

Clinical-Epidemiological Covid-19 Case Series Study in Endemic Period, from October 2022 to October 2023, in a General Medicine Office, in Toledo (Spain): Mild Symptoms should not Imply Mild Epidemiological Surveillance

Research Article

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Abstract

Background: Since the disappearance of the health alarm in many countries, covid-19 cases are not monitored, so it is not known if there have been changes in the clinical-epidemiological characteristics during the endemic period.

Objective: Know the clinical-epidemiological characteristics of current cases of covid-19.

Methodology: An observational, longitudinal and prospective case series study of adult patients with covid-19 infections in general medicine from October 1, 2022 to October 1, 2023. Descriptive epidemiological analysis considered a set of selected demographic and clinical features.

Results: 76 cases of Covid-19 were included during the study period. Of them, 28% were >65 years old, 63% women, and 17% socio-health workers. 3% presented moderate-severe severity. 63% had chronic diseases (19% Circulatory system, 18% Endocrine). 24% were re-infections. 38% of the symptoms were general (discomfort, asthenia, myalgia, fever, arthralgia), 27% were respiratory (cough, dyspnea, chest pain), and 25% were ENT (odynophagia, dysphonia, rhinorrhea, pharyngeal dryness-mucus).

Conclusion: In the general practice setting in Toledo, Spain, from October 1, 2022 to October 1, 2023, the mixture of natural immunity and that generated by vaccines that the vast majority of the population has means that it is frequent mild symptoms, but with a high percentage of risk comorbidities, re-infections, and frequent cases in socio-health workers. It is suggested to maintain clinical-epidemiological surveillance, since these symptoms are not specific to covid-19 and that populations remain vulnerable to future waves of re-infection with emerging variants of the virus SARS-CoV-2, which could change this apparent course towards endemicity and mild symptoms.

Keywords: COVID-19; SARS-CoV-2; Epidemiological characteristic; Symptoms; Case Series; General Practice

Introduction

Coronavirus disease 2019 (covid-19) is no longer in the epidemic/pandemic phase. Currently, high levels of immunity to the severe

acute respiratory syndrome coronavirus (SARS-CoV-2) are beginning to limit its impact and reach [1]. Epidemiologically, covid-19 can be defined as endemic when it exists at a predictable level that does not require special socio-health interventions [2]. It is true that the short-



term effectiveness of vaccines has been demonstrated with respect to the severity of SARS-CoV-2 infection [3]. But, on the other hand, there is increasing scientific evidence that shows that the protection generated by vaccination decreases over time, although it is reestablished with the inoculation of booster doses. In addition, the decrease in immunity as a result of the new variants must be taken into account [4]. Thus, it is accepted that it may be normal to be infected by SARS-CoV-2 several times throughout life [5-8]. SARS-CoV-2 evolves very quickly and new strains largely escape old vaccines [9-11].

Since the start of the pandemic, General Practitioners (GP) have been familiar with the hallmark covid-19 symptoms, which included loss of taste or smell, fever, cough, shortness of breath, and fatigue. But what happens now, more than three years later, when in many countries a large part of the population is vaccinated? The majority of patients with covid-19 after vaccination usually have mild disease [12], and although severe covid-19 is rare, populations remain vulnerable [13]. So how are covid-19 symptoms changing with new variants, in a landscape of mass vaccination, with immunity from a previous infection, with the evolution of omicron that seems to cause a less intense acute infection, and in the current era endemic? There are few data in this regard and much remains to be clarified. The appearance of multiple variants of SARS-CoV-2 with greater transmissibility, different virulence and different capacity for immunological escape can give rise to clinical-epidemiological aspects, in the current endemic phase, different from those previous in the pandemic phase [14].

In this scenario, understanding the clinical and epidemiological data of infection and re-infection is crucial to understand what the transition of SARS-CoV-2 to an endemic virus will be like, and whether the health system will be able to cope with it [15]. But it must be taken into account that just as very detailed epidemiological surveillance was carried out during the pandemic period, now in the endemic phase many of the community surveillance studies that tracked infection levels have ended [16,17]. In this context, we present an observational, longitudinal and prospective case series study of adult patients with covid-19 infections in general medicine from October 1, 2022 to October 1, 2023, with the objective of knowing the clinical-epidemiological characteristics of the new cases of covid-19, in this endemic period.

Material and Methods

Design and Emplacement

An observational, longitudinal and prospective study of covid-19 re-infections was conducted from October 1, 2020 to October 1, 2023 in a general medicine office in the Santa Maria de Benquerencia Health Center, Toledo, Spain, which has a list of 2,000 patients > 14 years of age (in Spain, the GP care for people > 14 years of age, except for exceptions requested by the child's family and accepted by the GP).

Outcome of Interest

Know and describe a set of selected clinical-epidemiological characteristics of new cases of covid-19 in the endemic period for one year (from October 1, 2022 to October 1, 2023).

Collected Variables

The following variables were collected:

A. Age and sex.

B. 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" [18], classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 [19].

C. If they were Health Care Workers.

D. Social-occupancy class (according to the Registrar General's classification of occupations and social status code) [20,21].

E. Problems in the family context and low income household based on the genogram and in the experience of the GP for their continuity of care and knowledge of the family (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) [22,23].

F. Ethnic minority (defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group") [24].

G. 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 $\leq 93\%$ with room air at rest, arterial partial pressure of oxygen/oxygen concentration ≤ 300 mmHg.) [25]; to simplify comparison, moderate and severe cases were counted together.

H. Date of covid-19 infection diagnosis.

I. Presence of re-infection (defined as a documented infection occurring at least 90 days after a previous infection) [26-28].

J. Vaccination status against covid-19 at the date of acute infection: vaccinated with 2 doses of vaccine [29], vaccinated with first booster [30], vaccinated with fourth dose (second booster) for fall-winter 2022 [31].

Ethical Issues

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

Results

76 cases of Covid-19 were included during the study period. Of them, 28% were >65 years old, 63% women, and 17% socio-health workers. 3% presented moderate-severe severity, 63% had chronic diseases (19% were from the Circulatory system, 18% Endocrine, 15% Genitourinary, 14% Digestive system, and 10% Mental). 7% had a complex family/problem in the family context, 3% were ethnic minority. 55% were vaccinated with 3 doses, and 28% with 4 doses. 24% were re-infections (Table 1&2). Regarding the symptoms, 38% were general (discomfort, asthenia, myalgia, fever, arthralgia), 27% were respiratory (cough, dyspnea, chest pain), and 25% ENT (odynophagia, dysphonia, rhinorrhea, pharyngeal dryness-mucus) (Table 3).



Table 1: Variables of Covid-19 Infections in the Period from October 2022 to October 2023.

Variables	Covid-19 Infections N=76
Mean age (Arithmetic mean +- Standard deviation; Range)	53.07+-16.54 (13-95 years)
>= 65 years	21(28)
=< 45 years	26(34)
Women	48(63)
Social-occupancy class of patients (people with some type of labor specialization)	31(41)
Health Care Workers	13(17)
Moderate-severe severity	2(3)
Chronic diseases	48(63)
Complex family/Problems in the family context	5(7)
Low income household	1(1)
Ethnic minority	2(3)
Asymptomatic	0
Not vaccinated	1(1)
Vaccinated only 1 dose	1(1)
Vaccinated only 2 dose	11(15)
Vaccinated only 3 dose	42(55)
Vaccinated 4 dose	21(28)
Re-infection	18(24)

(): Denotes percentages.

Table 2: Chronic Diseases of Covid-19 Infections in the Period from October 2022 to October 2023.

Chronic Diseases* According to WHO, ICD-10 Groups	Chronic Diseases in 76 Cases of Covid-19
I Infectious	1(1)
II Neoplasms	4(2)
III Diseases of the blood	3(2)
IV Endocrine	28(18)
V Mental	15(10)
VI-VIII Nervous and Senses	13(8)
IX Circulatory system	30(19)
X Respiratory system	6(4)
XI Digestive system	22(14)
XII Diseases of the skin	3(2)
XIII Musculo-skeletal	8(5)
XIV Genitourinary	24(15)
Total chronic diseases*	157(100)

(): Denotes percentages.

*Patients could have more than one chronic disease. The percentages of chronic diseases are over the total of chronic diseases.



Table 3: Symptoms of Covid-19 Infections in the Period from October 2022 to October 2023.

Symptoms Covid-19 Infection* According to WHO, ICD-10 Groups	Covid-19 I nfections N=76
General(discomfort, asthenia, myalgia, fever, artral- gias)	95(38)
Respiratory (cough, dyspnea, chest pain)	69(27)
ENT(Anosmia/ageusia, odynophagia, dysphonia, rhin- orrhoea, sneezing, pharyngeal dryness-mucus, ear pain)	64(25)
Digestive(anorexia, nausea/vomiting, diarrhea, abdom- inal pain)	6(2)
Neurological(headache, dizziness, photopsia, syn- cope)	14(6)
Psychiatric (anxiety, insomnia)	1(1)
Skin	0
Urological(dysuria, frequency)	2(1)
Total symptoms*	251(100)

(): Denotes percentages.

*Patients could have more than one symptom. The percentages are over the total of symptoms.

Discussion

Main Findings

The main results of our study were that the majority of covid-19 cases were mild, general symptoms predominated, followed by respiratory and ENT symptoms, they occurred in middle-aged women, with high frequency of chronic diseases (19% were from Circulatory system, 18 % Endocrine), without socio-economic problems, and vaccinated with 3 or 4 doses. One in 6 cases were social-health workers. Therefore, this indicates that the current cases are not more serious than the previous ones and are somewhere between those of a flu syndrome and a common cold. Possibly the high percentage of vaccinated people and previous infections are factors that prevent severity. But likewise, we see that cases occur in high-risk people due to their comorbidities, there are frequent reinfections despite the high vaccination rate, and there is a high frequency of cases in social-health workers.

Comparison with Other Studies

A disease that is not eradicated is, by definition, endemic; this would be a term to indicate that covid-19 is still present, but we no longer need to restrict our lives. But this does not necessarily mean that it is harmless. This situation is mediated by individual risk factors (age, underlying conditions, etc.) [2,32]. Understanding the variation of symptoms according to temporality is crucial for clinical practice; It could help speed diagnosis, predict outcomes more accurately, and guide treatment, especially as new variants emerge. Likewise, being able to reflect this variation in symptoms in public health messages can contribute to prevention. It has been suggested that future work should focus on symptom profile variation in emerging variants of the SARS-CoV-2 virus [33].

The presentation of symptoms has evolved and in the short space of a few years there have been surprising changes in the way covid-19 presents. At the beginning of the pandemic, a clinical spectrum of covid-19 was described [33-41] that varied from:

- a) Asymptomatic or paucisymptomatic forms.
- b) "Classic" presentation with the main symptoms in 2020 [cough (84%), fever (80%) and loss of smell]. Covid-19 patients also showed other symptoms, including chills, muscle pain, headache, fa-

tigue, and digestive problems such as nausea, abdominal pain, vomiting, or diarrhea. Approximately half of the patients reported one or more gastrointestinal symptoms; Among these, diarrhea was reported more frequently (38%) and vomiting less frequently (13%).

- c) Cases with mild-severe disease with non-pneumonia and mild pneumonia.
- d) Cases in which patients presented mainly non-respiratory symptoms affecting one or several organs, with multisystem involvement secondary to different immune responses.
- e) Critical clinical conditions characterized by respiratory failure.

During the course of the pandemic it was also found that the symptoms were different depending on the virus variant. From the original virus, to alpha, delta, and omicron, the symptoms seem to be lighter and upper respiratory tract. In the initial stage of the pandemic, the symptoms were related only to the initial strains of SARS-CoV-2 that circulated between April and September 2020. Later the symptoms were related to later variants such as Delta or Omicron. In first year of the pandemic, covid-19 presentations also occurred in unvaccinated people, and these varied from mild/asymptomatic symptoms to severe disease and mortality [33,35,42,43].

Later in the course of the pandemic it became clear that the symptoms with which covid-19 manifested itself in the vaccinated population were different from those at the beginning of the pandemic: fever was no longer the most permanent symptom, nor was it loss of taste and smell, and conversely, rhinorrhoea, sore throat or dry cough and headache appeared as very frequent symptoms in vaccinated people [44-46]. In 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), it showed that the most frequent were nasal congestion/ runny nose (77-82%), headache (75-78%), sneezing (63-71%) and sore throat (61-71%), and generally other mild symptoms such as cough and fatigue. Omicron subvariants BA.1 and BA.2 appeared to migrate from primarily infecting the lungs and nervous tissue to the upper respiratory tract. Thus, the symptoms of covid-19 with the BA.1 variant for many



people were little more than a severe cold [47,48]. In that period of 2022, in vaccinated people, and in the same population of the current study, symptoms of upper respiratory tract appeared as very frequent symptoms, such as runny nose, sore throat or dry cough, as well as headache [49-51].

The predominant variants in Spain during the period of our study were those of the XBB family. The XBB.1.5 lineage became dominant globally in February 2023 and in March in Spain. "Eris" variant (EG.5) descendant of omicron, also from the XBB family, spread rapidly since the end of July 2023 in the United States, Europe (including Spain) and Asia. And, in a very small proportion, there is currently another variant that is advancing in the world, the BA.2.86, which has been named as Pirola [52-58]. None of these variants have been shown to cause greater severity or greater escape from vaccines and symptoms remain largely similar to previous omicron variants [59,60].

Thus, there is nothing to indicate that the current cases are more serious. Even if BA.2.86 becomes widespread (and proves adept at dodging neutralizing antibodies, which seems likely, based on its peak mutation set), other forms of immunity will prevent most people from becoming seriously ill if infected. Ultimately, the chances of these latest virus variants proving to be more severe than existing variants or causing the level of disruption seen with the first waves of omicron are thought to be extremely low, due to widespread immunity [61].

The results of our study fit with what was described, confirming the infrequency of severity. The mixture of natural immunity and that generated by vaccines that the vast majority of the population has means that it is normal to pass the infection with mild symptoms: general symptoms (fever, myalgia, asthenia), respiratory (cough) and ENT symptoms (odynophagia, dysphonia, rhinorrhea, sneezing, pharyngeal dryness-mucus) were mainly found. But many of these symptoms are not specific to covid-19 and could also be a manifestation of other viral diseases [59], which makes diagnosis difficult without a specific test and complicates epidemiological surveillance.

Finally, it is worth asking, what makes the symptoms more or less severe besides the virus variant?: the host and environment. Vaccination status, viral load, underlying medical conditions (the presence of underlying health conditions such as cardiovascular diseases, diabetes, chronic respiratory diseases, hypertension and obesity, as well as immunosuppression and autoimmune diseases) influence in severity [14,59,62]. In our series, 63% had chronic diseases, of which 19% were from the Circulatory system and 18% from the Endocrine system. This is a high number of vulnerable or at-risk populations; this makes us cautious about the future evolution of covid-19 symptoms.

Limitations and strengths of the study

- 1) The case series was small, so some data may cause misinterpretation.
- 2) The cases treated by the GP may not be all existing cases, but given the situation of the GP as the gateway to the health system, the vast majority is likely to be present, and especially those with moderate-severe symptoms.
- 3) Asymptomatic cases that did not attend in GP consultation, as no surveillance or systematic screening was done, may have been missed.
- 4) Case series studies are studies of "numerators" only. No control group or controlled assignments of patients is involved.
- 5) The study has the strength of its longitudinality, characteristic of work in general medicine.

Conclusion

In the general practice setting in Toledo, Spain, from October 1, 2022 to October 1, 2023, the mixture of natural immunity and that generat-

ed by vaccines that the vast majority of the population has means that the normal thing is to pass the infection with mild general symptoms, upper respiratory tract and ENT. But also there are a high percentage of risk comorbidities, re-infections, and frequent cases in socio-health workers. It is suggested to maintain the clinical-epidemiological surveillance, since these symptoms are not specific to covid-19 and populations remain vulnerable to future waves of re-infection with emerging variants of the SARS-CoV-2 virus, which could change this apparent course towards endemicity and mild symptoms. "Mild" symptoms should not imply "mild" epidemiological surveillance.

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