection: retrospective cohort study. BMJ; 376: e068414. https://www.bmj.com/content/376/bmj-2021-068414?utm_source=etoc&utm_medium=email&utm_campaign=tbmj&utm_content=weekly&utm_term=20220211
31. Yaksi N, Teker AG, Imre A (2022) Long. COVID in Hospitalized COVID-19 Patients: A Retrospective Cohort Study. Iran J Public Health; 51(1): 88. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8837882/
32. Whittaker HR, Gulea C, Koteci A, et al. (2021) GP con-

sultation rates for sequelae after acute covid-19 in patients managed in the community or hospital in the UK: population based study. BMJ; 375: e065834. https://www.bmj.com/content/375/bmj-2021-065834

33. David J Pinato, Josep Tabernero, Mark Bower, et al. (2021) Prevalence and impact of COVID-19 sequelae on treatment and survival of patients with cancer who recovered from SARS-CoV-2 infection: evidence from the OnCovid retrospective, multicentre registry study. Lancet Oncology. https://doi.org/10.1016/S1470-2045(21)00573-8
34. Anonymous (2022) Long-term neurological sequelae of SARS-CoV-2 infection. Nat Med 28, 2269–2270 (2022). https://doi.org/10.1038/s41591-022-02018-4
35. Xu E, Xie Y, Al-Aly Z (2022) Long-term neurologic outcomes of COVID-19. Nat Med; 28, 2406–15. https://doi.org/10.1038/s41591-022-02001-z
36. Whitaker M, Elliott J, Chadeau-Hyam M, et al. (2022) Persistent COVID-19 symptoms in a community study of 606,434 people in England. Nat Commun; 13(1): 1957. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9005552/
37. Vargas Centanaro G, Calle Rubio M, Álvarez-Sala Walther JL, et al, (2022) Long-term Outcomes and Recovery of Patients who Survived COVID-19: LUNG INJURY COVID-19 Study. Open Forum Infect Dis; 9(4): ofac098. https://doi.org/10.1093/ofid/ofac098
38. Anonymous (2020) Meeting the challenge of long COVID. Nat Med; 26(12):1803. https://pubmed.ncbi.nlm.nih.gov/33288947/
39. Ledford H (2022) How common is long COVID? Why studies give different answers. Nature; 606: 852-3. https://doi.org/10.1038/d41586-022-01702-2
40. Reardon S (2022) Long COVID risk falls only slightly after vaccination, huge study shows. Results suggest that vaccines offer less protection against lingering symptoms than expected. Nature. https://doi.org/10.1038/d41586-022-01453-0
41. Raman B, Bluemke DA, Lüscher TF, Neubauer S (2022) Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. Eur Heart J; 43(11): 1157–72. https://doi.org/10.1093/eurheartj/ehac031
42. Evans RA, McAuley H, Harrison EM, et al. (2022) Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med; 9(11): 1275-87. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8497028/
43. 43.-PHOSP-COVID Collaborative Group (2022) Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. Lancet Respir Med; 10(8): 761-75. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9034855/
44. 44.-Wise J (2022) Long covid: Hair loss and sexual dysfunction are among wider symptoms, study finds. BMJ; 378: o1887. https://www.bmj.com/content/378/bmj.o1887?utm_source=etoc&utm_medium=email&utm_campaign=tbmj&utm_content=weekly&utm_term=20220805
45. Belluck P (2022) New Research Hints at 4 Factors That May Increase Chances of Long Covid. If further study confirms the findings, they could lead to ways to prevent and treat the complex condition. The New York Times; Jan. 25. https://www.nytimes.com/2022/01/25/health/long-covid-risk-factors.html?algo=combo_als_clicks_decay_96_50_ranks&block=5&campaign_id=142&emc=edit_fory_20220128&fellback=false&imp_id=236277209&instance_id=51501&nl=for-you&nlid=16392743&pool=pool%2Ffa8f6616-7b25-42bd-bdbf-7abdec20107e&rank=1&regi_id=16392743&req_id=244367620&segment_id=80946&surface=for-you-email-rotating-health&user_id=c5ce033f231235ecb64f4a6525782d31&variant=0_clicks_decay_96
46. Su Y, Yuan D, Chen DG, et al. (2022) Multiple early factors anticipate post-acute COVID-19 sequelae. Cell; 185(5): 881-95.E20. https://www.cell.com/cell/fulltext/S0092-8674(22)00072-1
47. Cervia C, Zurbuchen Y, Taeschler P, et al. (2022) Immunoglobulin signature predicts risk of post-acute COVID-19 syndrome. Nat Commun; 13: 446. https://doi.org/10.1038/s41467-021-27797-1
48. Sample I (2022) Long Covid: doctors find 'antibody signature' for patients most at risk. Low levels of certain antibodies found to be more common in those who go on to develop long Covid. The Guardian; Tue 25 Jan. https://www.theguardian.com/society/2022/jan/25/doctors-find-antibody-signature-long-covid
49. Mesa N (2022) Studies Identify Risk Factors for Long COVID. Two recent papers provide insight into possible risk factors for developing the chronic condition, including autoantibodies and diabetes. The Scientist: Jan 26. https://www.the-scientist.com/news-opinion/studies-identify-risk-factors-for-long-covid-69648?utm_campaign=TS_DAILY_NEWSLETTER_2022&utm_medium=email&_hsmi=202112998&_hsenc=p2ANqtz--1op-lj4K_cmbd4H-hwRo9cbf547tEYljlABwOfeXrBcVpYAtlVGaCasmJB-M9hG-yuYiovQoz8FZB_cq2Ejkof797jiDw&utm_content=202112998&utm_source=hs_email
50. 50.-Antonelli M, Penfold RS, Merino J, et al. (2022) Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. Lancet Infect Dis; 22(1): 43-55. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8409907/
51. Venkatesan P (2022) Do vaccines protect from long COVID? Lancet Resp Med. https://doi.org/10.1016/S2213-2600(22)00020-0
52. Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ (2022) Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. Lancet; 399(10343): 2263-4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9212672/
53. Topol E (2022) Paxlovid and Long COVID. Medscape; Nov 08. https://www.medscape.com/viewarticle/983718