ISSN: 3029-0716

Research Article

Journal of Infectious Diseases & Treatments

COVID-19 Symptom Changes in A General Medicine Office in Toledo, Spain, 2020-2024. From Multisystemic Disease to Common Cold Like to Flu Like

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Received: October 25, 2024; **Accepted:** November 04, 2024; **Published:** November 09, 2024

ABSTRACT

Background: It is not well known if there have been changes in the clinical characteristics during the evolution of covid-19 from the beginning of the pandemic to the current endemic

Objective: To know the variations the clinical features of cases of covid-19 from 2020 to 2024.

Methodology: Descriptive analysis and comparison of secondary data of cases of covid-19 from previous studies in 2020, 2021, 2022, 2023 and 2024 years, all of them carried out in the same population of patients treated in a general medicine office in Toledo, Spain.

Results: 100 covid-19 cases were included in 2020, 42 in 2021, 46 in 2022, 76 in 2023 and 54 in 2024. These cases from the respective samples differed in a statistically significant way in that they were progressively older and had a tendency to present greater number of chronic diseases in 2024 versus 2020. The statistically significant differences between symptoms were: 1) A tendency to present more General symptoms from 2020 to 2024; 2) A peak of increased frequency of ENT symptoms in 2022; And 3) A progressive trend to present fewer Digestive symptoms from 2020 to 2024.

Conclusion: In the general practice setting in Toledo, Spain, from 2020 to 2024, cases of covid-19 were mild in all years, showed a tendency to go from symptoms of multiple organ systems at the beginning of the pandemic, to a common cold-like syndrome in 2022, to a flu-like syndrome in 2024, and occurred in people progressively older with more chronic diseases.

Keywords: COVID-19, SARS-CoV-2, Epidemiological Characteristic, Symptoms, General Practice, Public Health Practice, Secondary Analysis

Introduction

The epidemiology of the coronavirus disease 2019 (COVID-19) has evolved during the five years since its detection [1]. The causal agent, the severe acute respiratory syndrome coronavirus (SARS-CoV-2), has evolved giving rise to different variants that have been predominant over time, and this has caused different degrees of virulence, pathogenicity, immunogenicity, transmissibility and capacity for immunity exhaust. These changes in the virus, together with the effectiveness of vaccines, treatment medications, diagnostics or other public health measures, and social changes may give rise to clinical aspects different over time from its pandemic beginning to the current endemic evolution [2,3].

When the omicron variant of SARS-CoV-2 began to spread rapidly and outperform other variants in late 2021, it became clear that this variant was quite different from previous ones; It caused less severe disease, but the number of cases broke records largely because a series of mutations in the virus's spike protein make vaccines much less effective at stopping infection than previous variants [4]. On the other hand, currently, high levels of immunity to SARS-CoV-2 are beginning to limit its impact and reach [5]. But, there is increasing scientific evidence that shows that the protection generated by vaccination decreases

Citation: Jose Luis Turabian. COVID-19 Symptom Changes in A General Medicine Office in Toledo, Spain, 2020-2024. From Multisystemic Disease to Common Cold Like to Flu Like. J Infect Dise Treat. 2024. 2(2): 1-7. DOI: doi.org/10.61440/JIDT.2024.v2.18

over time. Although it is reestablished with the inoculation of booster doses [6].

Therefore, it is to be expected that the symptoms of COVID-19 have also changed. However, although this symptom change is accepted, there is really little data and much remains to be clarified. Understanding the variation of symptoms by location and temporality is crucial for clinical practice; It could help speed diagnosis, predict outcomes more accurately, and guide treatment, especially as new variants emerge. Likewise, the fact of being able to reflect this variation in symptoms in public health messages can contribute to prevention. It has been said that future work should focus on symptom profile variation in emerging SARS-CoV-2 virus variants [7].

In this context, we present a study comparing symptoms of COVID-19 cases in 2020, 2021, 2022, 2023 and 2024, using secondary data from the same population attended in a general medicine consultation in these time periods, with the goal of approaching the knowledge of the evolution and change of symptoms.

Material and Methods

Design and Emplacement

This study compares data from previous observational, longitudinal and prospective studies of COVID-19 infections from March, 2020 to October, 2024, already published:

1. A study that included unvaccinated COVID-19 cases in 2020 [8].
2. Two studies of COVID-19 cases in vaccinated people in 2021 [8,9].
3. A case study of COVID-19 breakthrough infections in vaccinated people with vaccine booster in 2022 [10].
4. A study of COVID-19 infections in 2023 [11].
5. And a study of COVID-19 infections in 2024 [12].

All studies were conducted on the same population: patients saw in a general medicine office in Toledo, Spain, which has a list of 2,000 patients > 14 years of age (in Spain, GPs care for people > 14 years of age, except for exceptions). The GPs in Spain work within the National Health System, which is public in nature, and are the gateway for all patients to the system, and each person is assigned a GP [13]. The methodology of all studies has been previously published and here only the main elements will be repeated for the current study [14].

Outcome of Interest

To describe the variations in the clinical characteristics of COVID-19 cases from March, 2020 to October, 2024.

Diagnosis of COVID-19

The diagnosis was performed with reverse transcriptase polymerase chain reaction oropharyngeal swab tests or antigen testing performed in health services or at home [15].

Collected Variables

Variables for which data were available in all previous studies were:

- 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") and symptoms of COVID-19, both classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [16,17].
- If they were Health Care Workers
- 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.) to simplify comparison, moderate and severe cases were counted together [18].

COVID-19 Vaccination and Reinfections in The Study Cases

The vaccination schedule and reinfections were not included in this study (both variables can modify the incidence of cases). On the final data collection date, the included patients could have received 1, 2 doses of vaccine, first booster for fall-winter 2021, fourth dose (second booster) for fall-winter 2022 and fifth dose (third booster) for fall-winter 2023[17]. 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. Las vacunas adaptadas a ómicron XBB.1.5 Pizfer / BioNTech y Spikevax (Moderna) were used for the third booster in autumn-winter 2023. were used for the third booster in autumn-winter 2023.

Statistical Analysis

The bivariate comparisons were performed using the Chi Square test (X2) or test of Kruskal-Wallis. both with degrees freedom= 4. The formula for the degrees of freedom for a chi-square test was (r - 1) x (c - 1), where r is the number of rows and c is the number of columns in the contingency table.

Ethical Issues

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

Results

100 COVID-19 cases were included in 2020, 42 in 2021, 46 in 2022, 76 in 2023 and 54 in 2024. These cases from the respective samples differed in a statistically significant way in that they were progressively older [X2 (df=4) = 12.7967. p= .012313] and had a tendency to present greater number of chronic diseases in 2024 versus 2020 [X2 (df=4) = 19.478. p= .000633]. There were no statistically significant differences by sex, with respect to the presence of socio-health workers or with respect to Moderate-severe severity (Table 1, Figure 1). The statistically significant differences between symptoms were: 1) A tendency

to present more General symptoms (discomfort, asthenia, myalgia, fever, arthralgia) from 2020 to 2024 [X2 (df=4) = 12.5987. p= .013412]; 2) A peak of increased frequency of ENT symptoms (Anosmia/ageusia, odynophagia, dysphonia, rhinorrhea, sneezing, nasal congestion, pharyngeal dryness-mucus, ear pain, epixtasis, facial pain) in 2022 (an increase from 2020 to 2022, and a decrease from 2022 to 2024) [X2 (df=4) = 22.1539. p= .000187]; And 3) A progressive trend to present fewer Digestive symptoms (anorexia, nausea / vomiting, diarrhea, abdominal pain) from 2020 to 2024 [X2 (df=4) = 20.8914. p= .000333] (Table 2, Figure 2).

Table 1: Comparison of Selected Variables Among the Cases of the 5 Included Samples

Variables	COVID-19 Cases in 2020 N=100	COVID-19 Cases in 2020 N=100	COVID-19 Cases in 2021 N=42	COVID-19 Cases in 2022 N=46	COVID-19 Cases in 2023 N=76	COVID-19 Cases in the 2024 N=54	Statistical Significance
> = 65 years	10 (10)	10 (10)	9 (21)	13 (28)	21 (28)	16 (30)	X2 (df=4)= 12.7967. p= .012313. Significant at p < .05.
Women	54 (54)	54 (54)	20 (48)	27 (59)	48 (63)	30 (56)	X2 (df=4)= 3.0736. p= .545593. NS
Socio-health workers	11 (11)	11 (11)	7 (17)	13 (28)	13 (17)	6 (11)	X2 (df=4)= 8.145. p= .08641. NS
Moderate-severe severity	3 (3)	3 (3)	4 (9)	1 (2)	2 (3)	2 (4)	X2 (df=4)= 4.5871. p= .332341. NS
Exitus	1 (1)	1 (1)	0	0	0	0	Test of Kruskal-Wallis (df=4): H= 1.45. p= .835. NS
Chronic diseases presence	51 (51)	51 (51)	22 (53)	35 (76)	48 (63)	44 (81)	X2 (df=4)= 19.478. p=-.000633. Significant at p < .05.

(): Denotes percentages; NS: Not significant; df= Degree's freedom

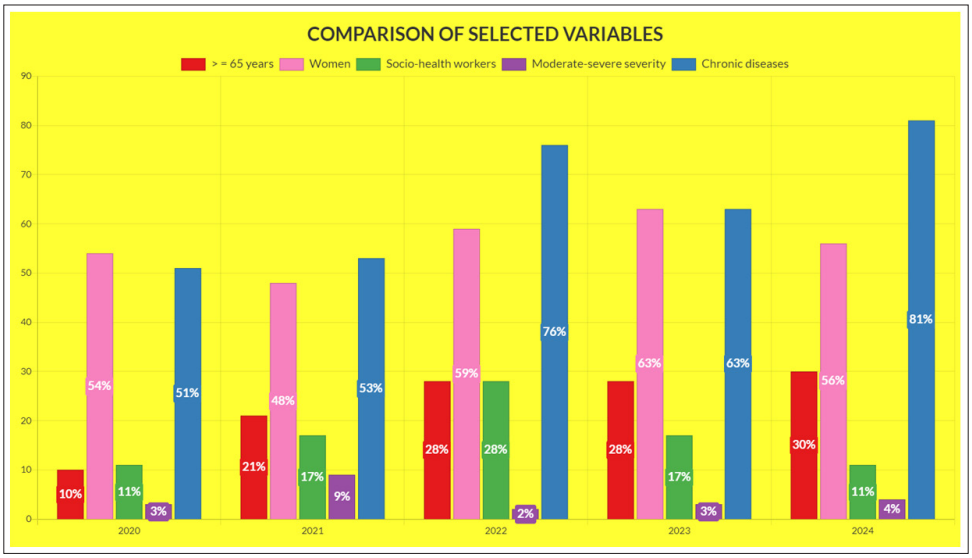

Figure 1

Table 2: Comparison of Symptoms Between COVID-19 Cases From 2020, 2021, 2022, 2023 and 2024

Symptoms COVID-19 Infection* According to who, ICD-10 groups	COVID-19 Cases in 2020 N=100	COVID-19 Cases in 2021 N=42	COVID-19 Cases in 2022 N=46	COVID-19 Cases in 2023 N=76	COVID-19 Cases in 2024 N=54	Statistical Significance
General (discomfort, asthenia, myalgia, fever, artralgias)	24 (31)	28 (29)	34 (31)	95 (38)	79 (47)	X2 (df=4) = 12.5987. p= .013412. Significant at p < .05.
Respiratory (cough, dyspnea, chest pain)	19 (25)	23 (24)	24 (22)	69 (27)	42 (25)	X2 (df=4) = 1.5029. p= .826125. NS
ENT (Anosmia / ageusia, odynophagia, dysphonia, rhinorrhea, sneezing, nasal congestion, pharyngeal dryness-mucus, ear pain, epixtasis, facial pain)	8 (10)	30 (31)	41 (37)	64 (25)	33 (19)	X2 (df=4) = 22.1539. p= .000187. Significant at p < .05.
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	9 (12)	7 (7)	3 (3)	6 (2)	2 (1)	X2 (df=4) = 20.8914. p= .000333. Significant at p < .05.
Neurological (headache, dizziness, photopsia, syncope, mental confusion -brain fog, sleepiness)	7 (9)	9 (9)	8 (7)	14 (6)	11 (6)	X2 (df=4) = 2.1553. p= .707214. NS
Psychiatric (anxiety, insomnia)	8 (10)	0	0	1 (1)	0	Kruskal-Wallis (df=4): H= 0.78. p= .941, NS
Skin (chilblains, flictenas, rash, petechiae)	2 (3)	0	0	0	0	Kruskal-Wallis (df=3): H= 0.29. p= .990. NS
Urological (dysuria, frequency, pollakiuria-urinary incontinence)	0	0	0	2 (1)	1 (1)	Kruskal-Wallis (df=4): H= 2.45. p= .653. NS
Ophthalmologic (conjunctivitis)	0	0	0	0	1 (1)	Kruskal-Wallis (df=4): H= 1.16. p= .884. NS
Total, symptoms*	77 (100)	97 (100)	110 (100)	251 (100)	169 (100)	---

(): Denotes percentages; NS: Not significant; df= Degree's freedom; * Patients could have more than one symptom. The percentages are over the total of symptoms

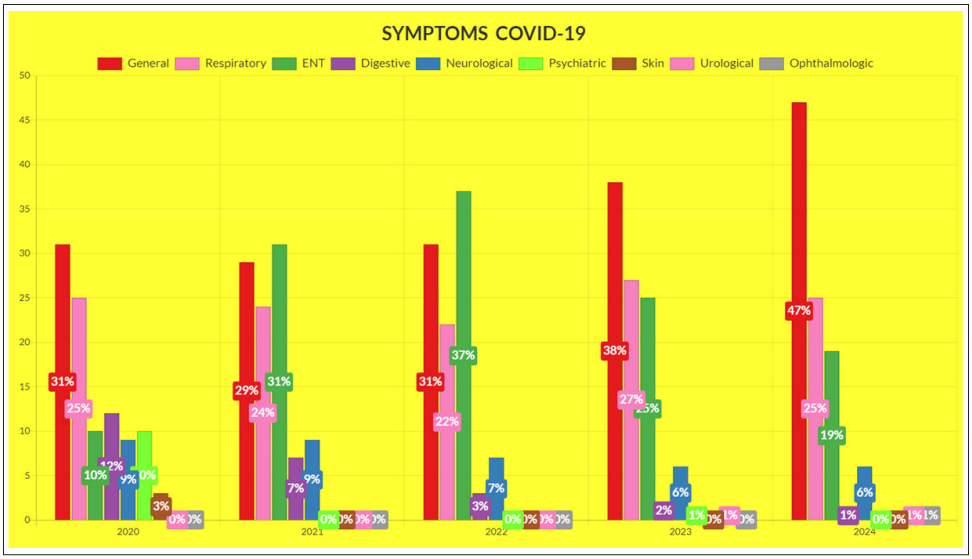

Figure 2

Discussion

Main Findings

The main results of our study are:

1. Most cases were mild in the 5 years studied.
2. An evolution of the clinical presentation of COVID-19 cases is observed, which goes from symptoms of various organic systems at the beginning of the pandemic in 2020, to a syndrome similar to the common cold in 2022, and finally a syndrome more similar to the flu in 2024.
3. There is a progressive trend from 2020 to 2024 that COVID-14 cases occur more frequently in older people and with an increasing number of chronic diseases.

Comparison with Other Studies

It is often said, perhaps too generally, that the most common symptoms of COVID-19 have not changed much since the start of the pandemic and remain the same in the latest dominant variant, JN.1, and include fatigue, sore throat, congestion, runny nose, headache, body aches, and cough [19]. The biggest admitted change is that symptoms are milder; severe cases are much less frequent now than during the early years of the pandemic [19]. However, in our study there was no statistically significant difference in the percentage of moderate-severe cases, with the vast majority being mild.

Looking more deeply into the changes in symptoms, it is admitted that gastrointestinal problems, such as nausea, vomiting, and diarrhea, are currently rarer. As well as, one of the most notable symptoms at the beginning of the pandemic, loss of taste and smell, also seems to be less frequent today [19]. Similarly, dermatological symptoms have tended to disappear at present, and were reported by 11% of people during the wave caused by the omicron variant, compared to 17% in the delta variant wave, where symptoms also tended to last longer [20].

The truth is that the coronavirus and the way people respond to it have changed over time. Symptoms of COVID-19 in 2024 do not look the same as they did before for many people. In this evolution, it may be very difficult to distinguish it from a common cold or even the flu. Some experts indicate that in general, COVID-19 currently tends to look more like a cold, with a sore throat, runny nose, and perhaps fever and aches [21]. Fever could not be the most permanent symptom now; and runny nose, sore throat or dry cough and headache appear as very frequent symptoms in people with the vaccine [22,23].

Since the start of the pandemic, SARS-CoV-2 has been mutating [3]. In the period from March to April 2020, the A lineage of the coronavirus predominated in Spain, especially SEC7 and SEC8, and from summer to December 2020, the 20E (EU1) variant [24]. During 2021, the dominant variant in Spain was first delta and finally omicron [25]. The predominant variants in Spain during 2023 were those of the XBB family. The XBB.1.5 lineage became dominant globally in February 2023 and in March in Spain. The "Eris" variant (EG.5), a descendant of the omicron, also of the XBB family, spread rapidly since the end of July 2023 throughout the United States, Europe (including Spain) and Asia. None of these variants demonstrated to cause increased severity or increased escape from vaccines and symptoms remained largely similar to previous omicron variants [26-30]. In November 2023, several recombinant variants were circulating in Spain, particularly XBB arising from two Omicron BA.2 sub lineages [31]. In January 2024 in Spain, XBB.1.5-like + F456L accounted for 42% and BA.2.86 for 44% of positive cases [21]. In July and August 2024, the KP.3 lineage was detected in 84% of cases [32]. In September 2024, the incidence of the XEC variant of the coronavirus, a new Omicron subvariant first identified in May 2024, was increasing markedly in Spain, where it accounted for around 1% of total cases. 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% [33,34].

Thus, a chronological description of the evolution of COVID-19 symptoms could be made

1. In the early stage of the pandemic, symptoms were related only to the initial strains of SARS-CoV-2 that circulated between April and September 2020 and were not related to later variants such as delta or omicron. Presentations of COVID-19 in unvaccinated people in this first period of the pandemic (In 2020 there were still no vaccines against COVID-19) have ranged from mild/asymptomatic symptoms to severe disease and mortality. Symptoms compatible with COVID-19 were initially defined as acute respiratory symptoms consisting of sudden onset in the last 10 days of any of the following symptoms: cough, dyspnea, sore throat, or runny nose, with or without fever. Likewise, official list of COVID-19 symptoms was later updated to include sore throat, fatigue, headache, and there were frequently multi-organ symptoms (lower respiratory tract with pneumonia, digestive, dermatological and even psychiatric) [35].
2. Regarding 2021, omicron variant appears to replicate rapidly in the upper respiratory tract and its main symptoms include a runny nose, headache, fatigue, sneezing, and sore throat [36]. An observational study evaluating reported clinical symptoms of 63,000 confirmed cases of COVID-19 over two time periods (June to November 2021 when the delta variant predominated and December 2021 to January 2022 when Omicron predominated), showed that the most frequent were nasal congestion (80 %), headache (80%), sneezing (65%) and sore throat (65%) [37]. So, among vaccinated adults' symptoms during 2021 were more closely related to the common cold [10-38].
3. Now, in 2024, symptoms are determined by a much more complex cocktail of factors, including how many times that person has already been vaccinated infected by the virus, their vaccination status, and whether their vaccination-induced immunity might be waning [20]. On the other hand, the omicron versions behind the latest surge in infections in summer 2024 are JN.1 and KP .2; the latter shares many genetic features with JN.1, but displays two distinctive mutations in its spike protein, earning it the nickname "FLiRT" as a way of describing specific amino acid changes. Although KP.2 has a higher reproductive number than JN.1, suggesting that it is more transmissible, the virus itself has been found to be up to 10 times less infectious [20].

This FLiRT variant presents a set of symptoms that, so far, appear to be similar to those observed with other variants of the virus. These include common manifestations such as fever and cough, as well as the presence of nasal congestion and discharge. Those affected may also experience a sore throat, accompanied by muscle and head aches, as well as chills [39]. Thus, it can be said that in 2024 the symptoms seem to correspond more to a flu-like syndrome. Our study supports this description [40]. In this situation, it may be practically impossible for GPs to distinguish the symptoms of COVID-19 from those of influenza without the aid of a diagnostic test [20].

In summary, the symptoms of COVID-19 have evolved, in the period from 2020 to 2024, from a severe multi-organ disease to a syndrome similar to the common cold and even a more flu-like syndrome in 2024, which, although mild, tends to affect older people and those with more chronic multimorbidity. This is why it is necessary to perform a diagnostic test to differentiate it and choose a treatment and vaccination plan.

Limitations and Strengths of the Study

1. The samples were small, so some data may cause misinterpretation.
2. Asymptomatic cases were missing because they did not attend GP consultation, as no surveillance or systematic screening was done.
3. The lineages of the infections were not sequenced. Therefore, it cannot be completely ruled out of the causal variant
4. There may be an underreporting of infections to GP of patients with a positive test at home. But given the situation of the GP as the gateway to the health system, the vast majority of positive COVID-19 tests at home, is likely to be reported in GP office.
5. The study has the strength of its longitudinality, characteristic of work in general medicine.
6. All the studies were carried out in the same general medicine practice and carried out by the same researcher, which gives coherence to the results.

Conclusion

In the general practice setting in Toledo, Spain, from 2020 to 2024, cases of COVID-19 showed a tendency to range from symptoms of multiple organ systems at the beginning of the pandemic, to a common cold-like syndrome in 2022, until to a flu-like syndrome in 2024, and occurred in people progressively older with more chronic diseases. These results have practical implications; 1) Since mild COVID-19 can resemble a cold or flu, it is important to get tested if you have symptoms or have been exposed to the virus; Making a definitive diagnosis may affect treatment and isolation time. 2) Vaccination booster adapted to prevalent variants remain advisable in older people with multimorbidity.

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