MedPress
Public Health and Epidemiology

SARS-CoV-2 Infection Post-Acute Specific Sequels Case Series in General Medicine from March 15, 2020 to October 31, 2022, in Toledo, Spain

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Research Article

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Article Information

Received: 22-12-2022;
Accepted: 03-01-2023;
Published: 03-01-2023.

Abstract

Background

It is likely that the burden of disease secondary to covid-19 is not limited to acute disease alone, but the potential sequels are not well known.

Objective

To study in general medicine clinical-epidemiological characteristics of patients with specific covid-19 sequels (pathologies that persist during acute infection or after apparent recovery from acute covid-19 infection and that are not part of acute covid-19 infection).

Methodology

An observational, longitudinal and prospective study of patients with covid-19, to detect those with specific covid-19 sequels, in a general medicine office in Toledo (Spain) was carried out from March 15, 2020 to October 31, 2022.

Results

During the study period, 25 covid-19 cases were included, presenting 29 sequels, predominantly those of the circulatory system [32%; pulmonary embolism (2), atrial fibrillation (3) arterial hypertension (2), macular ischemia in both eyes, stroke]. Of the 25 cases with sequels, 32% were women and 28% were >=65 years old. 48% had moderate-severe severity in the primary infection with predominant symptoms of the respiratory group (cough, dyspnea, chest pain); 56% had chronic diseases, predominantly symptoms of the circulatory system (20%), endocrine (18%), mental (15%) and nervous and senses (15%); 44% were not vaccinated at the time of acute covid-19. Almost half of the cases of acute covid-19 that subsequently caused sequels occurred in 2021 (48%).

Conclusion

In the context of general medicine in Toledo (Spain), the cases of covid-19 with sequels were predominantly middle-aged, had been admitted to hospital with moderate-severe severity of respiratory symptoms in primary infection and the sequels more frequent were of the circulatory system and endocrine in patients with previous chronic diseases also of the circulatory system and endocrine. Special surveillance by the general practitioner is suggested to detect specific sequels of covid-18 in patients who presented an acute infection of moderate-severe severity and have chronic diseases of the circulatory system and endocrine.

Key Words: Post-coronavirus disease 2019 syndrome; COVID-19; Post-acute sequels of SARS-CoV-2 infection; General Practice

Introduction

The global repercussions of the disease caused by SARS-CoV-2 (covid-19) were rapidly evident since January 2020, for which reason the WHO declared covid-19 a public health emergency of international concern and in March same year it was granted the category of pandemic. Despite many extensive studies that led to the approval of vaccines and antivirals, the global spread of SARS-CoV-2 continues, and since the publication of the first reported cases in Wuhan, China, in December 2019, covid-19 has been one of the most devastating pandemics in recent times (1, 2). Although most infected people recover, a significant proportion continues to experience symptoms and complications after their acute illness (3).

It is well known that many survivors of serious illnesses suffer lasting consequences of physical, cognitive and mental health (4). As the covid-19 pandemic has progressed, there is increasing evidence that after the acute phase of the disease, people with covid-19 may develop post-covid-19 conditions or persistent covid-19 conditions. There are a variety of names for these post-COVID-19 conditions, such as persistent covid-19, long-standing covid-19, post-acute covid-19, post-acute sequels of SARS CoV-2 infection, persistent effects long-term of covid-19 and chronic covid-19 (5).

These post-covid-19 conditions may involve pulmonary and extrapulmonary organ manifestations (1). Characterization of covid-19 in patients who have survived for at least 30 days after SARS-CoV-2 infection has allowed the identification of incident sequels beyond the respiratory system, including nervous system disorders, neurocognitive disorders, and health mental disorders, metabolic disorders, cardiovascular disorders, gastrointestinal disorders, malaise, fatigue, musculoskeletal pain, and anemia (6).

Given the number of cases of covid-19, it is expected that the number of affected patients with sequels will increase significantly (4). On the other hand, many covid-19 survivors receive long-term care from general practitioners (GPs) at the primary care level. Therefore, the recognition of post-covid-19 conditions is crucial for the GP (4, 6). In addition, GPs play a key role in managing the sequels following the acute phase of covid-19 due to their expertise in integrative medicine, coordination of care, encompassing patient self-management, and long-term knowledge of the medical history of patients and their families (4).

In any case, covid-19 is not a known disease and, therefore, neither are its potential sequels. How long these consequences can last and how they can be resolved are questions that must be resolved with research, taking into account that it is not known how long SARS-CoV-2 will be part of our lives (7). The burden of disease secondary to this pandemic is likely to be enormous and not limited to acute disease alone, thus epidemiological studies are needed to further investigate the long-term impact of this pathology (8).

In this context, more research is needed on post-covid-19 conditions, clarifying the terms and inclusion criteria, and at the primary care level (4). So, we present an observational, longitudinal and prospective case series study of patients with specific covid-19 sequels, based on a prospective cohort of covid-19 patients in a family medicine office in Toledo (Spain) from March 15, 2020 to October 31, 2022.

Material and Methods

Design and emplacement

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

Objective

Describe the clinical-epidemiological characteristics of cases with specific sequels of acute covid-19 infection.

Inclusion criteria

Basically, specific sequels of acute covid-19 infection were diagnosed, when there were persistent symptoms or pathologies during the acute infection or after an apparent recovery from the acute covid-19 infection, and which are not part of the acute covid-19 infection (9).

Patients who met the criteria for specific sequels of acute infection were included:

1. Pathologies that are not part of the acute infection, persistent, appearing during covid-19 infection
2. Pathologies that are not part of the acute infection, persistent, with appearance after resolution of the initial symptoms (covid-19 post-infection pathologies)
3. Pathologies that are not part of the acute infection but appear as a consequence of the organic damage produced by the severe infection (true sequels of covid-19).

These pathologies, for example, include thromboembolic disease, pulmonary fibrosis, myopericarditis, and multiple mononeuritis. Complications were excluded. Complications were considered health problems that originated as a result of acute covid-19 infection or the treatments performed. For example, those cases that presented acute respiratory infection, dyspnea, tachypnea, clinical and/or radiological signs of pneumonia (10).

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 (11); since the beginning of the pandemic in mid-March 2020, PCR tests were only performed in the hospital context until mid-May 2020, when they began to be performed in general medicine as well. In mid-December 2020, rapid antigen tests began for symptomatic patients with less than 5 days of evolution. The PCR tests were performed both in symptomatic patients and in asymptomatic contacts. 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 (12).

Collected variables

Age; sex; acute covid-19 date; specific sequels of covid-19 and 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" (13), both classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 (14); symptoms in covid-19 acute phase in cases with sequels; social-occupancy class (according to the Registrar General's classification of occupations and social status code) (15, 16);

complex family based on the genogram and in the experience of the general practitioner for their continuity of care and knowledge of the family (genogram was 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" genogram identified families with psychosocial problems) (17-20); Ethnic minority, defined as a “human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group” (21); and severity of the disease (mild cases: clinical symptoms are mild and no manifestation of pneumonia can be found on images; moderate cases: with symptoms such as fever and respiratory tract symptoms, and the manifestation of pneumonia can be seen on the imaging tests; and 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.) (22). To simplify comparison, moderate and severe cases were counted together; vaccination status against covid-19 at the date of acute infection.

Results

During the study period, 25 covid-19 cases were included in the general medicine clinic, presenting 29 sequels. Circulatory system sequels predominated [32%; pulmonary embolism (2), atrial fibrillation (3) arterial hypertension (2), macular ischemia in both eyes, stroke], followed by endocrine [18%; diabetes mellitus type 2 (3), hypothyroidism, dyslipidemia], mental [14%; pathological grief (2), anxiety/depression (2) and respiratory system [14%; dyspnea under study (4)] (TABLE 1).

Of the 25 cases with sequels, 32% were women and 28% were >=65 years old. 48% had moderate-severe severity in the primary infection, 56% had chronic diseases, 44% were not vaccinated at the time of acute covid-19, 32% were ethnic minority, and 28% were people with some type of labor specialization. Almost half of the cases of acute covid-19 that subsequently caused sequels occurred in 2021 (48%) (TABLE 2).

The 25 patients with sequels presented 34 chronic diseases, predominantly those of the circulatory system (20%), endocrine (18%), mental (15%) and nervous and senses (15%) (TABLE 3).

Table 1: Specific Sequels of Covid-19, Classified According to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019

DISEASES GROUPS	COVID-19 WITH SEQUELS N=25
-I Infectious	1 (3) [Positive persistent covid-19]
-II Neoplasms	1 (3) [Significant lymphoma progression]
-III Diseases of the blood	1 (3) [Muscle hematoma, hepatic hematoma, hemoperitoneum, hypovolemic shock]
-IV Endocrine	5 (18) [Diabetes mellitus type 2 (3), hypothyroidism, dyslipidemia]
-V Mental	4 (14) [Pathological grief (2), anxiety/depression (2)]
-VI-VIII Nervous and Senses	1 (3) [Parkinson's disease aggravation]
-IX Circulatory system	9 (32) [Pulmonary embolism (2), atrial fibrillation (3) arterial hypertension (2), macular ischemia in both eyes, stroke]
-X Respiratory system	4 (14) [Dyspnea on study]
-XI Digestive system	1 (3) [Fecal incontinence]
-XII Diseases of the skin	0
-XIII Musculo-skeletal	2 (7) [polyarthralgia]
-XIV Genitourinary	0
TOTAL chronic diseases**	29 sequels in 25 patients

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

Table 2: Variables of Covid-19 with Sequels.

VARIABLES	COVID-19 WITH SEQUELS N=25
Age in years (Arithmetic mean + - Standard deviation; Range)	54.52+-14.41 (Range: 19-76)
> = 65 years	7 (28)
< 45 years	5 (20)
< 18 years	0
Women	8 (32)
Social-occupancy class of patients (people with some type of labour specialization)	7 (28)
Health Care Workers	1 (4)
Ethnic minority	8 (32)
Complex family	1 (4)
Moderate-severe severity of primary infection	12 (48)
Hospitalization in acute phase	12 (48)
Readmission after hospital discharge	1 (4)
Chronic diseases presence	14 (56)
Reinfection	0
Not vaccinated at the time of acute covid-19	11 (44)
Vaccinated covid-19 with 1, 2 or 3 doses at the time of acute covid-19	14 (56)
Acute covid-19 date in 2020	9 (36)
Acute covid-19 date in 2021	12 (48)
Acute covid-19 date in 2022	4 (16)

( ): Denotes percentages

Table 3: Chronic Diseases in Covid-19 with Sequels

CHRONIC DISEASES	COVID-19 WITH SEQUELS N=25
-I Infectious	0
-II Neoplasms	2 (6)
-III Diseases of the blood	0
-IV Endocrine	6 (18)
-V Mental	5 (15)
-VI-VIII Nervous and Senses	5 (15)
-IX Circulatory system	7 (20)
-X Respiratory system	1 (3)
-XI Digestive system	2 (6)
-XII Diseases of the skin	0
-XIII Musculo-skeletal	3 (9)
-XIV Genitourinary	3 (9)
TOTAL chronic diseases*	34 (100)

( ): Denotes percentages; *Patients could have more than one chronic disease; the percentages of chronic diseases are over the total of chronic diseases

Regarding the symptoms in the acute phase of the cases that subsequently presented sequels, those of the respiratory group (cough, dyspnea, chest pain) predominated (TABLE 4).

Discussion

Main findings

The main findings of our study are: 1) Specific sequels of covid-19 (defined as persistent symptoms or pathologies during acute infection or after apparent recovery from acute covid-19 infection, and not part of acute infection by covid-19) occur in patients who presented an acute infection of moderate-severe severity; 2) These sequels were more frequent of the circulatory system and endocrine; and 3) These sequels occur in patients with previous chronic diseases also of the circulatory system and endocrine.

Table 4: Symptoms in Covid-19 Acute Phase in Cases with Sequels

SYMPTOMS*	COVID-19 ACUTE PHASE IN CASES WITH SEQUELS N=25
General (discomfort, asthenia, myalgia, fever, artralgias)	20 (31)
Respiratory (cough, dyspnea, chest pain)	29 (45)
ENT (anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus)	13 (20)
Digestive (nausea / vomiting)	1 (2)
Neurological	0
Psychiatric (anxiety, insomnia)	1 (2)
Skin	0
Total symptoms*	64

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

Comparison with other studies

People infected with SARS-CoV-2 may experience a broad spectrum of debilitating sequels or chronic health problems involving pulmonary and extrapulmonary organs, including persistent fatigue, dyspnea, decreased quality of life, impaired lung function, myocarditis, neurological and psychiatric diagnoses, slow and stagnant recovery of olfactory and taste function, which persist for months or more (5, 23). Post-covid-19 conditions can be difficult to recognize, as there is no test to diagnose them and patients may have symptoms that may be due to other health problems (5). It is hypothesized that inflammation of certain parts of the organism can be transmitted to others and dysregulate other types of cells (24). Therefore a holistic approach is needed and that is the place of the GP (25, 26).

It is basically agreed that post-covid-19 conditions are more common in those who became severely ill in the acute phase and in patients who had underlying conditions before covid-19 (5). Our study coincides with these data, finding that 48% of patients with sequels had moderate-severe severity of primary infection, and 56% had chronic diseases.

Patients have been described who, after infection, remain with cardiac sequels after having suffered a myocardial infarction or myocarditis (7). It is thought that the frequency of cardiac involvement resulting from SARS-CoV-2 disease may be mainly associated with the severity of the clinical course of the pathology and the presence of comorbidities, including previous silent or undiagnosed lesions (8). Thus, the link between post-covid-19 cardiac sequels of myocardial dysfunction and the presence of pre-existing coronary artery disease has been described (27, 28). We found that sequels of the circulatory system predominated [32%; pulmonary embolism (2), atrial fibrillation (3) hypertension (2), macular ischemia both eyes (1), and stroke (1)].

Previous studies have indicated that diabetes mellitus is associated with an increased risk of severe covid-19 (1). But, a bidirectional relationship between these two pathologies has been described. The diabetogenic potential of SARS-CoV-2 has been hypothesized, not only because of the targets used by the virus but also because of the inflammatory stress secondary to the disease (8). After covid-19, patients of all ages and genders have a high incidence for new-onset diabetes (1). We found results that coincide with what has been published, since endocrinological sequels are the second most frequent in our study [18%; diabetes (3), hypothyroidism, dyslipidemia], and diabetes mellitus predominates among them.

Thrombosis associated with the virus has been one of the most frequent reasons for consultation in patients without underlying hematological diseases (7). In some patients who presented severe pulmonary involvement during the early stages of the disease, thrombotic phenomena were observed, not only in the lungs but also in other locations (7). We found, among the 29 sequels detected, 2 pulmonary embolisms, 1 macular ischemia in both eyes, and 1 stroke.

Patients have been described who, after infection; remain with psychological sequels, such as anxiety or insomnia and even depression or post-traumatic stress (7). In our study we found that the frequency of mental sequels was third in frequency [14%;

pathological grief (2), anxiety/depression (2)].

It has been reported that there are brain changes in genetic activity that were more extensive in people who had severe SARS-CoV-2 infections (29, 30). And people who have had covid-19 are at long-term risk of developing seizures (31). However, we only found a sequel to the Nervous system [Aggravation of Parkinson's Disease].

Likewise, stressful life events (such as the death of a loved one, financial insecurity, or a new disability) have been described as increasing the risk of persistent symptoms after recovery from an acute SARS-CoV-2 infection (32). In our study, the results of the socio-economic variables are mixed: 72% of the patients with sequels did not have any type of labour specialization, 32% were an ethnic minority, and only 4% were classified as members of families with problems.

Half of our cases of sequels (48%) occurred in patients with acute infection in 2021. In Spain, in the period from January 2021 the alpha variant predominated, and from the summer-autumn of 2021 was delta variant (33, 34).

Finally, it has been established that people who are not vaccinated against covid-19 and become infected may also be at higher risk of post-covid-19 conditions relative to people who become infected while vaccinated (5). In our study, more than half of the patients with sequels if they were vaccinated (44% were not vaccinated) at the time of acute covid-19

Study limitations and strengths

1. Case series studies are "numerator" studies only. No control group or controlled patient assignments are involved.
2. The number of cases was relatively small.
3. Asymptomatic cases of covid-19 may have been missed in the acute phase.
4. The study has the strength of its longitudinality, characteristic of the work of the GP.

Conclusions

In the context of general medicine in Toledo (Spain), the cases of covid-19 with sequels were predominantly middle-aged, had been admitted to hospital with moderate-severe severity of respiratory symptoms in the primary infection, and the sequels more frequent were of the circulatory system and endocrine in patients with previous chronic diseases also of the circulatory system and endocrine. Covid-19 is a complex and multifaceted condition that involves a variety of physical, cognitive, psychological and social implications. Special surveillance is suggested to detect specific sequels of covid-19 in patients who presented an acute infection of moderate-severe severity and have chronic diseases of the circulatory system and endocrine. This continuous long-term surveillance over time to detect possible post-covid-19 sequels is complex due to the number of covid-19 cases, the multiple new symptoms, the relationship with previous chronic conditions, and psychosocial factors involved, and so requires professionals with integrated approaches rather than specific organs or diseases, and that is the place of the GP in health services.

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Citation: Turabian JL. SARS-CoV-2 Infection Post-Acute Specific Sequels Case Series in General Medicine from March 15, 2020 to October 31, 2022, in Toledo, Spain. Medp Public Health Epidemiol. 2022; 2(1): mpphe–202212005.