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SEX-RELATED DIFFERENCES IN CLINICAL PRESENTATION OF COVID-19

FINAL DEGREE PROJECT

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"La invisibilització de les diferències entre sexes a la recerca biomèdica, és també una de les cares de la violència de gènere"

-Carme Valls Llobet-
Endocrinòloga especialitzada en medicina amb perspectiva de gènere.

CLARIFICATION: Before you begin reading this final degree project, we find it necessary to make the following clarification. Even though biomedical research and medicine use the terms "sex" and "gender" as interchangeably, they are totally different concepts. For this reason, in this project we want to highlight their differences. On one hand, "sex" concept is based on chromosomal configuration, hormones and mainly sexual organs. It can be understood in a binary way (male / female) but it would be more inclusive to refer it as a continuous spectrum where intersex people enter. On the other hand, gender is a social construction that can change according to culture. In our case, occident culture is mostly binary (male/Female) but we ought to keep in mind that gender is also a continuous and dynamic variable because there are more different gender identities.

In this project we focus on the biological role, that is why we use sex as a variable (male / female) except for the explanation of pandemic effects and for part of justification section of the work where we deal with the social role of women and then we use gender.

INDEX

1. ABBREVIATIONS

ACE2	Angiotensin-Converting Enzyme 2
ACovCS	Acute COVID-19 Cardiovascular Syndrome
AIDS	Acquired Immune Deficiency Syndrome
ARDS	Acute Respiratory Distress Syndrome
AKI	Acute Renal Injury
BMI	Body Mass Index
CAMFiC	Societat Catalana de Medicina Familiar i Comunitària
CD4	Cluster of cuadruple differentiation
CD8	Cluster of differentiation 8
CEIC	Comitè Ètic d'Investigació Clínica
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus 19 Disease
CoV	Coronavirus
DM	Diabetes Mellitus
DNA	Deoxyribonucleic acid
GPD	Gross Domestic Product
HC3	Historia Clínica Compartida de Catalunya
ICU	Intensive Care Unit
IFN	Interferon
Kg	Kilogram
M^2	Square Meters
MCR	Medical Research Council
MERS-CoV	Middle East Respiratory Syndrome-related Coronavirus
Mg	Milligram
NK cells	Natural Killer cells
PCR	Quantitative Polymerase-Chain-Reaction assay
pDCs	Plasmacytoid dendritic cells
RAAS	Renin-Angiotensin-Aldosterone System
RENAVE	Red de Nacional de Vigilacia Epidemiólogica
SARS-CoV	Sever Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Sever Acute Respiratory Syndrome Coronavirus 2
TLRs	Toll-like receptors
TMPRSS2	Transmembrane Protease Serine 2
UN	United Nations

WHO	World Health Organization
2019-nCoV	2019-novel coronavirus

2. ABSTRACT

Title: Sex-related differences in clinical presentation of COVID-19.

Author: Judit Río López

Background: Due to AIDS, Ebola and Zika epidemies, United Nations elaborate an analysis inform with recommendations for an effective response for future health crisis. One of the main recommendations is the importance of the gender perspective as a structural basis in all crisis policies, including research. This fact demonstrates it is key that information accuracy should be based on research segregated by sex and age.

However, to date, in the COVID-19 pandemic is not following these indications, research segregated by sex is being a minority. Consequently, it is already unclear if there are sex-related differences in clinical presentation of COVID-19 or even if these differences vary depending on age. It is currently known that the period highly infectiousness of COVID-19 is during the first week with symptoms.

Studying sex-related differences in symptom of COVID-19 during the first week with illness is not only key to containing the pandemic, but also not further magnifying social differences that the COVID-19 pandemic is exacerbating day by day.

Objective: We want to study main differences between females and males in clinical presentation of COVID-19: symptoms and recognizable signs by the patient) and its distribution in the first week with symptoms. As a secondary objective, we are going to study if differences in clinical presentation between sex in the first 7 days of symptomatology, could be influenced by age.

Design: This study will be an observational prospective cohort study.

Participants: In our study we will include people with symptoms of COVID-19 who tested positive for SARS-CoV-2 on quantitative polymerase-chain-reaction assay (PCR) or on rapid antigen test.

Data collection and analysis: A non-probabilistic consecutive sampling method will be used for data collection. We will assess the association between the dependent variables and sex by means of logistic regressions, controlling for the covariates.

Keywords: COVID-19, SARS-CoV-2, symptoms and sex.

3. BACKGROUND

3.1. CONCEPT OF COVID-19

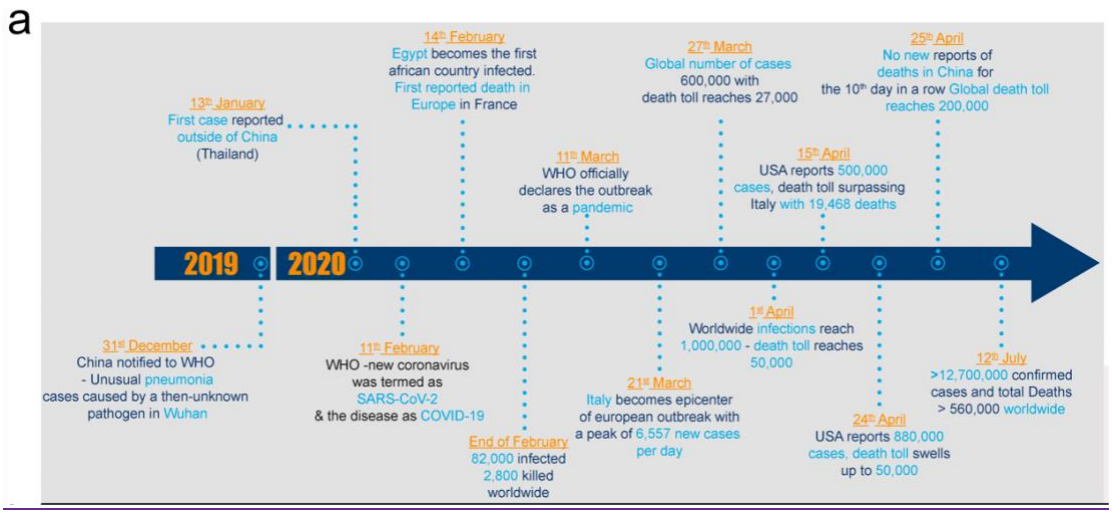
COVID-19 is the disease caused by a new coronavirus called SARS-CoV-2. This novel coronavirus was initially named 2019-novel coronavirus (2019-nCoV) (1). The name is now Sever Acute Respiratory Syndrome Coronavirus 2 (SARS CoV-2) (2).

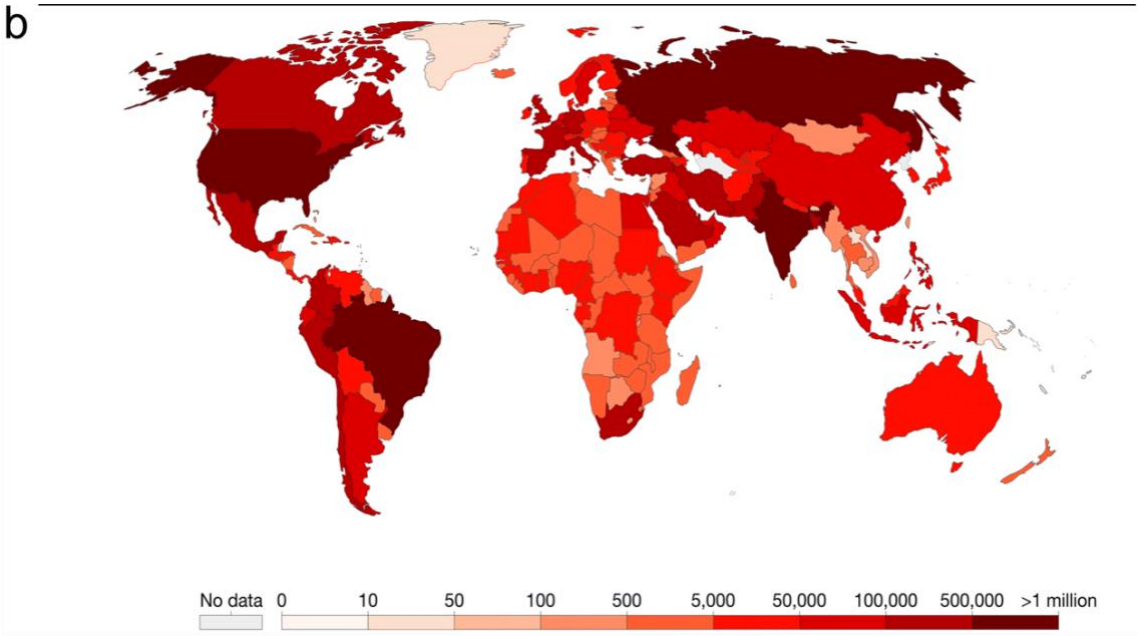
3.2. COVID-19, THE PANDEMIC

3.2.1. TIMELINE OF GLOBAL COVID-19 PANDEMIC:

In December 2019, an atypical pneumonia induced by a novel coronavirus was first reported in Wuhan, China (2). World Health Organization (WHO) was notified of this new virus on 31 December 2019, following a report of a cluster of cases with an unidentified form of viral pneumonia with shared history of visiting the Huanan seafood market in Wuhan, China (3). Since the first reported case, there has been a rapid increase in the number of cases, with outbreaks being reported in countries all over the world. WHO declared the outbreak as a Public Health Emergency of International Concern on January 30, 2020 and an official pandemic on March 11, 2020 with more than 118,000 cases in over 110 countries (4). To date of writing, SARS-CoV-2 have infected nearly 100 million people and caused more than 90 millions of deaths. Globally, as 17 January 2021, there have been 92.983.900 confirmed cases of COVID-19 and 2.009.781 deaths reported to WHO (4).

***FIGURE 1**: A) Timeline of the global COVID-19 pandemic to December 31st, 2019 to July 12th, 2020. B) World map shows global distribution and incidence of reported COVID-19 cases in each country, at the time of 12th of July 2020* (5).





"When you are thinking about a pandemic, you have to differentiate between what comes from being infected and what comes from being affected", points out Clare Wenham, assistant professor of Global Health Policy, London School of Economics and Political Science, UK. That is why we want to do a little review of indirect effects of COVID-19 pandemic: socioeconomical impact and mental health impact.

3.2.2. SOCIOECONOMICAL IMPACT

In order to control the risk of further spread among population, most countries adopted several public health measures to reduce person-to-person transmission of infection of SARS-CoV-2. The implemented measures were: face mask use, social distancing, movement restrictions, business interruptions, isolation of symptomatic patients and quarantine for individuals with history of contact with infected people and in some countries temporal lockdown (6,7). These measures largely affected economic activity. The unprecedented lockdown put in risk the economic activity in most countries. The World Bank (8) the deepest global recession in eight decades, with a 5.2% contraction in global gross domestic product (GDP) in 2020.

According to a study done by a Think tank dedicated to economic and social research (9), it warns that the impact of the pandemic is asymmetric and it has great potential to generate greater social inequality, since the jobs that have been most affected are those with the lowest incomes (hospitality, catering, cleaning, transportation, local commerce, etc.).

For this reason, as well as other inequalities, COVID-19 pandemic has exacerbated gender inequality. UN (United Nations) policy brief published in April 2020 "Across the globe, women

earn less, save less, hold less secure jobs, are more likely to be employed in informal sector. They have less access to social protections and are the majority of single-parent households. Their capacity to absorb economic shocks is therefore less than that of men". In August of 2020, Talha Burki published an article in The Lancet Infectious Diseases (10) which reflects some of the indirect impact of COVID-19 on women. Some of them are exposed bellow:

- 740 million women are employed in the informal economy and in developing nations, this work constitutes more than 2/3 of woman employment.
- During the lockdown mothers in UK were 1.5 times more likely than fathers to have either quit their job.
- The UN has warned that many women who have escaped from extreme poverty are at risk of falling back.
- 243 million women have experienced sexual or physical abuse at hands of intimate partner the last 12 months. Many of these women have been confined with their abuser. France, and dozens of other countries, reported in the first week of lockdown, gender violence had surged by 30%.

3.2.3. IMPACT IN MENTAL HEALTH

Economic distress, changes in job situation, social restriction, closed schools or telematic education, stress about getting infected and physical activity limitations are a potential trigger for a wide range of mental health problems in the short and long term, such as panic disorders, anxiety and depression (11).

There is a growing evidence showing an increase of phycological and psychiatric disorders during acute phase of the pandemic (11–13). As the economic impact, mental health, is worse in those with low socioeconomical status. The latest studies suggest that there are mental health inequalities and women are more affected than men (11).

Other vulnerable collective are healthcare professionals, in which women are overrepresented. A national multiple-cohort study of mental health impact of COVID-19 pandemic in Spain among healthcare workers (14) reported that 45% of health workers had a high risk of mental disorder as a result of the first wave of COVID-19. Also shows approximately 8,4% of hospital workers has 30-day suicidal thoughts and behaviors during the first wave of Spain COVID-19 pandemic. The study also showed that professionals more affected were nursing assistants and nurses, again a collective made up mostly of women.

3.3. COVID-19, THE DISEASE

3.3.1. EPIDEMIOLOGY

Around the world, at time to 17 January 2021:

- 92.983.900 people have been diagnosed with SARS-CoV-2 infection (4).
- 2.009.781 of people have died of COVID-19 (4).

We have to take into account, that not all cases have been diagnosed, in particular asymptomatic and specially in first pandemic months regarding the lack of test. Thus, the true number of both infections and deaths is probably much higher.

In Spain, according to reports made by Red Nacional de Vigilancia Epidemiologica (RENAVE) (15), which have collected data from May 10, 2020 to January 5, 2021, indicate that:

- In Spain, 1,748,941 cases of COVID-19 have been diagnosed.
- The age group with the highest incidence is the working age population, aged 15-59.
- 52,5% of cases are in women.
- 4.6% of cases are health and social health, being significantly higher in women than in men (6.9% vs. 2.1%). 78% of the health or socio-health personnel diagnosed with COVID-19 are women.

SEVERITY OF COVID-19

To assess the severity of COVID-19, governments used those variables: i) hospitalization ii) ICU admission and iii) deaths. In Spain 105.670 (6%) of the cases have been hospitalized, 9.130 (0.5%) admitted to the ICU and 21.921 (1.3%) people with COVID-19 have died (15). About those variables is interesting to report that:

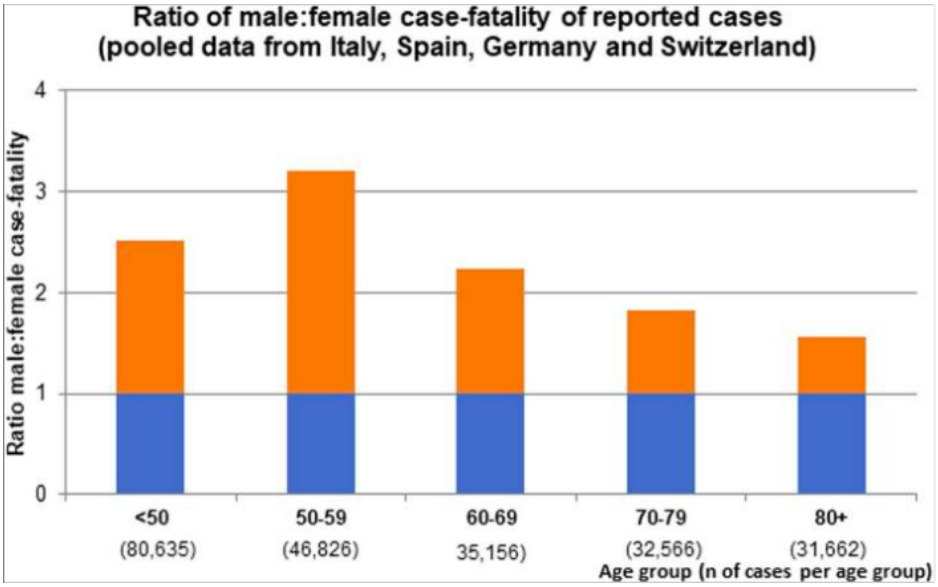
- *BETWEEN AGES:* In Spain hospitalizations and deaths increase with age, and are 28.7% and 12.8% over the age of 79, respectively (16). And it is a trend that is maintained in the other European countries (17).
- *BETWEEN SEXES*: In Spain, not all of these variables are disaggregated by sex. Data not sex-segregated is a global problem, according to *COVID-19 sex data tracker** December update(18), ”Only a half of the countries tracked reported any sex-disaggregated data on their COVID-19 epidemics over the pasts months” and “the sex of half a million deaths is also unknown”. Nevertheless, a Lancet article (10) exposes that although not every country provides sex-disaggregated data, a clear trend has emerged: 48 of 55 countries which are

providing sex-disaggregated data on COVID-19, show higher male dead among confirmed cases.

**COVID-19 sex data tracker* is the world's largest database of sex-disaggregated data on COVID-19 health outcome reported by WHO GLOBAL HEALTH 50/50.

- *SEX AND AGE:* There are significant differences in the male to female COVID-19 case fatality ratio (deaths divided by confirmed cases) between ages. Male to female case fatality ratio is elevated thought all ages but less pronounced at advanced ages. Figure 2 shows it.

FIGURE 2: *Ratio of male: female case fatality of reported cases. Data from Italy, Spain, Germany and Switzerland. A mortality ratio of 1 would reflect sex balance, the red bars reflect male predominance* (19).



TRANSMISSION OF COVID-19

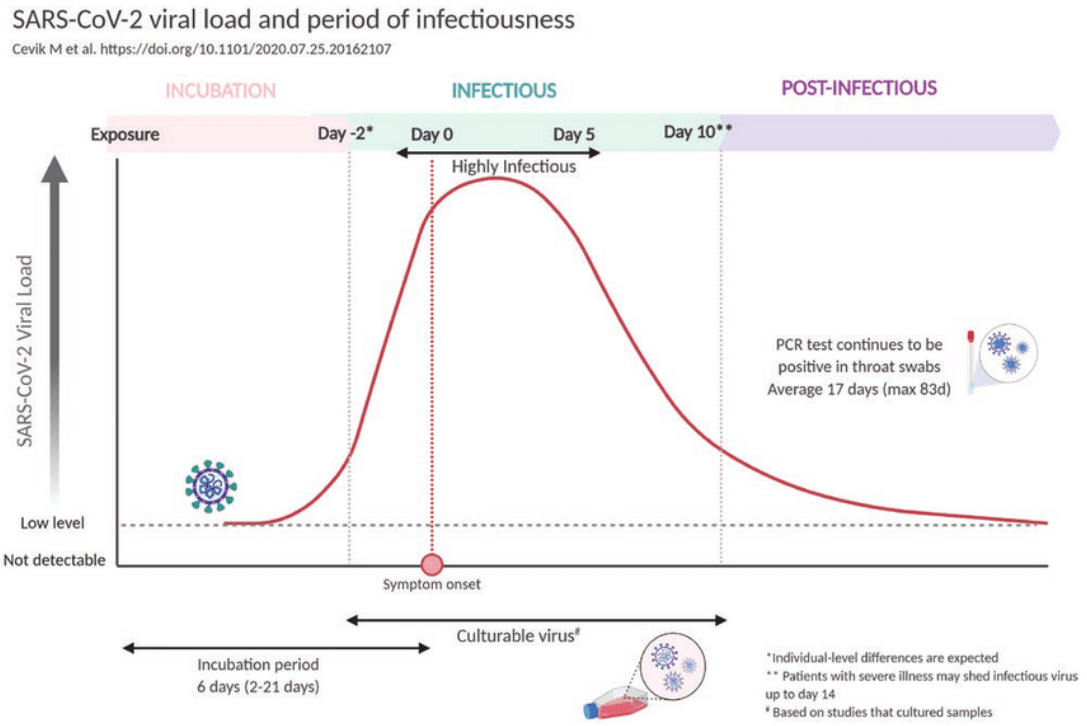
SARS-CoV-2 is highly contagious, to measure this variable epidemiologist use R_0. R_0 indicates the average number of infections one case can generate over the course of the infectious period on uninfected population. R_0 of COVID-19 is estimated around 2,0-3,0 (20).

The ability of an infected person to transmit the disease is directly proportional to the viral load of their respiratory tract (21). An excellent review on viral load dynamics and infectiousness was recently published (22). It exposes that the highest viral load in the respiratory tract is just before -one to two days before symptoms onset- or within the first five days after symptom onset. So, individuals with SARS-CoV-2 infection are likely to be most infectious the two days before the onset of symptoms and the first week with symptoms. The article emphasizes the importance of immediate insolation with symptom onset in the course of disease.

Asymptomatic individuals (those with no symptoms during the infection) can transmit the infection but their relative degree of infectiousness seems to be limited (21,23).

One of the main reasons why SARS-CoV it is minimal contagiousness compared to SARS-CoV-2, is because SARS-CoV highest viral loads were detected during the second week of symptoms enabling early case detection in community (24). That is why it is very important a quick diagnosis to isolate the infected person with COVID-19 as soon as possible.

FIGURE 3: *SARS COV-2 viral load dynamics and period of infectiousness* (25).



For more information of COVID-19 transmission, SARS-CoV-2 virology, molecular structure and life cycle in virus susceptible host cell see ANNEX 1.

3.3.2. RISK FACTORS

3.3.2.1. RISK FACTORS FOR COTRACTING SARS-COV-2 INFECTION

According to the latest published evidence (26–28) those are the risk factors to contract SARS-CoV-2 infection:

- Advanced age
- Immigrant of low- or middle-income country.
- Living in a senior living community
- Residing in a neighborhood with financial insecurity
- Housing insecurity.
- Level of education

- Health or socio-health worker.
- Chronic kidney disease
- Cancer
- Dementia
- Chronic liver disease
- Vitamin D deficiency

3.3.2.2. RISK FACTORS FOR SEVERE COVID-19

- **Age:** The mortality rate of COVID-19 increases with age (29,30). According to the data of Red Nacional de Vigilancia Epidemiologica de España (RENAVE) (16) the percentage of hospitalizations and deaths with COVID-19 increases with age, reaching 29 % and 12.9% in those over 79 years of age, respectively.
- **Sex:** Not every country provides sex-disaggregated data, but a clear trend has emerged: distribution of cases seem to be about equal globally or more in females, but in european region males account 70% of admissions to intensive care unit and 57% of deaths from COVID-19 (10).
- **Smoking:** Smoking, current or past, is associated with severe COVID-19 and higher mortality in COVID-19 patients (31). The pathophysiological explanation may be that smokers experience increased expression of ACE2 receptor in their upper respiratory tract (32).
- **Cardiovascular disease:** Latest systematic reviews and meta-analysis indicate that heart failure, hypertension, acute cardiac injury, arrhythmia and coronary artery disease were significantly associated with higher rates of ICU admissions and COVID-19 mortality (33,34).
- **Diabetes Mellitus (DM):** People with type 2 DM present a greater risk of severe COVID-19 (35). People with type 1 DM or gestational DM may also present a higher risk of severe COVID-19, but there is limited evidence in these groups (36).
- **Chronic respiratory disease:** Chronic obstructive pulmonary disease (COPD) is associated with severe COVID-19. People with COPD have over five-fold increased risk of severe COVID-19 (37), instead of, a systematic review and meta-analysis reported no assosiation between asthma and severe COVID-19 (38). Evidence is limited with other chronic lung pathologies such as cystic fibrosis (35).
- **Chronic kidney disease:** The presence of chronic kidney disease increases the risk of severe COVID-19 and acts as an independent risk factor for developing acute kidney damage as a complication of COVID-19 (39).
- **Chronic liver disease or non-alcoholic fatty liver disease:** Patients with cirrhosis or non-alcoholic fatty liver have a higher risk of death from COVID-19 (40,41). The 30-day

mortality rate is higher in patients with cirrhosis, the leading causes of death are respiratory complications and sudden worsening of liver function (42).

- **Cerebrovascular disease:** Affectation on blood supply to the brain such as stroke might increase risk of severe illness from COVID-19 (35).
- **Dementia:** Dementia and Alzheimer's were the most common comorbidities in COVID-19 related deaths between March and June 2020 in England (35).
- **Cancer:** People with malignant neoplasm are 76% more likely to have severe COVID-19 than those who do not have malignant neoplasm (43). Specifically, hematological neoplasms present a higher risk compared to solid neoplasms (44).
- **Sickle cell disease** (35).
- **Use of corticosteroids** (>=10mg/day prednisone) **and use of disease-modifying antirheumatic drugs** (45).
- **Solid organ transplantation:** COVID-19 hospital admission rates for solid organ transplant recipients are disproportionately higher than non-transplanted patients (46).
- **Obesity:** Individuals with Body Mass Index ≥ 30kg/m2 have a higher risk of suffering from severe-COVID-19. They also have a higher risk of complications such as venous thromboembolism or acute renal failure (47).
- **Pregnancy:** Pregnancy should be considered a risk factor for severe-COVID-19 (48).

3.3.3. PATHOGENESIS OF SARS-COV-2 INFECTION

Similar to other coronaviruses, SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor on epithelial cells (49). This target host receptors -ACE2- are principally expressed in human airway epithelial cells, which explains respiratory symptoms (25).

Clinicians have observed a spectrum of symptoms indicating that COVID-19 is a complex disease which no way consist only of respiratory infection. Emerging literature suggest that cardiovascular, hematological, gastrointestinal, hepatobiliary, endocrinologic, renal, neurologic, ophthalmologic and dermatologic systems can be affected (50).

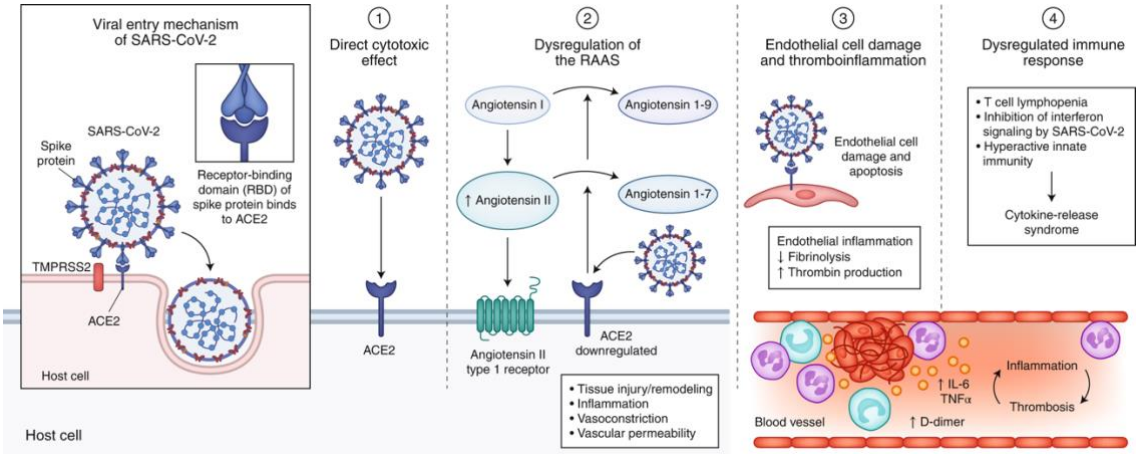
Key mechanism that may can explain the pathophysiology of multi-organ injury for infection of SARS-CoV-2 include:

1) **Direct viral toxicity:** A part of respiratory tract, the receptor ACE2 is also found in renal, myocardial, neurologic, pharyngeal and gastrointestinal tissues. Lymphocytic endothelitis of lung, liver, kidney and heart has been observed in postmortem pathology examination

as well myocardial infarct and as liver cell necrosis in patients who died of COVID-19 (50,51). These findings may explain partially extrapulmonary symptoms of COVID-19.

2) **Endothelial cell damage and thromboinflamation**: Infection of SARS-CoV-2 can cause endothelial injury which would be characterized by high levels of von Willebrand factor. In addition, infection will cause endothelialitis. These two mechanisms can trigger amount of thrombin production, activate complement pathways and inhibit fibrinolysis creating thromboimflamation and leading to vascular dysfunction and microthrombus deposition. Hypoxia-mediated hyperviscosity subsequent to acute lung injury may also contribute to prothrombotic state (51–53).
3) **Dysregulation of immune response and cytokine-release syndrome:** These two mechanisms are key in severe-COVID-19 presentations (54). More explained in next section 3.3.4.
4) **Dysregulation of renin-angiotensin-aldosterone-system (RAAS):** RAAS is a cascade of regulatory peptides that regulates fluid and electrolyte balance, vascular permeability, blood pressure and tissue growth (55). For the correct function of this system is necessary ACE2, which divide angiotensin I into inactive angiotensin 1-9 and divides angiotensin II into angiotensin 1-7, which has a vasodilator, antifibrotic and anti-proliferative proprieties. Thus, ACE2 is a counter-regulator of RAAS pathway. This can lead us to suspect that RAAS dysregulation as a consequence of downregulation of ACE2 related to viral entry, can also be involved in physiopathology of COVID-19. Moreover, may have implications for organ-specific clinical manifestations of COVID-19 as renal or cardiovascular symptoms (50,56).

FIGURE 4: *SARS-CoV-2 entry in host cell (far left) and proposed mechanism for COVID-19. (1)Direct virus-mediated cell damage (2) Dysregulation of the RAAS (3) Endothelial cell damage and thromboinflmation and (4) Dysregulation of immune response and hyperinflammation* (50).



3.3.4. HUMAN IMMUNE RESPONSE AGAINS SARS-COV-2

Immune responses to SARS-CoV-2, as well as most viruses, consist of two phases:

a) **Innate immunity response:** It involves rapid containment mediated by antiviral Type 1 interferons (IFNs), macrophage and neutrophil activation which leads to proinflammatory cytokine production and NK cells (57).
b) **Adaptative immunity response**: It is active when innate immunity response is not able to eradicate the pathogen. This response generates a sophisticated and specific immunity that should be able to eradicate the pathogen and -hopefully- produce long-lasting immunological memory. It is a coordinated attack by CD8+ cytotoxic T cells, CD4+ T helper cells, plasma cells, specific antibody and finally memory T and B cell subsets (57,58). SARS-CoV-2 antibody response is often detectable by day 14 (25).

The cases who have an effective innate and adaptative immune response able to containment virus-replication, will not develop severe COVID-19. This is why is crucial a fast and efficient innate response and especially of Type 1 INFs, for the viral replication containment (25).

Those cases in which there is a late or ineffective activation of innate immunity led to excessive viral replication and it is then when severe symptomatology occurs (25).

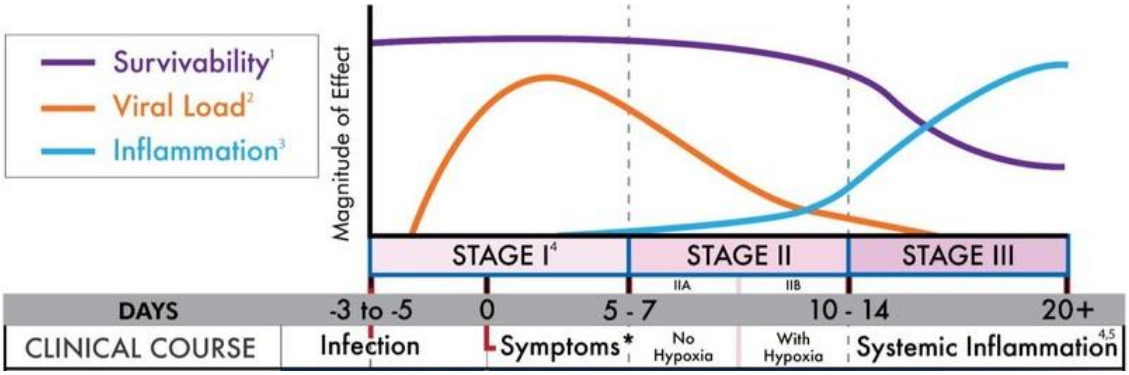
This excessive viral replication will have two consequences:

1- Spread of SARS-CoV-2 infection beyond the upper respiratory tract: Causing pneumonia, Acute Respiratory Distress Syndrome (ARDS) and septic shock. Furthermore, SARS-CoV-2 have the capacity to spread to those tissues with ACE2 expression, especially vascular endothelium, resulting in multiorgan failure with vaso-occlusion, enhanced coagulation and impairment of vital functions (25,59).
2- Exaggerated proinflammatory state: This excessive viral replication leads to recruitment of neutrophils and monocytes that will secrete large amounts of proinflammatory cytokines, generating a cytokine storm or cytokine realize syndrome. Cytokine storm will aggravate air exchange capacity by causing lung tissue damage, resulting in pulmonary edema, more occlusion of small airways. This process will contribute to the physiopathogenesis of ARDS (59).

WHY THERE ARE CASES WHOSE INNATE IMMUNITY ACTIVATION IS LATE OR INEFFECTIVE?

SARS-CoV and MERS-CoV have mechanisms of evasion of the immune response based mainly on reduction of the response of INF type 1. As we have exposed Type 1 INF is crucial to inhibit viral replication. Taking into account the sequential similarities between SARS-CoV-2 with SARS-CoV and MERS-CoV it could be possible that SARS-CoV-2 adopts similar pathway to evade immune response because with delayed type 1 IFN production allows for highly efficient viral replication. (58).

FIGURE 5: *COVID-19 Clinical Stages. STAGE I: Infection in upper respiratory tract. Initial symptoms. If initial host immune response is able to control the infection, it will lead to the recovery. STAGE II: Infection of lower respiratory tract. This stage is divided into two sub-stages IIA if the patient is NOT hypoxemic and IIB if the patient is hypoxemic. STAGE III: Acute respiratory distress syndrome (ARDS), characterized for severe infection and cytokine storm. Adapted from* (60)



For more information about COVID-19 natural history see ANNEX 2.

3.3.5. SEX RELATED DIFFERENCES IN IMMUNE RESPONSE AND COVID-19 PROGRESSION

Females and males differ in their immunological response to self-antigens and external (for example, viruses, bacteria, parasites, allergens…) and show distinctions in innate and adaptative immune responses (61).

Some of these sex-based immunological differences are constant throughout life, whereas others show up before aging or after puberty. Precisely, this fact demonstrates that not only is important the chromosomic factor, but also there is a crucial role of sexual hormones (61–63).

It is remarkable, these immunological sex differences contribute directly to variations in host susceptibility to infectious disease and as a consequence, can contribute to different clinical characteristics between sexes (63).

In this section we discuss sex related differences in immune response against SARS-CoV-2.

3.3.5.1. SEX DIFFERENCES IN SARS-COV-2 ENTRY

At the entrance of SARS-CoV-2 to the host cells may reside some of the key points that explain the prognostic differences between female and male. The key components to SARS-CoV-2 entry are ACE2 and TMPRSS2.

1) PAPER OF ACE2

As discussed in the previous point, ACE2 is the receptor that allows the entry of SARS-CoV-2 into human cells, specifically there is a binding between the spike (S) glycoprotein of SARS- and the ACE2 receptor (64,65).

Regarding ACE2, a lower expression of ACE2 has been correlated with reduced risk to present sever COVID-19 (66). Although ACE2 is encoded by the X chromosome, studies have demonstrated that ACE 2 expression is higher in sputum of males (67) and in circulating plasma concentrations of male with heart failure (68,69). This could be the explication for the higher virus entry and therefore the worse prognosis.

Data suggests that those differences in ACE2 levels can be explained by the paper of estrogens, which downregulates the expression of ACE2 (70). These findings lead us to think that estrogens play a protective role behind ARDS and as a consequence protect premenopausal and pregnant female behind developing severe COVID-19 (57). Emphasizing the term premenopausal since, postmenopausal female has a radically different hormonal pattern.

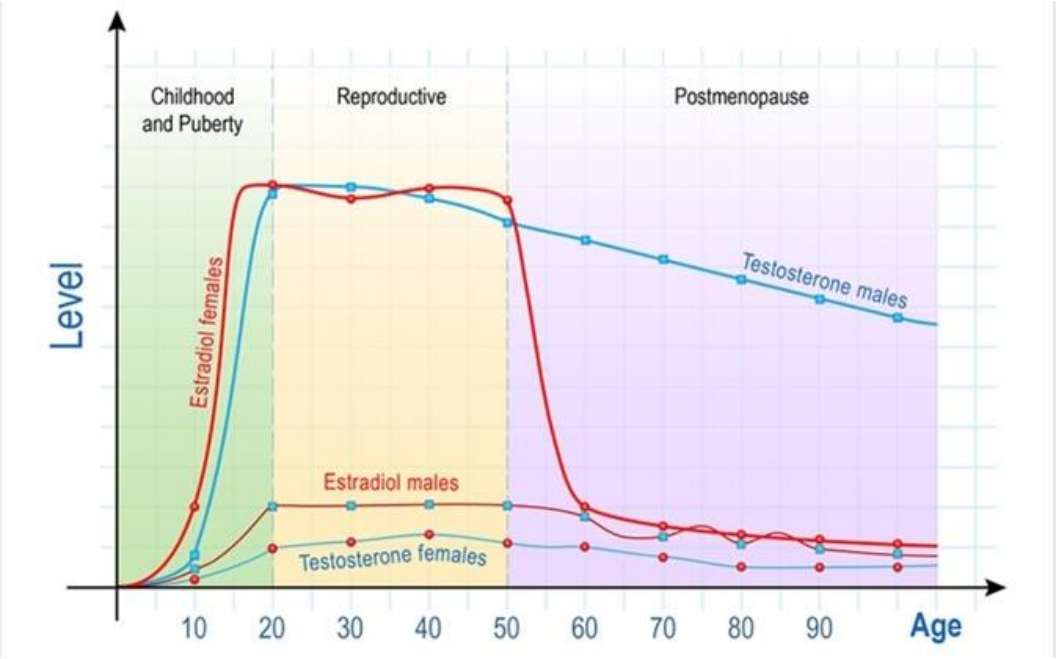
However, the role of ACE2 in SARS-CoV-2 infection is likely more complex since it also has an important anti-inflammatory function ACE2 is an enzyme that catalyzes the reaction in which angiotensin II passes angiotensin 1-7. Angiotensin 1-7 plays an important role on activating interferons during respiratory tract infections, promoting lung function (68,71).

2) PAPER OF TMPRSS2:

The expression of transmembrane protease serine 2 (TMPRSS2) has been described to facilitate virus entry (64,65).

The expression of TMPRSS2 is enhanced by the action of androgens. Studies have demonstrated that androgen deprivation therapies for prostate cancer provides partial protection against SARS-CoV-2 infection. Besides, there are reports of high rates of androgenetic alopecia from hospitalized severe COVID-19 patients. This leads us to think that androgen sensibility is a likely determinant of COVID-19 severity, and as a consequence males -except the children- are more susceptible host than females due to this hormone pattern (72,73).

FIGURE 6: Sex hormone production in humans through life. (74)



In conclusion, there are substantial sex-related differences in SARS-CoV-2 entry. Studies are needed to determine whether ACE2 expression in upper respiratory tract and lung tissue differs between males and females during SARS-CoV-2 infection and whether in infected female there is a potentiation of ACE2 expression resulting in an anti-inflammatory action that gives a better prognosis. But the emerging understanding of the mechanism lead us to consider males as more susceptible host for SARS-CoV-2 than premenopausal females. This can be the reason why ratio of male:female case fatality is less elevated at advanced ages (57).

3.3.5.2. SEX DIFFERENCES IN INNATE MMUNE RESPONSE AGAINS SARS COV 2

In general, females develop stronger adaptative and innate immune response against most viral infections and vaccines (61) and significant sex differences in B and T cells function and induction of type I interferons – including IFN-α and IFN-β- responses have been described. (75)

Specifically, SARS-CoV-2 is detected in nasal swabs for longer periods of months in males than in females, suggesting that males (76,77) have a reduced capacity to restrict viral replication than females. The current studies point out that these differences may be related to the response of INF and the expression of TLRF.

Infections of ARN virus, as SARS-CoV-2, are detected by Toll-like receptors (TLRs), including TLR7. These receptors stimulate plasmacytoid dendritic cells (pDCs) to produce interferons alpha and Betha (IFN-α and IFN-β). These interferons have showed the capacity to inhibit SARS-CoV-2 in cultured cells (78). TLR7 is encoded by the X chromosome and studies demonstrated higher TLR7 protein expression in females than males leukocyte population (79). Also, several studies have showed that plasmacytoid dendritic cells produce more IFN-α and IFN-β in females than males (80). A retrospective study suggests that using IFN-α as a therapeutic intervention in early SARS-CoV-2 infection can reduce mortality. However, there's a potential bias because were included few females. (81). It is remarkable other study which have showed genetic loss-of-function variants of TLR7 in four man with sever COVID-19 (82), further highlighting the important role of TLR7 and IFN in COVID-19 pathogenies.

In conclusion, emerging evidence is highlighting female immune system have the efficient mechanisms to restrict virus replication and therefore prevent the spread of SARS-CoV-2 infection through superior respiratory tract.

3.3.5.3. SEX DIFFERENCES IN ADAPTATIVE IMMUNE RESPONSES AGAINS SARS COV 2

Together with B and T cells, antibodies are the most important part of the adaptative immune system.

Several studies have shown that female develop more antibodies and more quickly to face infections and vaccinations than males. Studies in mouses have reported that hormones could be the explanation for these sex differences: testosterone decreases the development of antibodies while estrogens promote his formation's (61,63). Regarding vaccination, males with the worst response to Influenza vaccine have also been shown to be males with high testosterone levels. (83).

Table 1 expose a summary of the response to different vaccines by sex and age (61).

On the chromosomal level, it has also been found that the X chromosomes encode proteins that contribute to better induction of antibodies as well as their maintenance (61).

TABLE 1: Sex differences in response to vaccines in humans (61).

Target group	Vaccine	Sex difference in Immune response	Sex difference in adverse reactions	Age (years)
Children	Hepatitis B	Greater in females	Not defined	<12
	Diphtheria	Greater in females	Not defined	<2
	Pertussis	Greater in females	Not defined	<2
	Pneumococcal	Greater in females	Not defined	6–9
	Rabies	Greater in females	Not defined	6–9
	Measles	Greater in females or equivalent in both sexes	Increased in females	<3
	RTS,S vaccine against malaria	Greater in females	Increased in females	<2
	Human papillomavirus	Greater in females	Increased in females	5–17
Adults	Influenza	Greater in females	Increased in females	18–49
	Hepatitis B	Greater in females	Increased in females	>18
	Herpes virus	Greater in females	Not defined	>18
	Yellow fever	Greater in females	Increased in females	>18
	Rabies	Greater in females	Not defined	>18
	Smallpox	Greater in females	Not defined	>18
Aged adults	Influenza	Greater in females	Increased in females	>65
	Td/Tdap	Greater in males	Increased in females	>65
	Pneumococcal	Greater in males	Increased in females	>65
	Shingles	Not defined	Increased in females	>65

Analysing table 1, we see that there is a better response to vaccines in female than males, but this difference becomes not so evident in the elderly population. This demonstrate that not only exist differences between immune system of males and females, but also, between ages there are important immune variances as is not the same to talk about a young female -with high levels of estrogens - than about an elderly female -with low levels of estrogens-. For this reason, it is vital to analyse the data segregated by sex and age (61).

3.3.6. CLINICAL FEATURES OF COVID19

3.3.6.1. SPECTRUM OF CLINICAL MANIFESTATIONS.

In the past months, a plethora of symptoms have been described, indicating that COVID-19 is a complex disease which it is not only a respiratory infection.

The spectrum of symptoms of COVID-19 can be to asymptomatic to Acute Respiratory Distress Syndrome, which is a type of respiratory failure characterized by shortness of breath (dyspnea), tachypnea and cyanosis (84). But there's also other extra-respiratory symptoms -musculoskeletal, gastrointestinal among others-. Recently an excellent review has been published in the journal

Nature on extrapulmonary presentation in COVID-19 patients (50). Here are the possible clinical manifestations of COVID-19:

0- Asymptomatic infection: According to a living systematic review and meta-analysis 20% of people infected with SARS-CoV-2 remained asymptomatic, but biases in study designs limit the certainty of this estimate (21).

1- Respiratory symptoms: Most prevalent respiratory symptoms are fever, cough and shortness of breath. According to a systemic review, including 148 articles comprising 24,410 hospitalized patients with COVID-19, the most common symptoms were fever (78%), cough (57%) and fatigue (31%). The limitation of this review is the individuals of the included studies are hospitalized patients, therefore, they are the one's who have moderate-severe disease. It is likely that this review over-estimate the true prevalence of symptoms in the population (85). During the last months, much cohort data has been published. Nevertheless, almost all data applies to patients who were admitted to hospitals, indicating selection bias towards more symptomatic and severe patients (86–90).

2- Musculoskeletal symptoms: Including myalgia, joint pain, headache and fatigue, its prevalence is 15-40%. (87,89). A recent review shows headache was observed in 11-35% of hospitalized patients with COVID-19 (91).

3- Gastrointestinal symptoms: Including diarrhoea, nausea, vomiting, abdominal pain and anorexia. In the early Chinese studies, gastrointestinal symptoms were rarely seen, a systematic review and meta-analysis of 29 early studies -of which the majority are from China- reported 21% anorexia, nausea and/or vomiting (7%), diarrhoea (9%) and abdominal pain 3% (92). In the USA and Europe, higher prevalences of symptoms have been shown, for example, a study carried out in the USA shows that 34% of hospitalized patients suffered from anorexia, 33% from diarrhea and 26% from nausea) (93). In a register of 15.111 COVID-19 hospitalized patients of Spain, done for SEMI -Sociedad Española de Medicina Interna- indicates diarrhoea in 23,7%; nausea and vomiting were not studied (90). There are no studies showing whether these differences are due to geographical particularities or whether non-respiratory symptoms were not taken into account in early studies in China (50).

   Has been reported that gastrointestinal symptoms may be associated with a longer duration of illness but have not been associated with increased mortality (50).

4- Otorhinolaryngological symptoms: Including: rhinorrhoea, nasal congestion, sneezing, sore throat, anosmia and hyposmia. These symptoms are especially present in those people with mild or moderate COVID-19 and therefore those who do not require admission to the ICU (94).

Interestingly, these symptoms, like gastrointestinal symptoms, are seen much more in studies in Europe than in Asia. But it is again unclear whether it is due to geographical variations or because not initially recorded in China (86). In a study conducted in the US and UK a total of 2,618,862 participants including 28,401 confirmed cases of COVID-19, reported their potential symptoms of COVID-19 using a telephone application. In this study, it was found that 65% of the confirmed COVID-19 had a loss of smell, while only 21% of those who had a negative test had it. This is why it is believed that the loss of smell can be a good guide symptom for suspected COVID-19 (95).

5- Cardiovascular symptoms: There is a growing evidence of direct and indirect effects of COVID-19 in cardiovascular system. Clinically, numerous cases in which the infection of COVID-19 manifests with an acute cardiovascular syndrome, termed ACovCS (Acute COVID-19 Cardiovascular Syndrome) (96).

   Beside ACovC, a wide array of cardiovascular manifestations is possible: acute coronary heart syndrome, heart failure, acute cor pulmonale, cardiogenic shock, arrhythmia and myocarditis.

   Cardiac arrhythmias, including new-onset atrial fibrillation, ventricular arrhythmias and heart block occurred in 17% of hospitalized patients and 44% of patients in the ICU settings in a study from Wuhan, China. In New York in a multicentre cohort, 6% of 4,250 patients with COVID-19 had prolonged QTc at the time of admission (97).

   For this reason, the emerging evidence argue that in the face of a seemingly typical acute coronary syndrome, COVID-19 should be considered within the differential diagnosis, even in the absence of cough and fever (98,99).

6- Thrombosis, embolism: Thrombotic complications were first reported from ICUs in China and Netherlands in up to 30% of patients with COVID-19, including deep thromboembolism (DVP) or pulmonary embolism (PE) (50). Acute pulmonary embolism have been shown to occur mostly in critical or severe COVID-19, but also in mild and moderate COVID-19 presentations (100). In a retrospective multicentre study with 1,240 hospitalized patients with COVID-19, 8,3% had evidence for Pulmonary Embolism. In a multivariable analysis, male gender, large time from symptom onset to hospitalization, anticoagulation with prophylactic dose and elevated C-reactive protein were associated with developing PE (101).

7- Neurologic and neuropsychiatric symptoms: There is no clear evidence that SARS-CoV-2 has direct effects on the CNS (86). However, neurological symptoms have been reported in COVID-19patients, in a systematic review published by The Lancet (102) they found that the most common neuropsychiatric symptoms were: agitation, temporal-spatial disorientation, altered consciousness, insomnia, memory impairment.

   A multicentre observational study conducted in different hospitals in the New York metropolitan area showed that 13.5% of COVID-19 patients detected neurological disorders. Also, they found

those neurological disorders were associated with increased risk in-hospital mortality and decreased likelihood of discharge home. The most common diagnoses were: metabolic-toxic encephalopathy (6,8%), seizure (1,6%), stroke (1,9%) and hypoxic-ischemic injury (1,4%) (103). In addition, there are several observational series of specific neurological features as Guillain–Barré syndrome(104), myasthenia gravis (105) and Miller Fisher Syndrome (106).

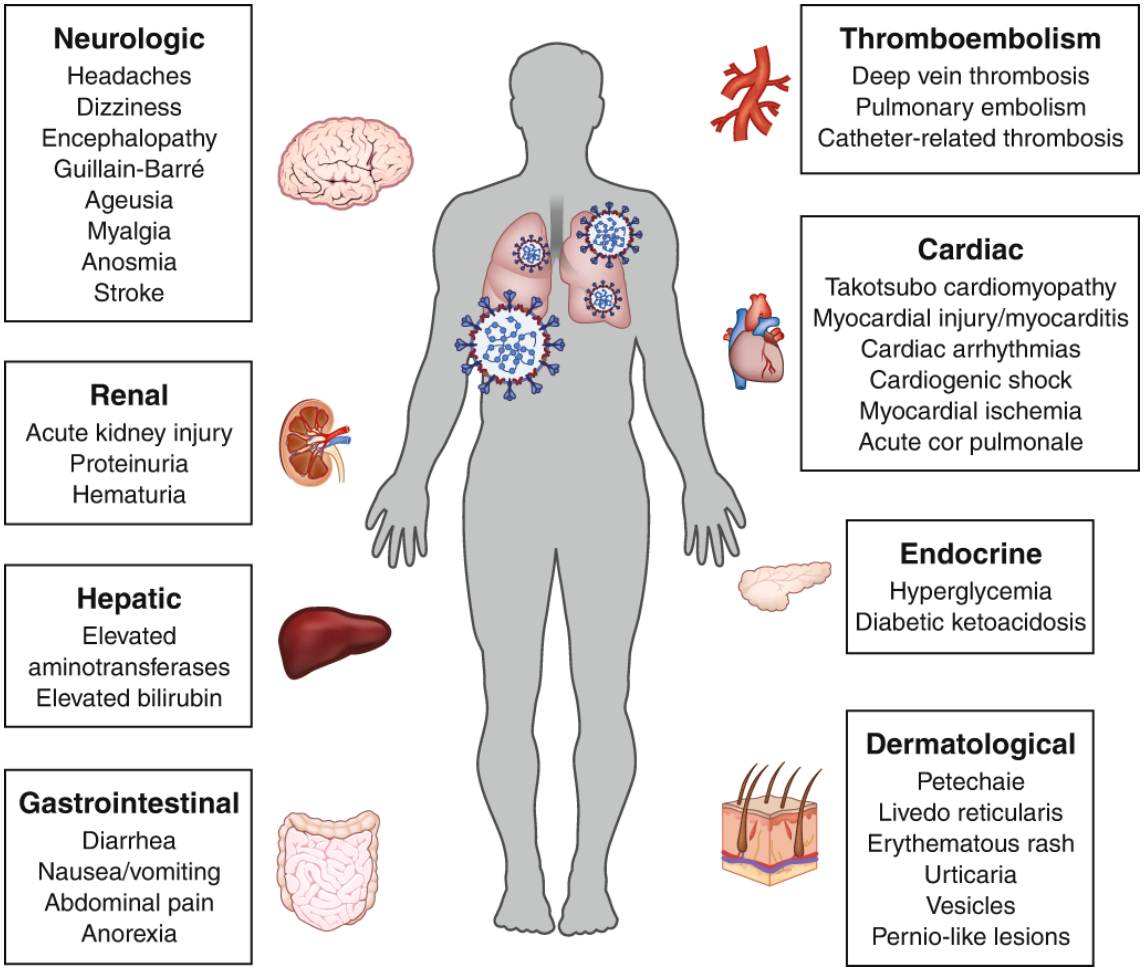
8- Dermatological symptoms: The dermatologic manifestations of COVID-19 were first reported in Italy, in a single-centre observational study, with a proportion of 20% of hospitalized patients. The cutaneous manifestations included erythematous rash, widespread urticaria and chickenpox-like vesicles (107). More recent studies have shown that the most prominent phenomenon is the so-called "COVID toes" are chilblain-line lesions in acral areas. These lesions can be asymptomatic, painful or sometimes itchy. "COVID toes" are more frequent in patients with mild- and moderate-COVID-19 (108).

   However, dermatologists point it should be kept in mind that not all cutaneous manifestations seen in patients with COVID-19 can be attributed to the SARS-CoV-2 infection. Co-infections or medical complications have to be considered (86).

9- Kidney affectation: A substantial portion of patients with severe-COVID-19 may show signs of kidney damage, most common clinical manifestations of this kidney damage are: Acute Kidney Injury (AKI), haematuria, proteinuria, metabolic acidosis and electrolyte abnormalities (hyperkalaemia, hyponatremia and hypernatremia) (50). A retrospective study analysed data from 5,449 positive COVID-19 patients admitted to 13 hospitals in the New York metropolitan area detected: Microscopic haematuria in 36,5% of patients, AKI developed in 36,6%, of these 14,3% required renal replacement therapy (109).

10- Endocrine manifestations: Clinical findings relating to the endocrinologic system are: hyperglycaemia and ketoacidosis including that in patients with previously undiagnosed diabetes or no diabetes (50). In a retrospective study from China, among a group of 658 patients hospitalized for COVID-19 6,4% presented ketosis in absence of diarrhoea or fever; and of these 64% did not have underlying diabetes (110).

FIGURE 7: Common extrapulmonary manifestations of COVID-19 (50).



In ANNEX 3 there is a summary of frequencies of principal symptoms of acute SARS-CoV-2 infection.

3.3.6.2. SEX DIFFERENCES IN CLINICAL MANIFESTATION OF COVID-19

According to sex-differences in immune system displayed in point 3.3.5.3, based on a different innate immunity, factors related to sex chromosomes and steroid hormones, it seems that females, are less susceptible to have complications related to viral infections compared to males. As a consequence, females may present different symptoms related to SARS-CoV-2 infection.

Even so, to date, there is no clinical study describing the sex differences in clinical features of COVID-19. Furthermore, in most of published studies, females are underrepresented in published evidence. The percentage of female are between 35-43% (87,89,90,97,111–113) taking into account that many studies do not report this data. Part of this is because the authors only included hospitalized patients, and hospitalized patients are majority (54%) males.

The fact that only the hospitalized population is being studied implies that mild or moderate symptoms remains unclear. Mild and moderate symptoms are the ones that women suffer most frequently (114).

An European Multicenter study (114) which aimed to describe clinical characteristics of mild-to-moderate COVID-19 patients, defined as patients who not require hospitalization in intensive care unit, concluded 1) The clinical presentation of mild-to-moderate patients in Europe mainly consist of headache (70%), loss of smell (70%), nasal obstruction (67%) and asthenia (63%). Thus respiratory symptoms as dyspnoea and fever would be more prevalent in moderate-to-severe patients. 2) There are substantially differences in clinical presentation between sexes. Loss of smell, headache, nasal obstruction, sore throat and fatigue seems to be more frequent in females. Males more frequently suffered from cough and fever. Females seems to have less complications but are more susceptible to develop post-infectious olfactory dysfunction. 3) there is substantially differences in clinical presentation between ages: Elderly individuals more frequently presented fever, fatigue, loss of appetite and diarrhoea while the young ones have more frequently ear, nose and throat symptoms as loss of smell, nasal obstruction, rhinorrea, headache and throat sore.

This study has important limitations, older patients are unrepresented (94% of participants were under 60 years of age) and the researchers only asked for general symptoms and otorhinolaryngological symptoms.

Another study done in non-hospitalized patients with the objective of determining the differences in olfactory and oral disorders of COVID-19 between the sexes (115), found that rhinorrhea was more frequent in females. We must bear in mind that the sample was small (N: 128) and there were no comorbidities as a covariate.

The official Spanish public data on the clinical characteristics of COVID-19 patients do not disaggregate by sex either (16). But, in the data published on COVID-19 cases in health workers (116) show that females have more digestive symptoms (diarrhoea or vomiting) and sore throat than males.

In conclusion, the available evidence segregated by sex seems to indicate that there are differences in clinical presentation, but there are few studies and with severe limitations.

4. JUSTIFICATION

We are currently immersed in a global pandemic that, apart from causing one of the most socio-economic impact in recent decades, it is increasing social inequalities, including sex inequalities. Scientific research is not independent of this inequality, but often reproduces it.

Nowadays, there is no doubt that exists sex-specific health needs based on biological difference between sexes, both by the chromosomal factor and by the hormonal factor. There is great scientific support to affirm that at the immune level there are important differences. This translates, among other things, into different manifestations in front of viral infections such as SARS-CoV, hepatitis C virus, Zika virus, respiratory syncytial virus, human immunodeficiency virus 1 (HIV-1), and influenza virus (62). These biological sex-related differences can be maintained throughout life or may vary according to age, for this reason, apart from segregation by sex, is essential also, segregation by age.

However, the underlying biological sex differences, there is little scientific evidence to account for these sex-related differences, and studies of COVID-19 are not an exception (117).

To date of writing, even remains unclear if there are differences of clinical presentation of SARS-Cov-2 infection between sexes. According to the few evidence published about seems to indicate that there are differences. Nevertheless, these studies have important limitations that must be considered such as: 1) Small sample studies 2) The participants are mostly hospitalized people and therefore only the most severe symptoms are contemplated 3) Most studies are done with data collected in the first wave which had shortage of diagnostic tests and therefore underdiagnosis of non-severe cases.

In infectious diseases it is vital to know the symptoms to achieve an early diagnosis and thus reduce transmission within the community. According to the latest studies, people with COVID-19 are contagious especially in the first 5-7 days after the onset of symptoms (22). For this reason, in order to achieve an effective containment of SARS-CoV-2, it is crucial to know well the clinical presentation especially during the first week of symptomatology. In Spain, It is observed that the average from the onset of symptoms and contact with a health centre is 2 days (16). If our hypothesis is confirmed, the study would give us a tool we could initiate public health campaigns that inform the population to be able to recognize early their symptoms and consult as soon as possible.

The role of women in the pandemic has been key: for their function as health workers -70% health professionals are women(118)-, their role as cleaning workers, chef workers and their role -mostly

unpaid- as caregivers of the elderly, dependents and children. Although, man have higher rates of mortality, woman have suffered also, the cruellest part of the pandemic: observational studies report that women have been more infected with SARS-CoV-2(16), they are twice as likely as men to suffer from persistent COVID-19 (119), have suffered more layoffs than men (10), have been more affected in terms of mental health respect for men (11) and have suffered a substantial increase in gender-based violence (10).

That is why, sex-segregated research is now more necessary than ever, to avoid increasing the social inequalities that the pandemic is aggravating day by day.

In conclusion, due to 1) reported biological differences between sexes, 2) the importance of determine clinical presentation of COVID-19 to contain the growth of the pandemic and 3) the lack of literature determining the differences between sexes in clinical presentation of COVID-19, we need a study that would evaluate the related-sex differences in clinical presentation of COVID-19 in the first week of symptomatology.

5. HYPOTHESIS

5.1. MAIN HYPOTHESIS

COVID-19 clinical presentation (symptoms and recognizable signs by the patient) and her distribution in 7 first days of symptomatology will be different in females and males.

5.2. SECONDARY HYPOTHESIS

Differences in clinical presentation between sex will be influenced by age.

6. OBJECTIVES

6.1. MAIN OBJECTIVE

We want to study differences between females and males in clinical presentation of COVID-19 (symptoms and recognizable signs by the patient) and her distribution in the first 7 days of symptomatology.

6.2. SECONDARY OBJECTIVE

Study if differences in clinical presentation of COVID-19 between sexes in the first 7 days of symptomatology, are influenced by age.

7. MATERIALS AND METHODS

7.1. STUDY DESIGN

This study is an observational prospective cohort.

7.2. STUDY POPULATION

In our study we will include people with symptoms of COVID-19 who tested positive for SARS-CoV-2 on quantitative polymerase-chain-reaction assay (PCR) or on rapid antigen test.

This test will be made to patients who came to Primary Health Care Centre as suspicious case of COVID-19, following the current protocol “Procediment d’actuació enfront de casos d’infecció pel nou coronavirus SARS-CoV-2” (120) done by Sub-direcció General de Vigilància i Resposta a Emergències de Salut Pública updated on 10th of October of 2020 .

For more information about COVID-19 diagnose see ANNEX 4.

6.2.1. Inclusion criteria

- Individuals at least 18 years old.
- Individuals with symptoms of COVID-19 who tested positive for SARS-CoV-2 infection on qualitative polymerase-chain-reaction assay (PCR) or on rapid antigen test.
- Individuals have to understand and sign informed consent form (ANNEX 6).

6.2.2. Exclusion criteria

- Individuals who do not meet inclusion criteria.
- Individuals who don't want/cannot comply and/or answer everything that the protocol of the study implies. For example, individuals diagnosed at the time of admission on ICU.
- Individuals with dementia and without a family or socio-sanitary support to answer the collection data sheet every day.
- Individuals with language barrier, with whom the health care providers or researchers cannot communicate and cannot make sure he or she understands everything needed.

7.3. SAMPLE

7.3.1. SAMPLE SELECTION

The cohort will be selected by contacting the "Xarxa de Centres d'Atenció Primària de la Regió Sanitaria de Girona[1]". The professionals of those primary health care centres will Invite to participate in the study those individuals who meet inclusion and exclusion criteria, at the time of diagnosis of COVID-19. An information sheet of the study (ANNEX 5) and informed consent (ANNEX 6) will be given. After informed consent signed, individuals will be enrolled in the study.

[1] Girona health region includes centers from Alt Empordà, Baix Empordà, Garrotxa, Gironés, Pla de l'Estany, Ripollés and Selva.

7.3.2. SAMPLE SIZE

We estimated the sample size using the free online software GRANMO, and the setting for two independent proportions.

We have calculated the sample size for each symptom of the study. In each estimation we have assumed an alpha risk (α) of 5% and a beta risk (β) of 20%, having a value or statistical power (1-β) of 80%. Estimated loss at follow up was 10%. The largest simple size was when we calculate

fatigue symptom, GRANMO recommended 2.285 males and 1.471 females to be sure that there is a significant difference (≥5%) between sexes, being a total of 3.656 patients.

In ANNEX 7 are exposed the estimations for each sign and symptom (dependent variable).

Taking into account that the cumulative incidence of the Girona Health Region from March 1 to August 31 was 9776 people, to carry out our study we will need 2.25 months. This calculation may change due to the variability of the onset during the course of the pandemic.

7.4. VARIABLES AND METHODS OF MEASUREMENT

7.4.1. STUDY VARIABLE

Our variable of interest, or outcome variable, is the **Clinical presentation of infection of SARS CoV 2.**

When we talk about clinical presentation we want to refer to: 1) symptoms and 2) signs that the patient can recognize be himself.

We will focus the study on these variables because the aim of our study is to give a tool to the population to know how to identify as soon as possible those guide signs and symptoms indicative to have contracted coronavirus 19 according to her sex and age. The signs not recognizable for the patients are not of our interest.

We have reviewed the medical literature on COVID-19 to determinate all the necessary variables to carry out our study.

Clinical presentation will be, principally, defined to "GUIA PRACTICA CLÍNICA CAMFIC. MANIFESTACIONS PERSISTENTS DE LA COVID-19". It is the first Edition, published 15th of November of 2020, by CAMFIC (Societat Catalana de Medicina de Família I Comunitària). This guide, besides the information of management of persistent COVID-19, it provides information about acute infection of SARS-CoV-2, specifically it explains the signs and symptoms of presentation.

In addition, we have added other symptoms not considered in the guide, such as dermatological ones, taken from the bibliographic research carried out.

The signs and symptoms to study will be the following:

1- GENERAL SYMPTOMS

VARIABLE	DEFINED BY	TYPE OF VARIABLE	CATEGORY OF VALUES
Fever	Axillar temperature measured by own patient ≥37,5ºC	Dichotomous qualitative	Yes/No
Fatigue	State of being tired	Dichotomous qualitative	Yes/No

2- RESPIRATORY SYMPTOMS:

VARIABLE	DEFINED BY	TYPE OF VARIABLE	CATEGORY OF VALUES
Cough without expectoration	Cough without ejecting or expelling matter.	Dichotomous qualitative	Yes/No
Cough with expectoration	Cough ejecting or expelling matter.	Dichotomous qualitative	Yes/No
Dyspnoea/ Breathlessness	Modified Medical Research Council (MRC) Dyspnoea scale (121): 0- Breathless with strenuous exercise 1- Short of breath when hurrying on the level or walking up a slight hill 2- Walks slower than people of same age on the level or stops for breath while walking at own pace of level 3- Stops for breath after walking 100 yards 4- Too breathless to leave house or breathless when dressing.	Dichotomous qualitative	Yes (Any grade of dyspnoea except grade 0)/ No (No grade of dyspnoea or grade 0)

3- MUSCULOSKELETAL SYMPTOMS

VARIABLE	DEFINED BY	TYPE OF VARIABLE	CATEGORY OF VALUES
Myalgia	Muscular pain	Dichotomous qualitative	Yes/No
Join pain	Articulations pain	Dichotomous qualitative	Yes/No

4- GASTROINTESTINAL SYMPTOMS:

VARIABLE	DEFINED BY	TYPE OF VARIABLE	CATEGORY OF VALUES
Diarrhoea	Abnormally frequent intestinal evacuations with more or less fluid stools	Dichotomous qualitative	Yes/No
Nauseas	Sickness in the stomach accompanied by need or desire to vomit.	Dichotomous qualitative	Yes/No
Vomiting	Throwing up the contents of the stomach through the mouth	Dichotomous qualitative	Yes/No

Abdominal pain	Pain in abdomen	Dichotomous qualitative	Yes/No
Anorexia	Loss of appetite	Dichotomous qualitative	Yes/No

5- OTOLARYNGOLOGICAL SYMPTOMS:

VARIABLE	DEFINED BY	TYPE OF VARIABLE	CATEGORY OF VALUES
Rhinorrhoea	Excessive mucous secretion from the nose	Dichotomous qualitative	Yes/No
Sneezing	To make a sudden violent spasmodic audible expiration of breath through the nose and mouth.	Dichotomous qualitative	Yes/No
Sore throat	Pain in the gullet	Dichotomous qualitative	Yes/No
Anosmia	Loss or impairment of the sense of smell.	Dichotomous qualitative	Yes/No
Ageusia	Absence or impairment of the sense of taste	Dichotomous qualitative	Yes/No
Otalgia	Pain in the ear	Dichotomous qualitative	Yes/No

6- CARDIOVASCULAR SYMPTOMS:

VARIABLE	DEFINED BY	TYPE OF VARIABLE	CATEGORY OF VALUES
Thoracic pain	Pain in the part of the body between neck and the abdomen.	Dichotomous qualitative	Yes/No
Edema	Abnormal infiltration or excess accumulation of serous fluid in connective tissue.	Dichotomous qualitative	Yes/No
Palpitations	Abnormal rapid or irregular beating of the heart.	Dichotomous qualitative	Yes/No
Syncope	Loss of consciousness.	Dichotomous qualitative	Yes/No

7- NEUROLOGICAL AND NEUROPSYCHIATRIC SYMPTOMS:

VARIABLE	DEFINED BY	TYPE OF VARIABLE	CATEGORY OF VALUES
Headache	Pain in the head.	Dichotomous qualitative	Yes/No
Dizziness	Having a whirling sensation in the head with a tendency to fall.	Dichotomous qualitative	Yes/No
Agitation	State or feeling of being restless.	Dichotomous qualitative	Yes/No
Temporal-spatial disorientation	Loss of sense of time and place.	Dichotomous qualitative	Yes/No
Altered consciousness	Loss state of being aware.	Dichotomous qualitative	Yes/No
Memory impairment	Loss of ability to memorise.	Dichotomous qualitative	Yes/No

8- DERMATOLOGICAL SYMPTOMS:

VARIABLE	DEFINED BY	TYPE OF VARIABLE	CATEGORY OF VALUES
Petechia	Purplish spot containing blood that appears in skin or mucous, which measures <3mm.	Dichotomous qualitative	Yes/No
Livedo reticularis	Mottled reticulated vascular pattern that appears as a lace-like purplish discoloration of the skin.	Dichotomous qualitative	Yes/No
Erythematous rash	Change of human skin to red colour.	Dichotomous qualitative	Yes/No
Urticaria	Kind of skin rash with red, itchy bumps, they also burn or sting.	Dichotomous qualitative	Yes/No
Vesicles	Small anormal elevation of the outer layer of skin enclosing a watery liquid.	Dichotomous qualitative	Yes/No
Pernio-like lesions	Painful, itching swelling on the skin, typically on a hand or foot.	Dichotomous qualitative	Yes/No

7.4.2. INDEPENDENT VARIABLE

The independent variable is sex: Male or female. It is a nominal dichotomous qualitative variable.

7.4.3. COVARIABLES

The covariables will be mainly the risk factors associated with more risk to develop severe-COVID-19 and therefore could be possible confounders of association between the dependent variable and the independent variable.

1- SOCIODEMOGRAPHIC VARIABLES:

- **Age (in years).**

  It is a continuous variable

- **Socioeconomic status**:

  Defined as social class, constructed with occupation and education level as in Domingo et al(122). It is a categorical qualitative variable.

- **Immigrant of low- or middle-income country**: (yes or no)

  Low- or middle-income country will be defined by GNI per capita, calculated using World Bank Atlas method.(123). It is a dichotomous qualitative variable.

- **Living in a senior living community – nursing home**-: (Yes/No)

  It is a dichotomous qualitative variable.

2- VARIABLES FROM CLINICAL HISTORY:

- **Smoking:** Current-smoker, past-smoker or non-smoker.

It is a categorical qualitative variable.

- Use of corticosteroids (>=10mg/day prednisone) and use of disease-modifying antirheumatic drugs: (yes/no)

  It is a dichotomous qualitative variable.

- Pregnancy: (yes or no)

  It is a dichotomous qualitative variable.

- Obesity: (yes/no)

  Defined by Body mass index (BMI)≥30kg/m^2. To calculate it we will collect the weight (kg) and the height (m). It is a dichotomous qualitative variable.

- Diagnose of Cardiovascular disease in clinical history: (yes/no)

  Including heart failure, hypertension, acute cardiac injury, arrhythmia and coronary artery disease. It is a dichotomous qualitative variable.

- Diagnose of Diabetes Mellitus type 2 in clinical history: (yes/no)

  It is a dichotomous qualitative variable.

- Diagnose of Chronic respiratory disease in clinical history: (yes/no)

  Including Chronic obstructive pulmonary disease (COPD), asthma and interstitial lung disease. It is a dichotomous qualitative variable.

- Diagnose of Chronic kidney disease in clinical history: (yes/no)

  Defined as glomerular filtration rate of <60ml/min for 3 months or morphological alterations. It is a dichotomous qualitative variable.

- Diagnose of Chronic liver disease or non-alcoholic fatty liver disease in clinical history: (yes/no)

  It is a dichotomous qualitative variable.

- Diagnose of Cancer in clinical history: (yes/no)

  It is a dichotomous qualitative variable.

- Diagnose of Sickle cell disease in clinical history: (yes/no)

  It is Dichotomous qualitative variable

- Clinical history of solid organ transplantation: (yes/no)

  It is a dichotomous qualitative variable.

7.5. DATA COLLECTION

A non-probabilistic consecutive sampling method will be used for data collection.

All data will be collected from Historia Clínica Compartida de Catalunya (HC3) and dependent variable (Clinical presentation) will be picked up using a specific Case Report Form done specifically for this study (ANNEX 8).

All patients diagnosed with COVID-19 - by PCR or antigen tests - will be informed of their positive result by a call of their doctor, following the current protocol "Procediment d'actuació enfront de casos d'infecció pel nou coronavirus SARS-CoV-2" (120) done by Sub-direcció General de Vigilància i Resposta a Emergències de Salut Pública updated on 10th of October of 2020 . The ones who meet the inclusion and exclusion criteria will be informed of the study, in the same call, then there are two possibilities:

1. CASE A) *The patient is interested in being part of the study and can receive information online.* His/ her doctor will write down your email and will send it to the research team. The research team will send you the information sheet (ANNEX 5), the informed consent (ANNEX 6) and a contact number to answer any questions.
2. CASE B) *The patient is interested in being part of the study but cannot receive information online.* The doctor will write down her telephone number and send it to the research group. The research group will contact him or her in order to reach her the sheet of information (ANNEX 5) and informed consent (ANNEX 6).

Each time a patient agrees to be part of the study by filling out informed consent (ANNEX6), the research group will review their Clinical History (HC3) to collect data from covariates (sociodemographic, diagnoses, and treatments).

Then, the research group will send an e-mail with the following three pieces of information:

1) Confirm the data collected from HC3 and request those items that are not included.
2) Explanation of the questionnaire: explanation of all symptoms and signs. The explanation will include photographs of dermatological lesions to facilitate their recognition.
3) Explanation of how to fill it out: Explain that they need to fill in the questionnaire with the symptoms they have had in previous days. For example: Participant X began symptoms on January 3rd, received the diagnosis on January 5th, agreed to enter the study on January 6th, received our email on January 6th. In this case, on January 6th, participant X will have to fill in and send 4 forms: the first form with symptoms on day 3rd of January, the second form with the symptoms on day 4th of January and so on until

they arrive to the present day. Because the first form has to be with the information of the first day with symptoms. In order to collect data on dermatological signs, photographs of the lesions would be requested and mailed to the research team.

From there, patients would fill out the questionnaire daily with the symptoms they were having and send the questionnaire directly.

Participants with lack of resources or not used to manage technologies would be contacted by telephone for the research group to collect his data.

The language chosen for the online questionnaire has been Catalan, with the option that research group translate it to Spanish or English if the participant needs it.

8. STASTISTICAL ANALYSIS

8.1. DESCRIPTIVE ANALYSES

First, we will summarize the dependent variables by means of proportions. Then, we will create cross-tables between the dependent variables and sex, and we will evaluate the relationship between them using the proportions by row.

We will stratify these cross-tables by the covariables. Age will be categorized in quintiles.

8.2. BIVARIATE INFERENCE

The differences in the proportions of the dependent variables by sex will be assessed by means of chi-square tests. When the expected number of counts in each cell was lower than 5 we will use the Fisher exact test.

We will stratify these analyses by the covariables. Age will be categorized in quintiles.

8.3. MULTIVARIATE ANALYSIS

We will assess the association between the dependent variables and sex by means of logistic regressions, controlling for the covariates.

9. WORK PLAN AND CHRONOGRAM

9.1. RESEARCH TEAM MEMBERS

- **Study coordinator:** His/her function is to supervise all aspects of the study.
- **Data collectors**: His/her function will be to collect all the data and solve any doubt of participants. They will be professionals from the health field.
- **Statistical specialist:** His/her function is to perform the statistical analysis.

9.2. STUDY STAGES

STAGE 0: Protocol elaboration. November 2020- February 2021.

- Including a literature review and describe all practical considerations for the study design.

STAGE 1: Ethical evaluation. February 2021-March 2021

- We will submit our protocol to the Clinical Research Etical Committee (CEIC) of Hospital Universitari Doctor Josep Trueta de Girona for its approval. Make any necessary modifications to the protocol if necessary, to achieve CEIC's conditions.

STAGE 2: Training of data collectors. March 2021- April 2021

- Data collectors will receive a training by study coordinator. The coordinator will clarify her role in the study and will explain the phases of the study. Coordinator and data collectors will keep in contact via email and/or telephonic messages.

STAGE 3: Participants recruitment and data collection. April 2021 – September 2021.

- Although, in 2,25 months we can have all the cases. To be realistic and do a correct monitorization of the information we will estimate this phase will be done in 5 months.
- Data collectors will be responsible for collecting data from participants in their medical history as well as ensuring that they answer the questionnaires daily. They will also be available for any questions from participants.

STAGE 4: Statistical analysis. September 2021 – November 2021.

- The whole data will be organised and sent to the statistical specialist who will process these data performing a descriptive analysis, bivariate and multivariate analysis.

STAGE 5: Interpretation and elaboration of final report. November 2021 – January 2021

- A final meeting with all the researcher team members will be held with the aim to discuss the results and draw conclusions.

STAGE 6: Publication of the results and dissemination of the results. January 2021 – February 2022

- At this stage the research team will publish the study to share the results with the scientific community. The dissemination of the results will be at national and international congresses.

9.3. CHRONOGRAM

	2020		2021												2022	
	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F
STAGE 0 Protocol elaboration																
STAGE 1 Ethical evaluation																
STAGE 2 Training of data collectors																
STAGE 3 Participants recruitment and data collection.																
STAGE 4 Statistical analysis																
STAGE 5 Interpretation and elaboration of final report																
STAGE 6 Publication of the results and dissemination of the results																

10. ETHICAL CONSIDERATIONS

The study will be developed under the basic ethical principles established by the Helsinki Declaration and the European agreement on Human Rights and Biomedicine (last actualization October 2013) with regards to autonomy, risk-benefit ratio, and protection of vulnerable individuals.

All the information from participants included at the trial will be confidential, guaranteeing the anonymity of the participants involved in the study, according the *"Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal"* and the last adaptation *"Real Decreto-ley 5/2018, de 27 de julio, de medidas urgentes para la adaptación del Derecho español a la normativa de la Unión Europea en materia de protección de datos"*.

Participants will be given the information sheet (ANNEX 5) and they will be asked to sing the informed consent (ANNEX 6) in order to be included in the study. It will also be explained to the individuals that they are free to refuse.

The study protocol will be sent to the Comitè Ètic d'Investigació Clínica (CEIC) of Hospital Universitari Josep Trueta to be reviewed. The committee will ensure that the protocol fits the ethical requirements and any modifications proposed will be implemented to a modified protocol.

All investigators will have to declare no conflict of interest. They will also have to agree to publish all data and results with total transparency, including unfavourable data or events.

11. STUDY LIMITATIONS

This study has some potential limitations that should be considered in order to reduce them:

- The participants will answer the questionnaire voluntarily and this may cause a volunteer or self-selection bias: only those who have not several symptoms would answer it, whereas those who have severe symptoms would not.
- We must take into account the possibility of information bias because the participants could not know how to classify or identify their signs and symptoms well. Even so, it is not expected that this bias is greater between males than females. Consequently, it only reduces the power for the null hypothesis but does not imply a bias for the comparison between the two groups. In spite of this fact, precisely due to minimize this bias, the participants would have a telephone and mail contact with the research team to resolve any questions.
- Regarding the dermatological signs, exist the possibility that patients do not recognize them and therefore do not send their photographs to data collectors, fact that would cause an information bias. As a way of minimizing this, in the e-mail with study information we will include photographs of dermatological lesions to facilitate their recognition. In addition, it is likely that participants who have lack of resources or not used to manage technologies could not be able to send the photographs, leading to another information bias.
- Even thought, the follow up of the participants is very short -7 days-, we can have a bias due to possible loss of participants, mainly because they get worse in their health as well as if they are hospitalized.
- Although, it is an observational prospective cohort, some of the data collected are about the symptoms they had before entering at the study and this, could cause a memory bias in the data collection.
- The consecutive non-probabilistic sampling method could lead us to a selection bias and not obtaining the most representative population. To minimize this and ensure a good external validity, the designed inclusion criteria are extensive and exclusion criteria aim to reduce confusing factors.

12. BUDGET

EXPENSES	COST
1- Personal expenses	
1.1. Data collector	3.500€
1.2. Statistician	3.000 €
2- Executive expenses	
2.1. Printing expenses	400€
3- Publication	
3.1. Paper publication (open access)	2000€
3.2. Paper proofreading	500€
4- Dissemination	
4.1. Registration to national congress	500€
4.2. Registration to international congress	800€
4.3. Travel accommodation and food	
National congress	1.000€
International congress	1.700 €
TOTAL	13.400€

- **Personal expenses:** For our study we will need to hire a data collector, who have to be professional from the health field or student of health at his/her last year. They will receive a formation by study coordinator. He/she will be hired for 5 months part-time. We will pay him 700€/month.

  Also, we will need to hire a statistician that will perform the analysis of results. We have estimated approximately 50 hours of work will we needed to perform the statistical analysis; and we will pay 60€ per hour so the personal expenses will be of 3.000 €.

- **Executive expenses:** We will use an online data collection sheet to reduce costs. Only executive cost will be for printing the Information for the patient sheet and the informed consent sheet, we estimated 400€ for it.

- **Publication and dissemination:** If the researchers think is appropriate, the study will be published as a journal article and we will attend a national and international congresses to present the results and share our experience.

13. IMPACT ON NATIONAL HEALTH SYSTEM

It is important to mention the impact on the National Health System that this study could produce. As we have explained in introduction, COVID-19 is being a global health emergency, not only because of the data of contagions and deaths that even today are saturating the health system, but also for the socioeconomic and mental health impact of the prevention measures taken. As well as the long-term effects that the SARS-CoV-2 infection can develop, with the consequent burden on the national health system (119).

For this reason, now more than ever research is necessary to give self-care tools to the population and to develop a more individualized medicine.

In the face of an infectious disease, an early diagnosis is essential to stop the chain of infection. Currently, diagnostic tests have been developed that in a few minutes confirm the diagnosis of COVID-19 (120); and this has helped a lot to allow an early diagnosis. However, these tests in order to be carried out it is necessary that individuals consult. In Spain it is observed that the average from the onset of symptoms and contact with a health centre is 2 days (16). It is an important challenge for the health system to get them to consult as early as possible. To achieve this, it is necessary to have a population with knowledge of the alarm symptoms that make them go to the health system.

Women make up 50% of the world's population, but also currently, according to WHO data (118), they represent around 70% of health workforce. Therefore, it is useful, necessary and even urgent to know the peculiarities of her symptoms against COVID-19, especially given her daily contact with patients at risk and her crucial role in the national health system.

If our hypothesis is confirmed, the study would give us evidence about a new instrument that will allow us to initiate public health campaigns that inform the population of what the most frequent first symptoms are according to their sex and age group. In this way we would be providing the population with tools to be able to recognize early symptoms, consult before and receive an early diagnosis. Accordingly, we would be reducing infections of SARS-CoV-2, reducing morbidity and mortality and therefore the great burden on the health system.

14. FEASABILITY

We have considered our study feasible for several reasons.

Firstly, the research team of the study would be sufficiently qualified for their role. Secondly, infrastructure and materials needed to carry on the study would be only to telephone and computer with internet connection.

Finally, the recruitment period is estimated to last 5 months. As having the compromise of "Xarxa de Centres d'Atenció Primària de la Regió Sanitaria de Girona" and taking to account the predictions of incidence of COVID-19, we would not have any problems to obtain the number of participants wished.

15. FUTURE RESEARCH

If our study is finally carried out and the results show relevant differences, future research studies could consider studying whether transexual as well as intersex people present differences in the clinical presentation of SARS-CoV-2 infection.

Furthermore, we should find relevant, the sex disparity of COVID-19–related to clinical presentation, morbidity and mortality is likely explained by a combination of biological sex differences -those exposed in the background- and gender-specific factors (differential behaviours and activities by social and cultural/traditional roles). It may also be interesting to study whether the differences studied according to the sex variable are maintained with the gender variable.

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17. ANNEXES

ANNEX 1: TRANSMISSION OF COVID-19 AND SARS-COV-2 FEATURES

1. TRANSMISSION

The principal way of SARS-CoV-2 transmission is through the infected respiratory macro- droplets (5-10 µm) secreted by infected individuals while they are coughing, talking or sneezing without covering the nose and the mouth. (124,125). Most transmission occurs thought close range contact (such as 15 minutes face to face within 2m) (25).

Others ways of transmission of SARS CoV-2 occurs via:

- Aerosol (micro-dropeds ≤ 5µm) transmission during prolonged stay in crowded, poorly ventated indoor settings (126).
- Direct contact and transmission throught contaminated surfaces or objects (fomites) Scientists have reported that SARS-CoV-2 remains stable up to on cartoon, on plastic and stainless steel up to 72 h and more than 4 h on copper. However, it remains unclear whether the presence of the virus on the surface indicates viable infectivity (127).
- Verical transmission occurs rarely but transplacental transmissions has been documented (126).
- Fecal microbiota (FMT) isolated from SARS-CoV-2 positive people may also be a source for COVID-19 transmission according to recent FDA guidelines (128).

Sexual, fecal-oral and bloodborne transmission are theorized but have not been documented. (86)

The principal measures for reducing the transmission of SARS-CoV-2 are exposed in the TABLE1.

TABLE 1: Measures for reducing the transmission of SARS-CoV-2 (86).

Transmission route	Prevention
1. (Macro-)Droplets (> 5 µm)	Face masks + social distancing
2. Aerosol (micro-droplets, ≤ 5µm)	• Face masks • Improved ventilation (open doors and windows; upgrade ventilation systems) • Improved air filtering • Avoidance of crowded and closed spaces
3. Fomites	Handwashing

For mechanical systems, organizations such as ASHRAE (the American Society of Heating, Ventilating, and Air Conditioning Engineers) and REHVA (the Federation of European Heating, Ventilation and Air Conditioning Associations) have provided guidelines based on the existing evidence of airborne transmission (Morawska 2020b).

2. ABOUT SARS-COV-2

2.1. VIROLOGY

Coronaviruses constitute the subfamily Orthocoronavirinae, in the family Coronaviridae order Nidovirales and realm Riboviria(129). Coronaviruses are divided into four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus on the basis of their phylogenetic relationship and genomic structures (130).

SARS CoV 2 is a betacoronavirus, other beta family members include Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)(131). Prior to 2002 coronaviruses were considered exclusively veterinary pathogens (3). They are now considered a causative agent of human respiratory pathogens as demonstrated uring 2002–2003, 2012 and 2019 from the outbreaks of COVID19, SARS and MERS and COVID-19, respectively (132). Betacoronaviruses have been linked to sometimes fatal illness and have caused more than 10 000 cumulative cases in the past two decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV (133).

It is believed to have zoonotic origin and has close genetic similarity to bat coronaviruses, suggesting it emerged from bat-borne virus (134).

The spread of zoonotic disease from species that it evoled with to a new host is exacerbated by wildlife trafficking, habitat destruction, and climate change(135). These threats bring humans and animals closer together. Coronavirus is just an example of a string of pathogens that have come from wildlife trafficking, including SARS, Ebola, Bird Flu, and many more (134).

2.2. MOLECULAR STRUCTURE:

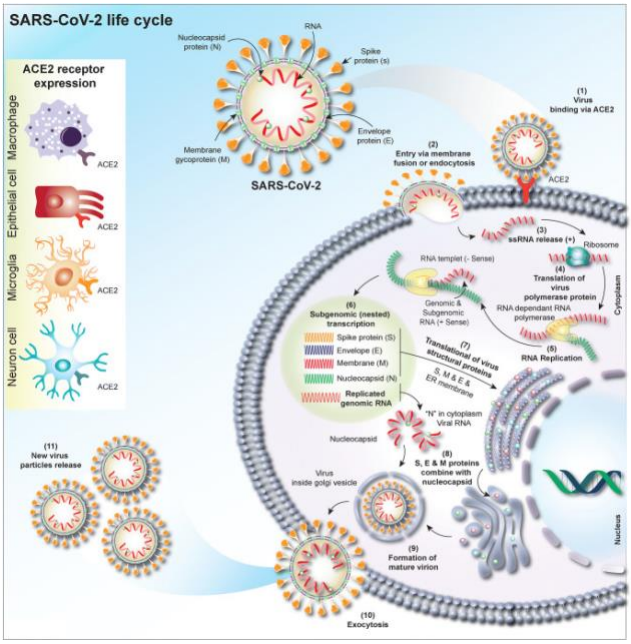
Coronaviruses are a positive-sense single-stranded RNA virus. They are spherical or pleomorphic, with a diameter of 80-160nm(5).

SARS-CoV-2 have envelope formed by lipid bilayer with defined transmembrane proteins. SARS COV 2 do not make their ouw lipids, they utilizes lipids from the host cell when they buds off to create a new virion. Within the envelope, SARS COV-2 have non-segmented positive-sense RNA genome which codes for 4 structural proteins: (5,136–138)

- Spike protein (S): Those proteins surround the surface of the virion providing them the appearance of solar corona and gives the virus its common name: Coronavirus.
- Nucleocapsid protein (N): Protect viral genome from outside host cells.
- Membrane protein (M)
- Envolve protein (E)

2.3. SARS COV2 LIFE CYCLE IN VIRUS SUSCEPTIBLE HOST CELLS:

FIGURE 1: *SARS-CoV-2 life cycle* (5)



Spike protein have a receptor-blinding Domain (RBD) which binds to the ACE2 of host cell. This blinding allows entry via fussion or Endocytosis. 2) Single-stranded RNA is released and 3) partially translated into SARS-COV-2 polimerase protein 4-5) and transcribed 6).

RNA replication 7) The host cell ER membrane take RNA translational S, M and E proteins and later combined with nucleocapsid protein (N) 8). In Golgi processing incorporate all the elements to form the mature virion 9) Finally virus inside golgi vesicle go to the cell membrane for exocytosis 10) of newly budded SARS CoV-2 particles.

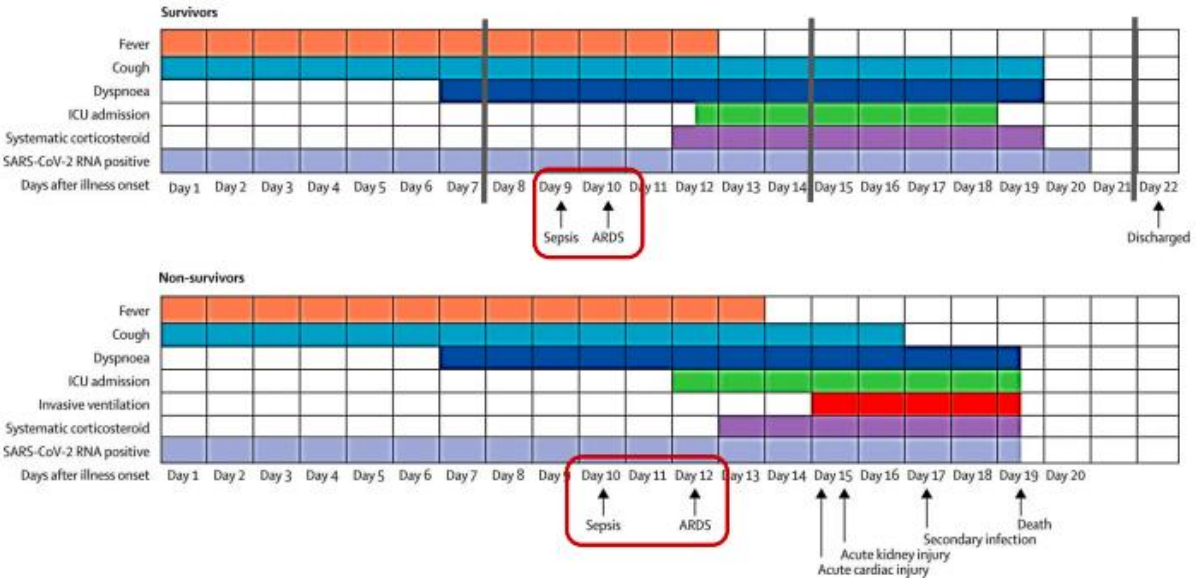
ANNEX 2: NATURAL HISTORY OF COVID19

1. STAGES OF COVID19

COVID19 is a disease with a biphasic pattern of illness that likely results from the combination of an early viral response and inflammatory phase (25).

- Incubation period: Period after exposure without symptoms. It is typically 5-6 days after the initial exposure.
- STAGE I: Clinical presentation of this phase is influenza-like illness -which includes fever, cough, malaise, myalgia, headache and tase and smell disturbance- but with some particularities exposed in point *Spectrum of clinical manifestations.*
  In this phase, after viral entry, the infected cells attract virus-specific T cells to the site of infection to eliminate infected cells before the virus spreads. (24)
  The duration of this phase is between 7-11days. (87,89,114). If initial host immune response is able to control the infection, it will lead to the recovery. But, in some cases, SARS-COV-2 can cause a severe disease.
- STAGE II: In some cases, SARS-CoV-2 can spread efficiently among lower respiratory airways, resulting in an apoptosis of pneumocytes it can cause decreased capacity of air exchange with the consequence of reduced oxygenation and finally requirement of respiratory support. For this reason, this stage is divided into two sub-stages IIA if the patient is NOT hypoxemic and IIB if the patient is hypoxemic.
- STAGE III: Attempts to the immune system to control viral dissemination in the lower respiratory tract can cause an exacerbation of immune reaction leading to cytokine storm or cytokine realize syndrome. Cytokine storm will aggravate air exchange capacity by causing lung tissue damage, resulting in pulmonary edema, more occlusion of small airways and finally leading to acute respiratory distress syndrome (ARDS).(57) This develops in 20% after a median of eight days of COVID-19. (58)
  There will be decreased capacity of air exchange with the consequence of reduced oxygenation and finally requirement of respiratory support.(57) (139). In the register of patients admitted by COVID-19 in Spain made by the SEMI (Spanish Society of Internists) during the first wave of COVID19 has shown that 33.1% of patients admitted for COVID19 developed ARDS, 8% required non-invasive ventilation and 6.6% required invasive ventilation. (90)
  Furthermore, SARS-CoV-2 have the capacity to spread to those tissues with ACE2 expression, especially vascular endothelium, resulting in multiorgan failure with vaso-occlusion, enhanced coagulation and impairment of vital functions leading to cardiovascular dysfunction, acute kidney Injury and thromboembolism among others in which we will delve into point "Spectrum of clinical manifestations" (140).
  It's estimed at 10-15% progress to Stage III, mortality within this stage is between 20-30%. Patients with severe-COVID19 have a mean duration of symptoms between 13-25 days. The duration increases with severity, 22 days for those hospitalized on the floor and 28 days for those admitted to the ICU

FIGURE 2: *Duration of symptoms and onset of complications and outcomes.* (112)



2. RECOVERY OF INFECTION, SEQUELS AND LONG COVID-19

Recovery time of SARS-CoV-2 infection is a variable that remains unclear. There is a large heterogeneity of study design, the evaluated population and the lack of standardization in the definition of the term "recovery time"; since in the methodology of the studies it is not contemplated to differentiate between the persistent symptoms, the aggravated previous symptoms. or symptoms resulting from the typical sequelae of severe bilateral pneumonia According to an analysis of studies carried out by CAMFIC (119), data seem to indicate:

- At 2 weeks of infection, 30-52% of people diagnosed with COVID-19 are fully recovered from COVID 19 symptoms.
- At 4 weeks of infection, 80% of people hospitalized with COVID19 fully recover from their symptoms.
- At 4 weeks from the onset of symptoms, only 40% of hospitalized people who have required oxygen flow or ICU admission are fully recovering from symptoms.

In conclusion, between 10-20% of patients diagnosed with COVID-19 present symptoms 4 weeks after diagnosis. In these cases we must distinguish 4 scenarios (119):

- **Long COVID19 or persistent COVID19:** Symptoms attributable to COVID-19 have persisted for more than 4 weeks since the onset of symptoms. In addition, persistent symptoms were part of the clinical presentation of acute COVID infection19.
- **Post-COVID19 symptoms o post-viral COVID19:** Post-COVID-19 symptoms were not part of the clinical presentation and appear in the post-viral phase. Symptoms may include: Thrombosis (3% post-discharge), perniosis, encephalitis, Guillain-Barré syndrome, gromerulonephritis, autoimmune cytopenias, thyroiditis, systemic autoimmune diseases including SLE.
- **Exacerbation of previous symptoms:** Symptoms already existed before acute SARS-CoV-2 infection and have aggravated after acute SARS-CoV-2 infection.

- **Post-COVID19 sequelae:** Symptoms are not part of the clinical presentation of acute SARS-CoV infection but appear as a consequence of organ-specific damage caused by severe-COVID19.

ANNEX 3: SUMMARY OF SYMPTOMS

TABLE 2: Summary of symptoms and signs of SARS-CoV-2 acute infection, described in a selection of publications including representative cohorts of more than 1000 patients (119).

	Símptomes	Freqüència n/N	%	Estudis (n)
Respiratori	Tos	107044/135767	78,8	15
	Dispnea	71604/166030	43,1	14
	Expectoració	12383/66211	18,7	10
	Dolor toràcic	9603/71793	13,4	6
Símptomes Generals	Febre	123188/168346	73,2	16
	Fatiga	60006/144955	41,4	12
	Calfreds/esgarrifances	7244/60661	11,9	5
	Sibilàncies	5109/63937	8,0	2
	Síncope	53/1841	2,9	2
	Edemes	30/1968	1,5	2
Reumàtics	Miàlgies	15337/76919	19,9	13
	Miàlgies i/o artràlgies	8277/55924	14,8	1
	Artràlgies	4619/61675	7,5	3
ENT	Odinofàgia	14252/123319	11,6	9
	Disgèusia	3483/38484	9,1	5
	Anòsmia	4494/56356	8,0	7
	Rinorrea	3519/65987	5,3	7
	Congestió nasal	2684/55924	4,8	1
	Hemòptisi	660/61775	1,1	6
	Otàlgia	631/75336	0,8	2
Digestius	Anorèxia	4084/19092	21,4	4
	Diarrea	20249/153778	13,2	13
	Nàusees o vòmits	17142/136902	12,5	13
	Dolor abdominal	7421/69573	10,7	4
Neurològics	Confusió / Alteració de la consciència	18434/70032	26,3	2
	Cefalea	17734/128233	13,8	12
	Conjuntivitis	782/138724	0,6	5

ANNEX 4: DIAGNOSIS AND TREATMENT OF COVID-19

1. DIAGNOSIS:

1.1. .LABORATORY TEST

The following laboratory tests can be used to diagnose COVID-19 (26,141):

TABLE 3: *Characteristics laboratory test used to diagnose of SARS-CoV-2 infection:*

	WHAT IT DETECTS	SAMPLE	SENSIBILITY AND SPECIFICITY
Real-time Reverse Transcription Polymerase Chain Reaction (rRT-PCR)	Detects the presence of viral RNA fragments of SARS CoV-2.	Nasopharyngeal swabs. However nasal swabs, sputum sample tracheal aspirate may also be used	Sensibility: 87,8%. Specificity: 87,7-100%
Rapid diagnosis tests based on antigen detection or antigenic test	Detect the presence of SARS-CoV-2 viral proteins (antigens) in respiratory tract using a lateral flow immunoassay.	Nasopharyngeal swabs. However nasal swabs or sputum sample may also be used	Sensibility: 98%.* Specificity: 99%%*

*First 5 days with symptomatology. The sensibility decreases after seven days with symptoms (S: 93% and E: 99%)

Another laboratory test used in COVID-19 are serological test or antibody test. This test is not recommended as for acute diagnosis and clinical management, but it can have an important role in some other situations: patients with negative PCR or antigenic test, patients with prolonged symptoms or seroprevalence surveys (26,141).

TABLE 4: *Characteristics of serological test or antibody test:*

LABORATORY TEST	WHAT IT DETECTS	SAMPLE	SENSIBILITY AND SPECIFICITY
Serological test or antibody tests	Detect antibodies (IgG and IgM) produced by human body in response to infection of SARS-CoV-2 by enzyme-linked immunosorbent assay (ELISA)-based test.	Blood serum	Sensibility: 96% Specificity: 99%

TABLE 5: *Table summary of the use of diagnostic tests in different healthcare settings.* (120)

	Atenció primària i urgències (CUAP i hospitalàries)	Entorns vulnerables (residències i centres de discapacitats)	Pacients ingressats en hospitals	Cribratges (qualsevol àmbit)
Simptomàtics				
< 5 dies evolució	Tests antigènics	Tests antigènics PCR posterior si test antigènic negatiu i alta sospita clínica	PCR o Test antigènics PCR posterior si test antigènic negatiu i alta sospita clínica	X
> 5 dies evolució	PCR	PCR	PCR	X
Asimptomàtics				
	PCR	PCR	PCR	PCR Pooling PCR

1.2. IMAGING TEST:

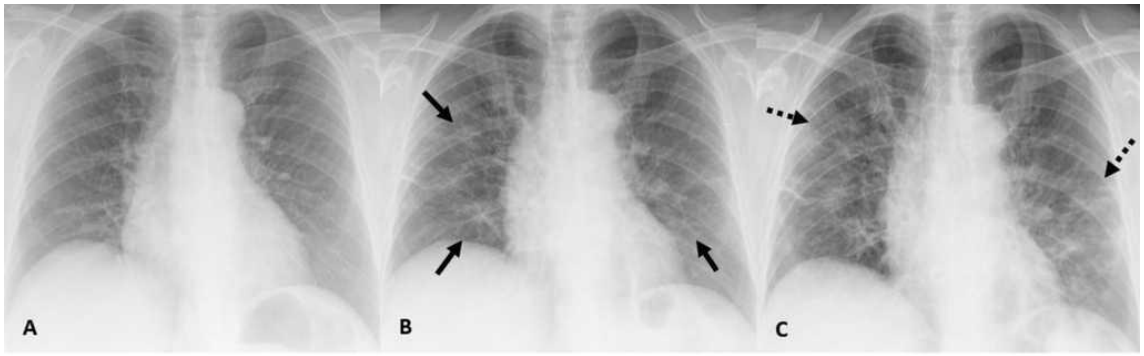
Radiological study is not recommended in non-serious (non-hospitalized) patients except for suspicion of pneumonia due to an etiology other than SARS-CoV-2.

To support the diagnosis of COVID19 we can use the following imaging tests:

TABLE 6: *Characteristics of radiological study in COVID19. Adapted from* (26,142,143)*:*

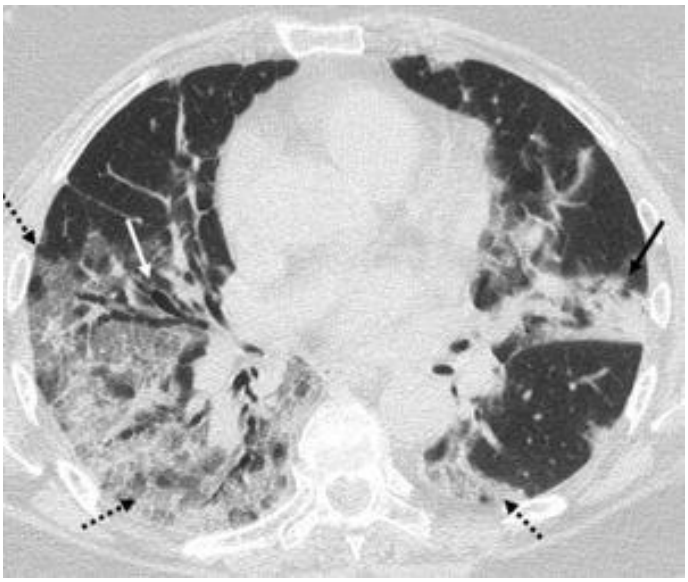
IMAGING TEST	INDICATIONS	RADIOLOGICAL FINDINGS
Chest X-Ray (CXR)	It is recommended should a clinical suspicion of pneumonia	Bilateral consolidations and ground glass opacities of chest-X-Ray by more than 75%. Distribution: Bilateral (75-88%), peripheral and predominant in lower lobe.
Chest Computed Tomography (CCT)	British Society of Thoracic imaging (BSTI) recommends computed tomography in cases with severe COVID-19 and normal or uncertain chest X-ray	Frequent radiological patterns are ground glass pattern ((50-80%) or interstitial pattern (13%). Distribution: as in X-ray, is usually bilateral, peripheral, and subpleural predominant in the lower lobe.
Pulmonary ultrasound	It is used in some centers as an alternative to X-ray or CT, but an expert radiologist is needed.	The predominant pattern to be found would be B lines or alterations to the pleural line.

IMAGE 1: *Chest X-Ray images of a 75-year-old patient who came to the emergency department and presented with 1-day history of COVID-19 infection-compatible symptoms and with a positive PCR result for SARS-CoV-2. (A) CXR image, at admission without initial radiographic abnormalities. (B) CXR image, 4 days later, in which bilateral ground-glass pattern are identified. (C) CXR image, 2 days later, in which a interstitial pattern is observed due to septal thickening with persistence of GGO.*(143)



Med Clin. 2020;155:36–40

IMAGE 2: *Chest Computering Tomography (CCT)of 60-year-old patient with a positive PCR result for SARS-CoV-2. This CCT shows one of most common patterns: peripheral ground-glass opacities were observed in both hemithorax (dashed arrows), a foci of consolidation in lingula (black arrow) and bronchiectasis (white arrow).* (143)



1.3. DEFINITION OF CASES:

According to "Pla d'actuació de l'Hospital Universitari de Girona Dr. Josep Trueta davant la infecció pel nou Coronavirus SARS-CoV-2" (144) the definition of cases is the following one:

a) **Suspicious case:** Anyone with a clinical case of acute respiratory infection of sudden onset of any type of severity that occurs, including fever, cough or shortness of breath. Other atypical symptoms such as odynophagia, anemia, agesis, muscle aches, diarrhea, chest pain, or headache, among others, may also be considered symptoms of suspected SARS-CoV-2 infection according to clinical criteria.

b) **Confirmed case of active infection:**

- Suspicious case with positive PCR or antigenic test.
- Suspicious case with negative PCR or antigen test and positive IgM result by high performance serology or immunochromatography.
- Asymptomatic person with positive PCR or antigen test.

c) **Confirmed case with resolved infection:** Asymptomatic person with positive IgG serology regardless of the result of PCR or antigen test.
d) **Probable case**: Patient with clinical and radiological criteria for COVID19 compatible with COVID19 with negative PCR or antigenic test and a epidemiological link with confirmed or suspected case. They will be treated as confirmed cases.
e) **Discarded case**: Suspicious case with PCR and negative antigen test, IgM also negative in which there is no high clinical suspicion or epidemiological vice with confirmed case.

2. TREATMENT:

2.1. RECOMMENDATIONS ACCORDING TO COVID19 DISEASE SEVERITY.

There is currently no evidence to recommend a specific treatment for SARS-CoV-2 infection. However, current knowledge allows us to make the recommendations detailed below (TABLE 3). The following treatment recommendations are proposed by the Ministry of Health and Consumer of Spain Government of Spain and Affairs and the Advisory Committee for the Pharmacological Treatment of CatSalut SARS-CoV2 infection. (145)

TABLE 7: Indications for assessing specific treatment. (146)

CLINICAL CASE	CXR/CTT	TREATMENT	ATTITUDE
MILD: No hypoxia, no shoetness of breath or mild	Not indicated except risk groups.	Symptomatic*	Home discharge except risk groups
	Initial radiographic abnormalities	Specific treatment for SARS-CoV2**	Domiciliary monitoring or hospital admission.
MODERATE: Hypoxemia and / or difficulty moderate respiratory	Normal	Symptomatic*	Hospital admission
	Any radiological pattern	Specific treatment for SARS-CoV2**	Hospital admission
SERIOUS (ICU, PICU): Severe hypoxemia, respiratory distress serious, bad look.	Any radiological pattern	Specific treatment for SARS-CoV2**	Hospital admission

*Symtomatic treatment: Paracetamol

**Specific treatment for SARS-CoV2: Remdesivir +/- Dexametasona +/- Tocilizumab

2.2. SPECIFIC TREATMENT FOR SARS-COV2

A) **Systemic corticoids:** The following criteria must be met for its administration: Severe patient with> 7 days of symptoms requiring supplemental oxygen, mechanical ventilation or ECMO. Therefore, do not use in patients who do not require oxygen therapy or in the first 7 days of symptoms. (147)
B) **Remdesivir:** The following criteria must be met for its administration Severe patient with> 7 days with symptoms requiring low-flow oxygen therapy (nasal goggles or simple mask) and meeting at least 2 of the following 3 criteria: Basal saturation <94%, Respiratory rate ≥24rpm or PaO2/FiO2 <300mmHg. (147)
Contraindicated in case of:

- Patients with high flow ventilation, non-invasive ventilation or invasive ventilation.

- Glomerular filtration <3ml / min, hemodialysis or peritoneal dialysis
- AST or ALT> 5 times by the normal upper limit
- Need for 2 ionotropics to maintain BP
- Evidence of multiorgan failure

C) **Tocilizumab:** Recommended for use in patients who are not mechanically ventilated and who progress despite treatment with corticosteroids or are not candidates for corticosteroids. (147)

2.3. ANTIBIOTIC TREATMENT

Antibiotics are not initially recommended for SARS-CoV-2 infection, except that clinical, analytical parameters - mainly PCR and procalcitonin - or radiological parameters may suggest that there is overinfection. It should especially be assessed if another etiology, associated sepsis or suspicion cannot be detected.(146)

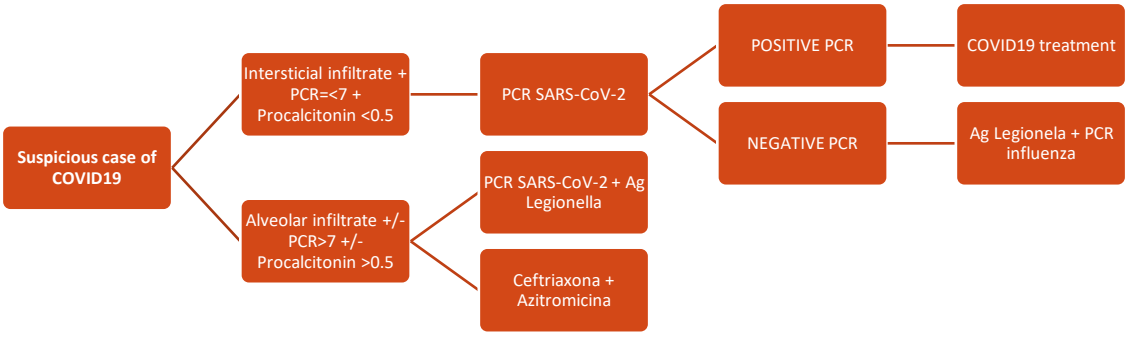
General recommendations for empirical treatment for community-acquired pneumonia (NAC) according to the "COVID19 Clinical Patient Management Protocol" of the "Ministerio de Sanidad de España" (146), based on the recommendations of SEPAR -Sociedad Española de Neumologia y Cirurgia Toracica. :

Table 8: *General recommendations for empirical treatment for community-acquired. Adapted from* (146)

	TREATMENT
OUTPATIENT	Amoxicillin or Clavulanate amoxicillin (if COPD or asthma) + Azithromycin or Clarithromycin (Macrolides)
HOSPITALIZED PATIENT	Ceftriaxone or cefotaxime + Azithromycin or Clarithromycin (Macrolides)
INTENSIVE CARE UNIT	Ceftriaxone, Cefotaxime, or Ceftaroline + Azithromycin or Clarithromycin

In addition, "COVID19 Clinical Patient Management Protocol" of the "Ministerio de Sanidad de España" (146), recommends evaluating the guides of each Hospital and health area. In the case of the Hospital Universitari Josep Trueta de Girona, they have the following diagram to follow:

DIAGRAM 1*: Indications for antibiotic treatment in suspicious case of COVID19. Adapted from "PROCEDIMENTS D'HOSPITALITZACIÓ A MEDICINA INTERNA DEL PACIENT COVID19" by Servei de Medicina Interna de l'Hospital Universitari de Girona Dr. Josep Trueta.* (147)



2.4. THROMBOPROPHYLAXIS

As we have commended, one of the complications of COVID19 is thromboembolic disease-causing deep thromboembolism (PVP) or pulmonary thromboembolism (PET). For this reason, in certain hospitalized patients there are recommendations for thromboprophylaxis. The following are the recommendations of the "HOSPITALIZATION AT INTERNAL MEDICINE OF PATIENT COVID19" protocol from the University Hospital of Girona Josep Trueta:

- Stable patients: Enoxaparin by weight and glomerular filtration.
- Patients with high thrombotic risk it will be assessed individually.
- In case of severe coagulopathy (Platelets <30,000 or fibrinogen <150 mg / dL or CID): Individualize and, if possible, maintain LMWH at a prophylactic dose.
- In case of DVT / PET: Anticoagulant at therapeutic dose with Enoxaparin, adjustable according to renal profile.
- At discharge, it is recommended to assess individually and re-evaluate after 21 days by a primary care physician.

2.5. INSOLATION

SARS-CoV-2 infection has high rates of contagion, for this reason part of the treatment is isolation to prevent further infections. The current CatSalut recommendations (120) -following the European and CDC recommendations- are detailed below:

- Confirmed cases of COVID19 that do not require hospital admission: Home isolation that will be maintained for at least 72 hours from the resolution of the fever and the clinical picture * with a minimum of 10 days from the onset of symptoms.
  If effective home insulation cannot be guaranteed, isolation will be indicated in hotels or other facilities enabled for its use and / or referral to social services.
- Confirmed individuals of COVID19 who require hospital admission: They will be isolated during their hospital stay according to their severity:
  - Mild or moderate patients: They must be isolated until they meet the following two criteria:
    1) 10 days of insolation since the first symptoms appeared
    2) At least 72 hours asymptomatic and afebrile (No use of antipyretics)
  - Severe or immunocompromised patients: They must be isolated until they meet the following two criteria:
    1) 28 days of insolation since the first symptoms appeared
    2) At least 72 hours asymptomatic and afebrile (No use of antipyretics)

ANNEX 5: INFORMATION SHEET

FULL D'INFORMACIÓ PER LA PERSONA PARTICIPANT

Títol de l'estudi: Diferències de presentació clínica de COVID-19 entre sexes.

Ens adrecem a vostè per convidar-la a participar en un estudi que pretén conèixer les diferències de símptomes i signes de la malaltia causa per la infecció de SARS-CoV-2 entre persones de sexe femení i persones de sexe masculí. Per així poder conèixer els signes d'alerta en funció del sexe de la persona i la seva edat.

Aquest estudi forma part del projecte de recerca de Fi de Grau de l'estudiant Judit Río López i està tutoritzat per la Dra Marta Conde, metgessa internista de l'Hospital Universitari Josep Trueta.

La seva participació és totalment voluntària i en qualsevol moment es pot desdir de participar-hi sense necessitat de justificació mitjançant l'ompliment del "Full De Revocació de Consentiment". La seva participació és totalment gratuïta i no obtindrà cap compensació econòmica per formar part de l'estudi.

La persona participant té dret a ser informada dels resultats de la investigació. Aquests resultats i les conclusions de la investigació serviran per beneficiar al participant així com un benefici a nivell poblacional i serviran de base per futures investigacions en aquest camp.

El present estudi es realitza en compliment amb la *Llei Orgànica* 15/1999 garantint la confidencialitat de les seves dades, per aquest motiu les dades recollides seran gestionades de manera anónima i amb l'únic fi de ser emprades per la investigació.

ANNEX 6: INFORMED CONSENT

CONSENTIMENT INFORMAT

Títol de l'estudi: Diferències de presentació clínica de COVID-19 entre sexes.
Jo (nom i cognoms), _____

- He llegit la fulla informativa sobre l'estudi que se m'ha entregat.
- He pogut fer totes les preguntes necessàries respecte l'estudi.
- He rebut suficient informació sobre l'estudi.
- He estat informat de les implicacions i finalitats de l'estudi.
- Entenc que la meva participació és voluntària.
- Entenc que es respectarà la confidencialitat de les meves dades.
- Entenc que puc retirar-me de l'estudi, sense haver de donar justificacions i sense afectar la meva assistència sanitària.

Accepto que els investigadors principals de l'estudi puguin contactar amb mi si en un futur es considera oportú: (Encercla la teva resposta)

Sí No

En cas afirmatiu, telèfon o correu electrònic de contacte: _____

Signatura de la persona investigadora, Signatura del participant,

Data:____/_____/_____ Data:____/_____/_____

REVOCACIÓ DEL CONSENTIMENT

Jo (nom i cognoms),_____, revoco el consentiment de participació a l'estudi a sobre indicat

Firma: Data:____/____/ _____

ANNEX 7: ESTIMATIONS OF SIZE SAMPLE

1- General symptoms

FEVER

FA-TI-GUE

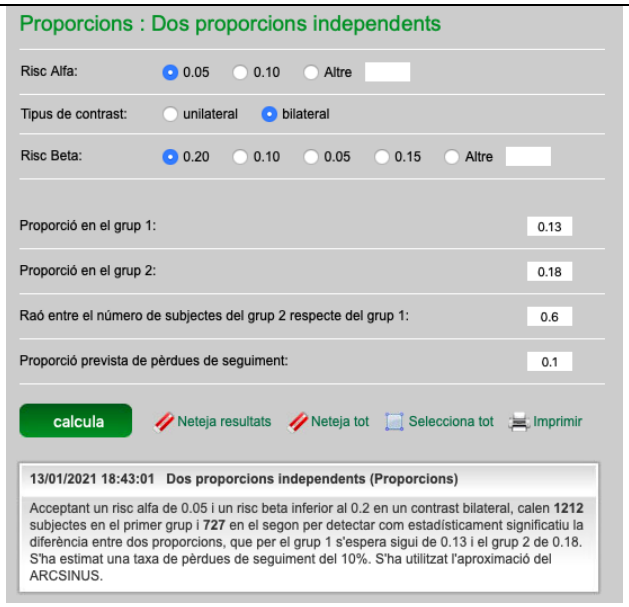
2- Respiratory symptoms:

Cough without expecto-ration	
Cough with expe-cto-ration	
Dys-pnoea	

3- Musculoskeletal symptoms

Mya-lgia	
Join pain	

4- Gastrointestinal symptoms:

Diarrhoea	
Nauseas	
Vomiting	

Abdominal pain	
Anorexia	

5- Otolaryngological symptoms:

Rhinorrhoea	
Nasal congestion	
Sneezing	

Sore throat	
Anosmia	
Ageusia	

Otalgia	

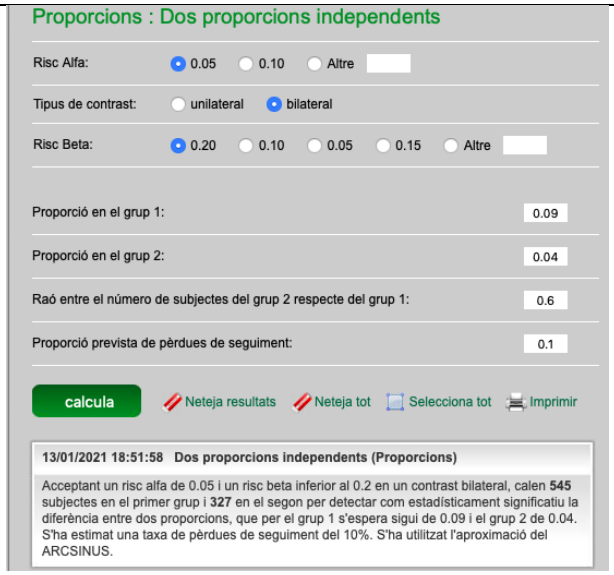
6- Cardiovascular symptoms:

Thoracic pain	
Edema	

Palpitations	
Syncome	

7- Neurological and neuropsychiatric symptoms

Headache	
Dizziness	
Agitation	

Temporal-spatial disorientation	
Altered con-sciousness	
Memo-ry impair-ment	

8- Dermatological symptoms:

Petechiae	
Erythematous rash	
Urticaria	

Vesicles	
Pernio-like lesions	

ANNEX 8: DATA COLLECTION SHEET

FULL DE RECOLLIDA DE DADES

DIA 1 AMB SIMPTOMES:

NOM COMPLET: _____

DATA: / /

Marqui amb una X la seva resposta:

SÍMPTOMA	SI	NO
Febre		
Fatiga/ Cansament		
Tos SENSE expectoració		
Tos AMB expectoració		
Dificultat per respirar: al puja escales, al caminar o al vestir-se		
Dolor muscular		
Dolor articular		
Diarrea		
Nàusees		
Vòmit		
Dolor abdominal		
Anorèxia/Falta de gana		
Rinorrea		
Esternuts		

SÍMPTOMA	SI	NO
Mal de coll		
Anòsmia		
Agèusia		
Mal d'orella		
Dolor toràcic		
Edemes		
Palpitacions		
Síncope		
Mal de cap		
Mareig		
Agitació		
Desorientació en temps o espai		
Alteració de consciència		
Pèrdua de memòria		
Lesions cutànies		

"Conèixer millor les diferències biològiques entre sexes

no ens ha de fer perdre mai de vista el fet que,

les dones, no estem oprimides per la nostra biologia,

sinó per un sistema social basat

en la dominació sexual i de classe"

-Barbara Ehrenreich i Deirdre English-