

Complications Originated as a Consequence of the Acute Infection of COVID-19 or the Treatments Performed. Case Series in General Medicine from March 15, 2020 to October 31, 2022, in Toledo, Spain

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Abstract

Background

Despite the abundance of information on covid-19, few studies have been carried out on complications originated as a consequence of the acute infection or the treatments performed.

Objective

Describe the clinical-epidemiological characteristics of cases with complications originated as a consequence of the acute infection of covid-19 or the treatments performed.

Methodology

An observational, longitudinal and prospective case series study of patients with complications originated as a consequence of the acute infection of covid-19 or the treatments performed based on a cohort of covid-19 patients in a family medicine office in Toledo (Spain) was carried out from March 15, 2020 to October 31, 2022.

Results

There were 52 complications in 36 patients (mean age 59 years, and 39% were ≥ 65 years). Respiratory system complications predominated (56%). 36% were women. 72% presented moderate-severe severity of primary infection. 56% were not vaccinated. 61% presented acute covid-19 infection in 2020. Chronic diseases were present in 83%, predominantly of Circulatory system (27%) and Endocrine (22%). Among the initial symptoms in covid-19 acute phase, general (37%) and respiratory (36%) symptoms predominated.

Conclusion

In the context of general medicine in Toledo (Spain), the main complications originated as a consequence of the acute infection of covid-19 or the treatments performed were of the respiratory system, in middle-aged men, with severe acute covid-19, not vaccinated, with chronic diseases of the circulatory system and endocrine, and during the year 2020.

KeyWords: COVID-19; SARS-CoV-2; Long-term complications after COVID-19; General Practice; Longitudinal Studies

Introduction

Since its appearance at the end of 2019, the Coronavirus disease 2019 (covid-19) caused by the SARS-CoV-2 virus, which is known for its multiple mutations (1) which increase in transmissibility and disease severity, has spread rapidly across the world, has posed a general threat to modern medicine, and has caused more than 6 million deaths as of December 2022 (2).

Covid-19 can have relatively mild and manageable symptoms

at home for most people. But in people who are older or have another disease, such as diabetes or heart disease, there is a higher risk of contracting the severe form of covid-19 (3). Patients with a certain degree of immunosuppression, due to their underlying pathology or due to the treatments they receive, also have an increased risk of complications and persistence of the virus (4).

Thus, SARS-CoV-2 infection can lead to severe primary disease,

such as pneumonia and acute respiratory distress syndrome. Infection can also give rise to numerous immune-mediated pathologies, such as lymphopenia, during the acute phase of the disease (5). In this sense, the course of the disease is uncertain with various forms of presentation. Therefore, the wide range of diseases related to covid-19 and organ damage weaves a complex prognostic picture (6).

Covid-19 has been known to be strongly associated with an exaggerated inflammatory response. This response leads to the release of a large amount of proinflammatory cytokines. The host's hyperactive immune response to SARS-CoV-2 produces an excessive inflammatory reaction. This situation is directly related to lung injury, multi-organ failure, and the unfavorable prognosis of severe covid-19. This overactive response is clinically characterized by overwhelming systemic inflammation, hyperferritinemia, hemodynamic instability, and multi-organ failure, and if left untreated, leads to death. This condition is due to the action of proinflammatory cytokines such as interleukin (IL)-1, IL-6, IL-18, interferon- γ , and tumor necrosis factor (TNF)- α and it has been seen in various viral infections (7).

In this scenario, complications during or after covid-19 appear to be frequent in hospitalized patients. Of the patients discharged from the hospital, more than one in 10 will die within six months (6) but the spectrum of symptoms in the mildest cases, as well as the epidemiology and pathophysiology of complications in covid-19 do not are now well understood. So, there is an urgent need to investigate these issues (8, 9).

In this context, we present an observational, longitudinal and prospective case series study of patients with complications originated as a consequence of the acute infection of covid-19 or the treatments performed, based on a prospective cohort of covid-19 patients in general medicine 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 complications originated as a consequence of the acute infection of covid-19 or the treatments performed 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 complications originated as a consequence of the acute infection of covid-19 or the treatments performed.

Inclusion criteria

Complications are considered health problems that originated as a result of acute covid-19 infection or the treatments performed. Complications due to covid-19 included those cases presenting acute respiratory infection, dyspnea, oxygen saturation less than or equal to 92%, tachypnea, clinical and/or radiological signs of pneumonia. In addition, those who required hospitalization (including admission to the intensive care unit) and death from covid-19 (10) were considered.

Specific squeals of acute covid-19 infection were excluded:

when there were persistent symptoms or pathologies during acute infection or after apparent recovery from acute covid-19 infection, which are not part of acute covid-19 infection (11).

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 (12); 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 (13). In the period from March to April, 2020, in Spain the A lineage of the coronavirus predominated, especially the SEC7 and SEC8, and from summer to December, 2020, the 20E (EU1) variant (14, 15). In the period from January 2021 the alpha variant predominated, and from the summer-autumn of 2021 the delta variant (16, 17). From January 2022 to October 2022, the omicron variant predominated (18-20).

Collected variables

The following variables were collected: age; sex; acute covid-19 infection date; complications; covid-19 treatments; acute phase symptoms; 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" (21), classified according to the International Statistical Classification of Diseases and Health-Related Problems, CD-10 Version: 2019 (22); social-occupancy class (according to the Registrar General's classification of occupations and social status code) (23, 24); 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) (25-28); Ethnic minority, defined as a "human group with cultural, linguistic, racial values and geographical origin, numerically inferior compared to the majority group" (29); vaccination status against covid-19 at the date of acute infection; 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 \geq 30 breaths / min., pulse oxygen saturation \leq 93% with room air at rest, arterial partial pressure of oxygen / oxygen concentration \leq 300 mmHg.) (30). To

simplify comparison, moderate and severe cases were counted together.

Results

From March 15, 2020 to October 31, 2022, 52 complications originating as a consequence of the acute infection of covid-19 or the treatments performed were recorded in 36 patients. Respiratory system complications predominated with 29 cases (56%) [iatrogenic pneumothorax, respiratory failure without pneumonia, pneumonia (27 cases)], followed by Infectious complications with 4 cases (8%) [Oral candidiasis, bacterial endocarditis, respiratory superinfection by *Aspergillus* and herpes zoster virus, bacteremia by *E. Faecium*] and Diseases of the blood also with 4 cases (8%) [muscular hematoma, hepatic hematoma, hemoperitoneum, hypovolemic shock, as a cascade of complications after jugular cannulation]. 6 patients died (17%) (TABLE 1).

The 36 patients had a mean age of 59 years (range: 39-80 years). 39% were ≥ 65 years. 36% were women. 72% presented moderate-severe severity of primary infection and 75% hospitalization in acute phase. 56% were not vaccinated. 61% had acute covid-19 infection in 2020. 83% had chronic diseases (TABLE 2).

Among the chronic diseases in patients who presented complications originated as a consequence of the acute infection of covid-19 or the treatments performed, Circulatory system (27%), Endocrine (22%), and Digestive system (12%) predominated (TABLE 3).

Among the initial symptoms in covid-19 acute phase in patients who subsequently presented complications originated as a consequence of the acute infection of covid-19 or the treatments performed, General symptoms predominated (discomfort, asthenia, myalgia, fever, arthralgia) (37%) and Respiratory (cough, dyspnea, chest pain) (36%) (TABLE 4).

Table 1: Complications Originated as a Consequence of the Acute Infection of COVID-19 or the Treatments Performed

WHO, ICD-10 GROUPS	COMPLICATIONS ORIGINATED AS A CONSEQUENCE OF THE ACUTE INFECTION OF COVID-19 OR THE TREATMENTS PERFORMED N=36
-I Infectious	4 [Oral candidiasis, bacterial endocarditis, respiratory superinfection by <i>Aspergillus</i> and herpes zoster virus, bacteremia by <i>E. Faecium</i>]
-III Diseases of the blood	4 [Muscular hematoma, hepatic hematoma, hemoperitoneum, hypovolemic shock, as a cascade of complications after jugular cannulation]
-IV Endocrine	2 [Hyperuricemia]
-V Mental	2 [Anxiety / Depression]
-VI-VIII Nervous and Senses	2 [Limb tremor, myopathy]
-IX Circulatory system	3 [Lower limb deep vein thrombosis, congestive heart failure, arterial hypertension, pulmonary thromboembolism]
-X Respiratory system	29 [iatrogenic pneumothorax, respiratory failure without pneumonia, pneumonia (27)]
-XI Digestive system	3 [gallstones, dysphagia, hepatic biochemical abnormality]
-XII Diseases of the skin	0
-XIII Musculo-skeletal	1 [Acute gout]
-XIV Genitourinary	2 [Renal colic, acute urinary retention, pyelonephritis]
TOTAL COMPLICATIONS	52 complications in 36 patients [1.44 per patient]
TOTAL COMPLICATIONS with EXITUS	6

Table 2: Variables of Complications Originated as a Consequence of the Acute Infection of COVID-19 or the Treatments Performed

VARIABLES	COMPLICATIONS ORIGINATED AS A CONSEQUENCE OF THE ACUTE INFECTION OF COVID-19 OR THE TREATMENTS PERFORMED N=36
Age in years (Arithmetic mean + - Standard deviation; Range)	59.27 +-11.16 (39-80 years)
> = 65 years	14 (39)
< 45 years	4 (11)
< 18 years	0
Women	13 (36)
Social-occupancy class of patients (people with some type of labor specialization)	15 (42)
Health Care Workers	4 (11)
Ethnic minority	9 (25)
Complex family	7 (19)
Moderate-severe severity of primary infection	26 (72)
Hospitalization in acute phase	27 (75)
Readmission after hospital discharge	2 (6)
Chronic diseases presence	30 (83)

Reinfection	0
Not vaccinated	20 (56)
Vaccinated covid-19 with 1, 2 or 3 doses	16 (44)
Covid-19 date in 2020	22 (61)
Covid-19 date in 2021	12 (33)
Covid-19 date in 2022	2 (6)

(): Denotes percentages

Table 3: Chronic Diseases in Patients Que Presentaron Complications Originated as a Consequence of the Acute Infection of COVID-19 or the Treatments Performed

CHRONIC DISEASES (WHO, ICD-10 GROUPS)	COMPLICATIONS ORIGINATED AS A CONSEQUENCE OF THE ACUTE INFECTION OF COVID-19 OR THE TREATMENTS PERFORMED
	N=36
-I Infectious	0
-II Neoplasms	4 (4)
-III Diseases of the blood	1 (1)
-IV Endocrine	20 (22)
-V Mental	5 (6)
-VI-VIII Nervous and Senses	4 (5)
-IX Circulatory system	24 (27)
-X Respiratory system	7 (8)
-XI Digestive system	11 (12)
-XII Diseases of the skin	0
-XIII Musculo-skeletal	7 (8)
-XIV Genitourinary	6 (7)
TOTAL chronic diseases*	89 (100)

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

Table 4: Initial Symptoms in COVID-19 Acute Phase in Patients Who Presented Later Complications Originated as a Consequence of the Acute Infection of COVID-19 or the Treatments Performed

SYMPTOMS*	INITIAL SYMPTOMS IN COVID-19 ACUTE PHASE IN PATIENTS WHO PRESENTED LATER COMPLICATIONS ORIGINATED AS A CONSEQUENCE OF THE ACUTE INFECTION OF COVID-19 OR THE TREATMENTS PERFORMED
	N=36
General (discomfort, asthenia, myalgia, fever, artralgiás)	50 (37)
Respiratory (cough, dyspnea, chest pain)	49 (36)
ENT (anosmia / ageusia, odynophagia, rhinorrhea, pharyngeal dryness-mucus, epixtasis)	17 (13)
Digestive (anorexia, nausea / vomiting, diarrhea, abdominal pain)	12 (9)
Neurological (headache, syncope)	4 (3)
Psychiatric (anxiety, insomnia)	2 (1)
Skin (chilblains, flictenas, rash)	1 (1)
Total symptoms*	135 (100)

The treatments carried out, mainly in hospitalization, were those corresponding to the existing protocols on the dates of presentation of the cases. These treatments included, in addition to appropriate medical procedures (for example, endotracheal intubation, high-flow oxygen therapy, chest drainage, prone decubitus, enteral nutrition, blood transfusion, etc.), antibiotics, corticosteroids, heparin, anticoagulation with acenocoumarol, antibody recombinant monoclonal (tocilizumab), anakinra (Immunomodulator; recombinant interleukin-1 receptor antagonist polypeptide), lopinavir/ritonavirhydroxychloroquine,

cough suppressants, bronchodilators, antihistamines, analgesics, NSAIDs, antidiabetics and hypotensives, among others.

Discussion

Main findings

The main results of our study were:

1. Patients tend to have more than one complication (1.44 in our study)
2. Respiratory system complications predominated (56%), which were mainly pneumonias

3. They not only occurred in older patients (39% were \geq 65 years), but in middle-aged patients
4. The complications predominated in men
5. They were slightly more frequent in those not vaccinated against covid-19
6. The complications were mainly in 2020
7. The complications predominated in patients with chronic diseases of the Circulatory system (27%) and Endocrine (22%)
8. The complications predominated in severe cases

Comparison with other studies

First of all, it should be noted that most researchers do not differentiate the terms of "persistent symptoms", "sequels" and "complications" of covid-19, using these words as interchangeable, when in reality they are different concepts that must be differentiated with definitions and clear criteria (10, 11, 31-34). In our study, a clear definition of "complications of covid-19" was used, but this overlapping of the criteria of long covid-19, sequelae and complications of covid-19 in the literature makes comparisons of results difficult.

It has been reported that most complications occurred in severe cases and in the hospital setting (35-37). Our study corroborates this fact, although the continued care of the GP allowed us to know the situation before hospital admission and upon discharge, as well as complications that did not require hospitalization.

Covid-19 is a multisystem disease, which can occur with complications at presentation or developing during the acute phase of the disease. A wide variety of complications have been reported. These complications can be 1) infectious (ranging from mild infections to life-threatening conditions; sepsis); 2) respiratory (decreased lung diffusing capacity for carbon monoxide, varying degrees of radiological abnormalities on chest CT scans, pulmonary fibrosis, respiratory failure, pneumothorax, and decreased respiratory muscle strength); 3) cardiovascular (myocarditis, cardiac arrest, ventricular fibrillation, acute myocardial infarction, high blood pressure, heart failure); 4) renal (acute renal failure and chronic kidney disease); 5) gastrohepatic (acute pancreatitis and pancreatic injury, severe intestinal obstruction, temporary dysbiosis of the intestinal microbiome); 6) thromboembolic (deep vein thrombosis, pulmonary thromboembolism); 7) neurological, and cerebrovascular infections (encephalitis, seizures, ischemic and hemorrhagic strokes, demyelinating diseases, and other conditions, such as major mood swings and cognitive decline); 8) mental (anxiety and depression); 9) endocrine (lipid disorders, obesity, newly diagnosed diabetes mellitus in patients after hospitalization and acute metabolic decompensation of pre-existing diabetes mellitus); 10) immunosuppression (due to an underlying pathology, for example, active malignant blood diseases, or due to the treatments these patients receive); 11) neuromuscular (myositis, rhabdomyolysis and Guillain-Barré syndrome); and 12) autoimmune and rheumatological diseases, among others (4, 6, 9, 28-59).

It has been reported that advanced age and being a man are risk factors for complications and greater severity of covid-19 (60, 61). Our results also suggest this data in relation to the male sex, but the complications not only occurred in older patients but in middle-aged patients.

It has also been pointed out that people who suffer from chronic diseases (such as diabetes and heart disease) are at greater risk of presenting complications and severity in covid-19. These excess risks were seen even in non-hospitalized patients with covid-19, although the risk of post-acute complications was higher in those who were sicker (3, 10, 53, 60). We also found that complications occurred in patients with chronic diseases, especially of the Circulatory system and Endocrine.

Regarding treatment complications, in our study, these were mainly due to instrumental interventions (for example, muscle hematoma, hepatic hematoma, hemoperitoneum, hypovolemic shock, as a cascade of complications after jugular cannulation). In any case, the treatments followed the norms established on the dates of acute infection, which were predominantly in the first year of the pandemic (2020) (62-64). In Spain at this data, the lineages of the coronavirus predominated were related closely to the initial Asian variants of SARS-CoV-2 (14, 15).

Limitations and strengths of the study

1. Case series studies are "numerator" studies only. It is not possible to calculate the frequency of appearance of the events.
2. The number of cases was relatively small.
3. 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), a wide range of complications originated as a consequence of the acute infection of covid-19 or the treatments performed throughout the all pandemic was found (from March 15, 2020 to October 31, 2022). The main complications were of the respiratory system (especially pneumonias), in middle-aged men, with severe acute covid-19, unvaccinated, with chronic diseases of the circulatory system and endocrine and during the year 2020. Given the wide range of possible complications that patients with covid-19 may experience there is a need for more integrated models of care to treat these patients, such as those that the GP can give.

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