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Inflammatory environment in patients with COVID-19: Systematic review

Ambiente inflamatorio en pacientes con COVID-19: Revisión sistemática

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ABSTRACT

The SARS-CoV-2 virus is the main cause of the pandemic viral pneumonia known as COVID-19. Some studies suggest that, in this disease, lymphopenia is the most common sign of infection, as well as increased CRP and IL-6 caused by a cytokine storm directed at the lungs. Therefore, the hypothesis of the study is to make a systematic revision of scientific studies linked to the immunological phenomenon known as COVID-19.
Objectives: The main aim is to study the cytokine storm of COVID-19, as well as to determine the role of IL-6 and T-lymphocytes.
Methods: A search strategy was made through the PICOS questions, based on the PRISMA method. The MeSH terms were looked up on PubMed, Google Scholar and SciELO (2019-2021). The level of quality was sought according to the ranking of Scimago institutions, and the H index of the journals was assessed.
Results: 43 articles were included, and clinic, diagnosis, treatment, and pathogenesis were compared. A decrease in TCD4 / CD8 lymphocytes was shown in patients with severe disease, as well as an increase in IL-6 and CRP.
Conclusions: The immunological phenomenon known as COVID-19 is characterized by lymphopenia and an increase in IL-6 amongst critically ill patients. Monitoring those parameters could help to understand the progression of the COVID-19 disease.

KEYWORDS: *COVID-19 - cytokine storm or cytokine release syndrome/pathology – interleukin-6 - SARS-CoV-2 – T lymphocytes*

RESUMEN

El virus SARS-CoV-2 es el responsable de la neumonía viral pandémica conocida como COVID-19. Algunos estudios sugieren que, en esta enfermedad, la linfopenia sea el signo más común de infección, así como el aumento de PCR e IL-6 provocado por una tormenta de citocinas

dirigida a los pulmones. Por ello, la hipótesis del trabajo es realizar una revisión sistemática de los estudios científicos relativos al fenómeno inmunológico de la COVID-19.
Objetivos: El objetivo principal es estudiar la tormenta de citocinas de la COVID-19, así como determinar el rol de la IL-6 y los linfocitos T.
Métodos: Se elaboró la estrategia de búsqueda a través de la pregunta PICOS en base al método PRISMA. Los términos MeSH se buscaron en PubMed, Google Scholar y SciELO (2019-2021). Se buscó el nivel de calidad según la clasificación de instituciones de Scimago, y se valoró el índice H de las revistas.
Resultados: Se incluyeron 43 artículos y se compararon clínica, diagnóstico, tratamiento y patogenia. Se mostró una disminución de los linfocitos TCD4/CD8 en pacientes con enfermedad grave y un aumento de IL-6 y PCR.
Conclusiones: El fenómeno inmunológico de la COVID-19 se caracteriza por linfopenia y aumento de IL-6 en pacientes críticamente enfermos. La monitorización de estos parámetros podría ayudar a entender la progresión de la enfermedad COVID-19.

PALABRAS CLAVE: *COVID-19 – síndrome de liberación de citocinas – interleucina-6 – virus del SARS – linfocitos T*

INTRODUCTION

Etiology

A new coronavirus known as SARS-CoV-2 emerged in December 2019, in Wuhan, China. (1) (2) In fact, on January 30, 2020, the World Health Organization declared COVID-19 a public health emergency of international concern. (3) (4) Severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) is responsible for the pandemic viral pneumonia known as COVID-19. (5) (6)

Epidemiology

COVID-19 patients are mainly adults over the age of 18 .(7) Mortality and/or progression to complications have been reported to be more exposed in men over 65 years of age with associated diseases. (8) (9) We assessed the prevalence of comorbidities in patients with COVID-19 infection and found that the underlying disease may be a risk factor for severe patients compared to non-severe patients. (10) (11) The incidence of severity and mortality from COVID-19 is much higher than that of the common influenza. (12) In Spain, a study analyzed the incidence and mortality in the autonomous communities to predict the evolution of the epidemic. (13) Interestingly, Peng et al. did not see significant responses reflecting geographical and temporal variations. (14) The impact of the breed is also characteristic since in a study Fogarty et al. reported a 3-4 times higher risk of thrombosis in the Caucasian breed than in the black breed. (15) Transmission of COVID-19 is through direct contact or through respiratory droplets such as coughing or sneezing. (16) As age progresses, the immune system seems to maintain mild inflammation. (17)

Signs and symptoms

Clinically, the most common symptoms are fever, cough, shortness of breath, fatigue and headache. (18) The SARS-CoV2 virus infects the lower respiratory tract and causes pneumonia in humans. (19) In a Hong Kong study, viral RNA was found in stool samples from 48.1% of patients with COVID-19. (20) Symptoms analyzed in another study included diarrhea (7.8%), abdominal pain, nausea and vomiting (5.5%).(21) For pregnant and nursing women with COVID-19, symptoms were relatively mild. (22)

Pathogenesis

In relation to COVID-19, severe or critical COVID-19 is characterized by increased markers of innate immune response, decreased markers of adaptive immune response, and increased markers of tissue damage and major organ failure. (23) As for the genome of the coronavirus, it is known to encode four main proteins: spike (S), nucleocapsid (N), membrane (M) and envelope (E). (19)

Three of the most important pro-inflammatory cytokines of the innate immune response are IL- 1, TNF-α, and IL-6. (24) The hyperinflammatory state of the cytokine storm in its most severe form has been marked by the elevation of IL-6, IL-10 and TNF-α among others.(25) (26) In viral infections, the release of pro-inflammatory factors leads to epithelial and endothelial apoptosis of the lung cells which causes ARDS leading to pulmonary fibrosis. (27) On the assessment of pulmonary infiltration in patients with ARDS, the large area of lung injury (50%) is closely correlated with the increase in il-6 level and the lymphocyte subgroup. (28) The binding of SARS-CoV-2 with angiotensin-converting enzyme 2 (ACE2) triggers hyperinflammation. Thus, imbalanced levels of the renin-angiotensin- aldosterone (RAAS) system may be partially responsible for the cytokine storm and the resulting lung damage. (29)

An increase in IL-6 levels has previously been observed in patients with respiratory dysfunction, implying a possible shared mechanism of cytokine-mediated lung damage caused by COVID-9 infection.(30) According to research, there would be a reliable relationship between the severity of IL-6 and COVID-19 that appears to exist. (31) (32)

IL-10 is a type 2 cytokine that inhibits the production of pro-inflammatory cytokines. (9) (33) With HLA class I and II peptides, CD8+ cells, and specific T cells were identified in 70-100% of COVID-19 patients. (34) An early response of CD4+ and CD8+ T cells against SARS-CoV-2 is likely to be protective. (34) The possibility cannot be ruled out that the reduction of peripheral blood T cells is the result of tremendous infiltration of these cells into lung tissues in early response to the effect of cytokines and subsequent apoptosis of these cells. (35)

Disease progression

The cytokine storm can lead to mortality in critically ill COVID-19 patients. (36) Even so, the mortality rate of patients with COVID-19 infection is lower than that of severe acute

respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). (37) The incubation period was 5.24 days on average. (38)

Diagnosis

The cytokine storm associated with rampant inflammation resulted in the release of proinflammatory cytokines and chemokines that severely damage lung tissues leading to death in severe COVID-19 patients.(39) CT findings are important as 92% of RT-CRT confirmed that patients have more frequent bilateral involvement on CT. (40) (41)

On the other hand, some laboratory inspections could predict the progress of COVID-19 changes. (42) The decrease of lymphocytes was closely associated with the severity of COVID-19. (43) However, to confirm these results, further studies are needed. (44) As for CRP, it is used as a diagnostic tool using nasal lavage, tracheal aspiration or bronchoalveolar samples. (45)

Treatment

In the early stages, treatment focuses on reducing viral load. (5) Controlling the cytokine storm through immunomodulators and cytokine antagonists would save patients' lives. (46) For example, anti-IL6 therapy has been proposed to reduce hyperinflammation produced by ARDS (47) and can be applied for the cure of cytokine storm syndrome in patients infected with SARS-CoV-2. The IL6R antagonist may be one of the best options for treating severe COVID-19 patients. (48)

Remdesivir works by inhibiting RNA-dependent viral polymerase. (19) The drug Tocilizumab is a humanized recombinant IL-6 receptor antagonist that interferes with the binding of IL-6 to its receptor (IL6R) and blocks signaling.(49) (50) Baricitinib intracellularly inhibits the proinflammatory signal of several cytokines by suppressing Janus kinase (JAK) JAK1/JAK2.(51) Many other therapeutic options, including Hydroxychloroquine combined with Azithromycin (52), mesenchymal stem cell therapy, and convalescent plasma, have been moved to clinical trials for COVID-19.(50)

Prevention

As vaccines are introduced, it will be essential to assess efficacy against serious diseases and the ability to minimize transmission if vaccination is to be safe and widely accepted by the public. (53) Hand hygiene is fundamental to avoid contamination and recommends wearing personal protective equipment in specific environments. (40) Meanwhile, it should be noted that young people showed higher levels of stress than older people in this sample of patients in the Basque Country.

Therefore, it is important to develop programs to support these groups. (54)

METHODS

A systematic review of the scientific literature on the immunology and inflammatory factors of COVID-19, specifically the cytokine storm in coronavirus disease 2019, was made.

Question PICOS

Based on the PRISMA method (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses)* and with the aim of increasing the sensitivity of the search process, the PICOS question was developed. The acronym in English refers to the study population *(Population),* the intervention *(Intervention),* the comparison of that intervention *(Comparison)* and the results *(Outcomes)*.(55) Finally, the "S" refers to study design.

Patients (P) who were included in the study were diagnosed with COVID-19. The intervention (I) was aimed at assessing the clinical, diagnosis, treatment, and pathogenesis of this virus.

Because several types of interventions were considered, the next question was developed, such as comparison (C). In this case, symptomatic patients were compared with asymptomatic patients in different age and severity groups, in relation to clinical, diagnosis, treatment and pathogenesis.

As for the results (O) obtained, it is expected to study the absence or presence of symptoms in relation to the cytokine storm.

Finally, in the study design (S), all those experimental or observational studies were chosen, see Table 1.

Table 1. PICOS question. Source: Own elaboration.

(P) Patients	Patients of any age diagnosed with COVID-19.
(I) Intervention	Assessment of the clinic of patients with COVID-19 and of imaging tests. Evaluation of the treatment used while they had symptoms of coronavirus 2019 disease. Evaluation of the pathogenesis of COVID-19.
(C) Comparison	To compare asymptomatic and symptomatic patients. Compare the clinic and the treatments of the different age groups. Compare pathogenesis as a function of severity.
(O) Results	Absence/Presence of symptoms in relation to cytokine storm. Symptomatic patients who have tissue damage from SARS-CoV-2 with asymptomatic patients who do not have it.
(S) Study design	Meta-analysis studies. Experimental studies (Clinical trials). Observational studies (Case-control)

Search strategy

We searched electronic databases, in a systematic and structured way based on experimental or observational studies. The search engines used were PubMed, Google Scholar and SciELO as of 2019.

The MeSH (Medical Subject Headings) terms in English were established through the DeCs website, whose acronym corresponds to Descriptors in Health Sciences, and these were used to perform the PubMed search. The MeSH terms were those described in Table 2.

Table 2. Search equation. Source: Own elaboration.

PubMed and MeSH search equation	RESULTS
COVID-19, "in the last 5 years, English", "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR ""2019 ncov""[All Fields] OR ""covid 19""[All Fields] OR ""sars cov 2""[All Fields] OR (((""coronavirus""[All Fields] OR ""cov""[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])"	81883
("COVID-19"[Mesh] AND "SARS-CoV-2"[Mesh]) AND "Interleukin-6"[Mesh]	279
("COVID-19"[Mesh]) AND "SARS-CoV-2"[Mesh]) AND "etiology" [Subheading]	218
COVID-19 AND SarsCoV2 AND cytokine storm	1010
"Cytokine Release Syndrome/pathology"[Mesh] OR "Cytokine Release Syndrome/virology"[Mesh]	198
("COVID-19"[Mesh] AND "SARS-CoV-2"[Mesh]) AND "T-Lymphocytes" [Mesh]	328
"Pulmonary Fibrosis"[Mesh] AND ("COVID-19"[Mesh] OR "SARS-CoV-2"[Mesh])	51

Inclusion criteria

The inclusion criteria were determined based on the PICOS question.

- Type of participants: We included studies whose patients had been diagnosed with COVID-19.
- Type of study: Observational and experimental studies in English or Spanish.
- No age or race limits applied.
- Only scientific articles published in high-impact journals.

Exclusion criteria

- Articles related to cytokine storm, COVID-19 immunological phenomenon and inflammatory markers were excluded.

Assessment of study quality

After the selection process, the quality level of the articles was sought according to Scimago classification of institutions, "*Scimago Journal & Country Rank (SJR)"*. The H index was assessed, which indicates the quality of an article based on how many times it has been cited and the

number of publications of the researcher. On the other hand, the quartile was assessed, which orders the journals from 1 to 4 according to the impact factor. Q1 would be the journals with the highest impact and Q4 the least. Once the articles had been selected, we would go on to describe the results.

RESULTS

After the critical reading of the selected articles, the results of the 43 articles are presented. First, the PRISMA flowchart of the literature search process is represented in Figure 1.

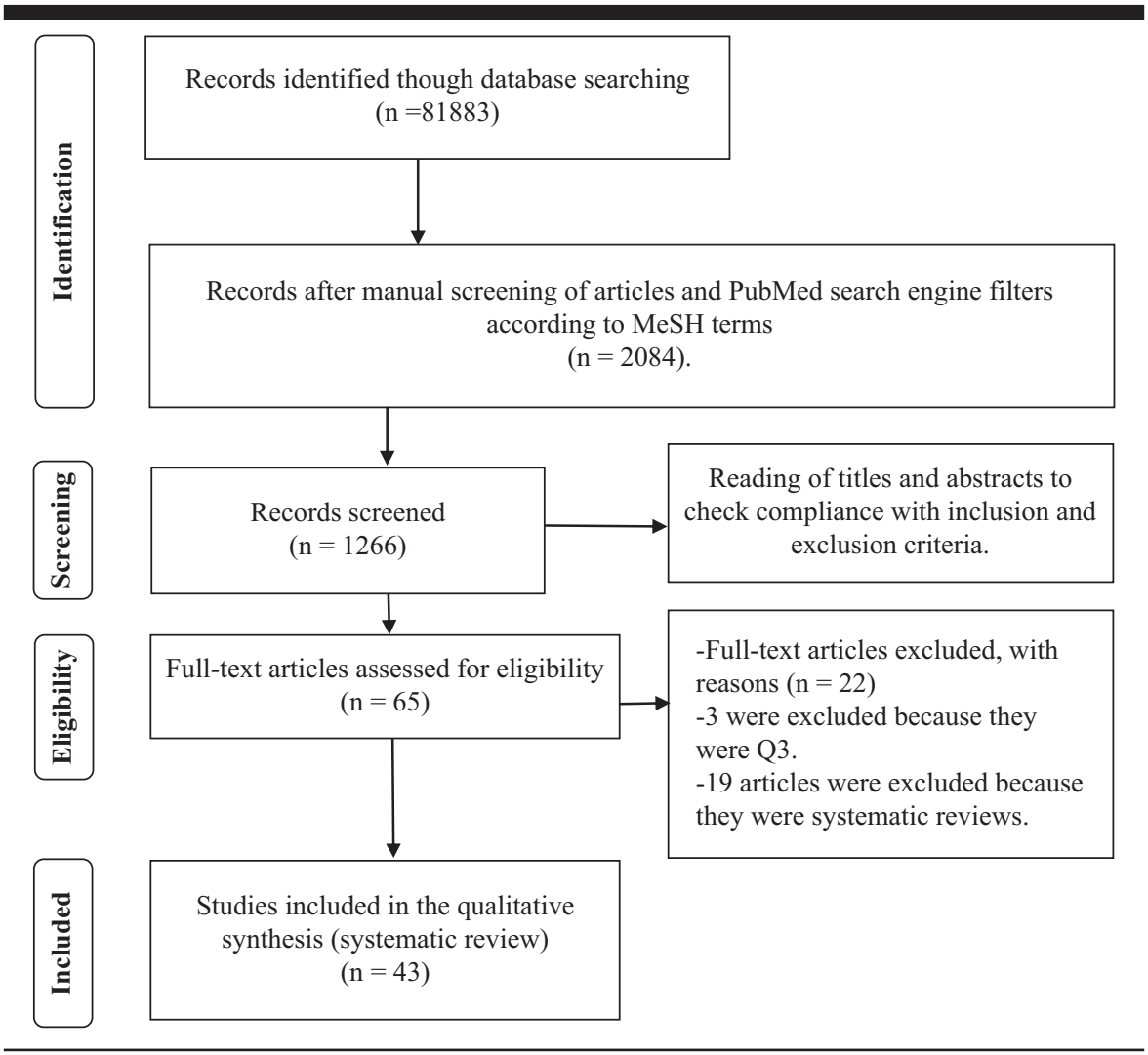

Figure 1. PRISMA flowchart. Source modified from article by Moher D. *et al*. (56)

The total number of patients was 277200. Of the total number of patients 198962 were studied on a clinical basis, 38011 in terms of treatment, 10447 in terms of diagnosis and 29780 in terms of pathogenesis. These data were represented by a pie chart. See Figure 2.

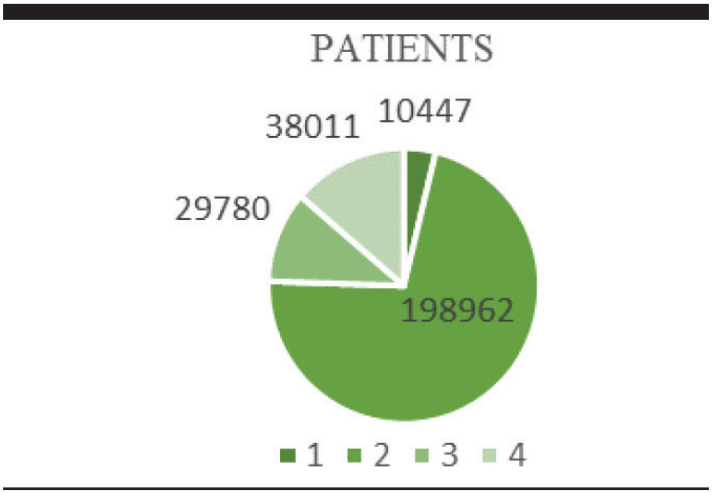

Figure 2. Number of patients in the selected articles. Source: Own elaboration.

The articles chosen for the review were mostly from China, followed by the United States and Italy. Of the 17 countries of the articles chosen in this systematic review, Spain ranks 9th along with Australia, France, and the Netherlands with 2 articles published. See the bar chart in Figure 3.

Figure 3. Countries of selected articles. Source: Own elaboration.

We found many of the articles published in May 2020 as shown in Figure 4.

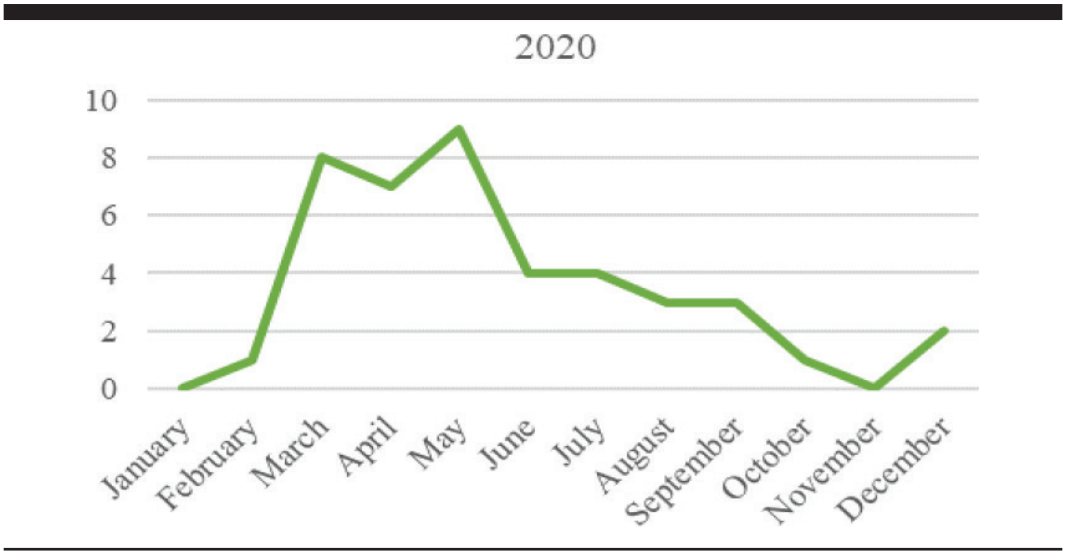

Figure 4. Month of publication of the selected articles. Source: Own elaboration.

Sixty percent of the journals in which the articles chosen for the systematic review were published were Q1, which is the highest quality. As this was an exclusion criterion, journals with a Q3 were excluded from our systematic review. See the pie chart in Figure 5.

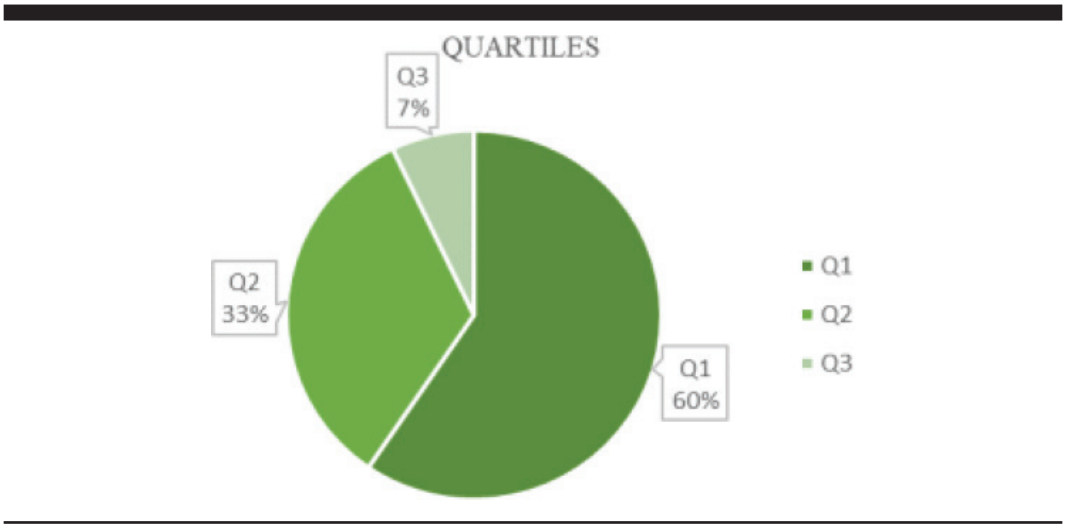

Figure 5. Percentage of the quartiles of the journals of the selected articles. Source: Own elaboration.

In Table 3 the journals are ordered from highest to lowest according to the quartiles. The H and *SJR* index that value the quality of journals were also added.

Table 3. Journals ordered from highest to lowest according to quartiles

	MAGAZINES	Quartile	SJR	H-Index
1.	JAMA - Journal of the American Medical Association	Q1	5.91	654
2.	Journal of Clinical Investigation	Q1	5.97	471
3.	PLoS ONE	Q1	1,02	300
4.	Annals of the Rheumatic Diseases	Q1	6.14	228
5.	American Journal of Cardiology	Q1	1.48	215
6.	European Journal of Immunology	Q1	2.12	194
7.	British Journal of Anesthesia	Q1	2.39	170
8.	Clinica Chimica Acta	Q1	0.88	135
9.	International Journal of Antimicrobial Agents	Q1	1.51	118
10.	Virus Research	Q2	1.19	114
11.	Journal of Medical Virology	Q2	0,86	111
12.	Clinical Biochemistry	Q2	0.78	107
13.	Epidemiology and Infection	Q2	1.12	106
14.	International Immunopharmacology	Q1	0.99	106
15.	Frontiers in Immunology	Q1	2.12	102
16.	Pediatric Pulmonology	Q1	0,93	102
17.	Journal of Infection	Q1	1.98	96
18.	Seminars in Thrombosis and Hemostasis	Q1	1.05	96
19.	Progress in Cardiovascular Diseases	Q1	2,08	94
20.	Immunogenetics	Q2	0,96	90
21.	Nutr Metab Cardiovasc Dis	Q1	1.1	90
22.	Cytometry Part A	Q1	1.23	84
23.	International Journal of Infectious Diseases	Q1	1.44	79
24.	Journal of Pharmacy and Pharmaceutical Sciences	Q2	0,4	75
25.	Cell Proliferation	Q1	1.26	70
26.	Clinical Research in Cardiology	Q1	2,11	65
27.	Medicina Clínica	Q3	0,25	64
28.	Journal of Investigative Medicine	Q2	0,7	63
29.	European Journal of Medical Research	Q2	0,54	55
30.	Psychiatric Quarterly	Q2	0.59	48
31.	Current Problems in Cardiology	Q1	1,04	46
32.	Brazilian Journal of Infectious Diseases	Q2	0.74	42
33.	Therapeutic Advances in Respiratory Disease	Q2	0.91	35
34.	Diabetes & Metabolic Syndrome: Clinical Research & Reviews	Q2	0,67	29
35.	Journal of global oncology	Q3	0,58	8
36.	Family Medicine and Community Health	Q3	0,16	7
37.	AGING			

The journals *"Clinica Chimica Acta", "European Journal of Immunology", "Journal of Clinical Investigation",* "Progress *in Cardiovascular Diseases",* with a Q1 and *"Journal of Medical Virology"* with a Q2, appear more than 1 time for having selected 2 articles or more for our studio.

The search process led to the inclusion of studies of different types, meta-analyses (82%) and research studies (18%). Figure 6 depicted in a pie chart shows the types of study with their percentages.

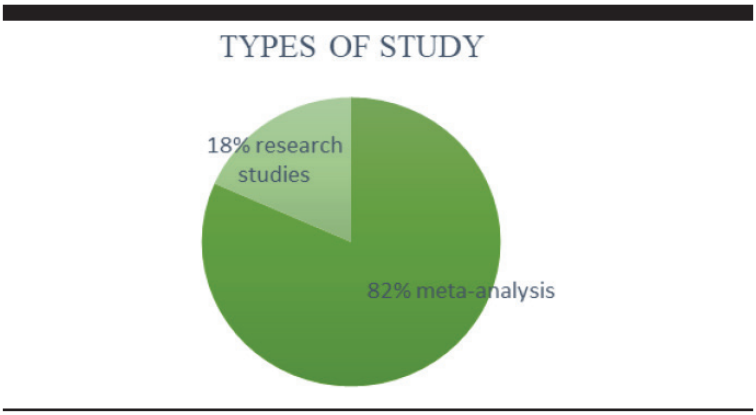

Figure 6. Types of study 82% meta-analysis and 18% research studies. Source: Own elaboration.

As depicted in Figure 8 by the bar chart, the average age for the patients studied was around 52-60 years.

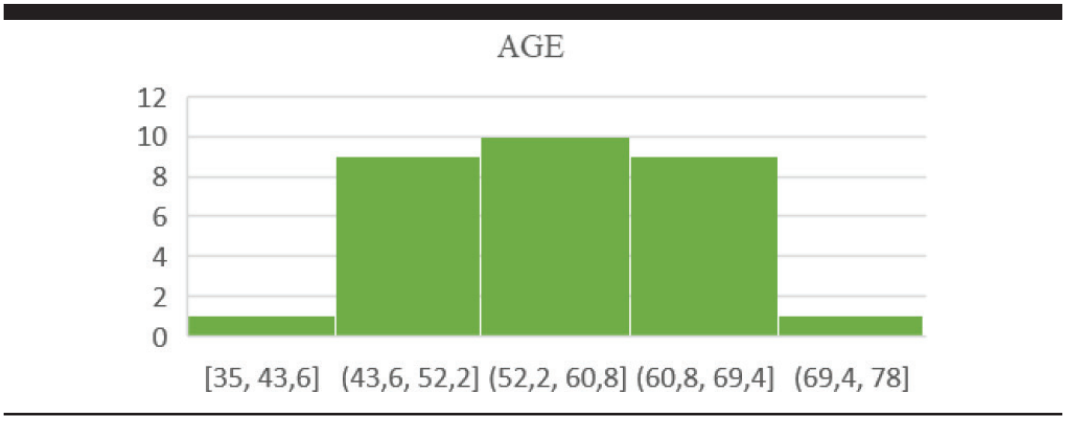

Figure 7. Ages of patients in the selected articles. Source: Own elaboration.

After analyzing the age of the patients, the gender of them was studied in which the male sex was de 62% and the female 38%. See the pie chart in Figure 8.

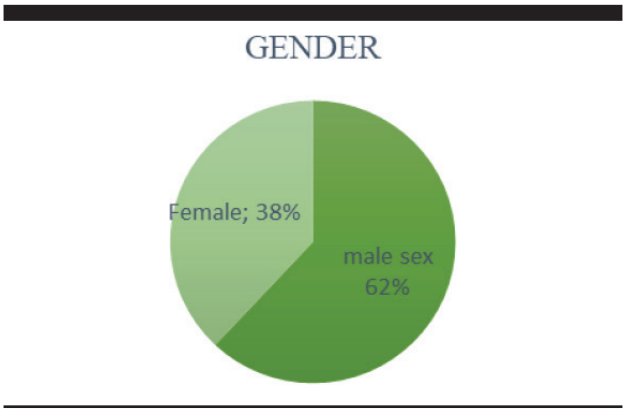

Figure 8. Gender of the patients in the articles. Source: Own elaboration.

Genetics

A multicenter case-control study from *"The New English and Journal of Medicine"* on the genome association of severe COVID-19 in patients with respiratory failure, included 1610 patients in the case group and 2205 participants in the control group of 7 hospitals in Italy and Spain. They identified a *cluster* of 3p21.31 genes as a locus of genetic susceptibility in COVID-19 patients with respiratory failure. (57)

Clinic

In a meta-analysis of Li, *Long Quan et al.* studied the clinical characteristics of COVID-19 patients as can be seen in Table 4. (58)

Table 4. Symptoms and laboratory data in COVID-19 patients. Source:(58)

Main symptoms of COVID-19	Minor symptoms of COVID-19	Most common laboratory data in COVID-19
Fever (88.5%), Cough (68.6%) Myalgia or fatigue (35.8%) Expectoration (28.2%) Dyspnea (21.9%).	Headache or dizziness (12.1%) Diarrhea (4.8%) Nausea and vomiting (3.9%)	Lymphocytopenia (64.5%) Increased CRP (44.3%) Increased LDH (28.3%) Leukocytopenia. (29.4%)

A study by Wang, *Bolin et al.* on COVID-19 risk factors identified hypertension, diabetes, COPD, cardiovascular disease and cerebrovascular disease as significant risk factors for COVID-19 patients as can be seen in Table 5. (72)

Table 5. Risk factors for COVID-19 patients Source: Own elaboration

Risk factors for COVID-19 patients		
Acute renal failure. (IRA)	The presence of AKI is associated with a 13-fold increased risk of mortality. (60)	
Cardiovascular disease. (CVD)	- 3 times higher probability of COVID-19 infection and 11 times higher risk of mortality from COVID-19. (61) - Pre-existing CVD risk or established CVD, increased risk of developing severe COVID-19 disease. (62) - Levels of cardiac biomarkers (TnI, CK-MB, NT-BNP, D- dimer and LDH) as well as inflammatory markers (CRP and IL-6) were significantly elevated in patients with severe COVID-19 infection. (64) - cTnI values were significantly increased in patients with severe SARS-CoV-2 infection. (65)	Heart disease and diabetes increase the risk of death twice as much as other risk factors. The overall proportion of hypertension, cardio-cerebrovascular diseases and diabetes was approximately 2 times, 3 times and 2 times, respectively, higher in ICU/ severe cases than in non-ICU/severe cases. (63)
Diabetes mellitus	- Diabetes in patients with COVID-19 is associated with a double increase in mortality. (66) - Pre-existing diabetes was associated with an approximately two fold increased risk of having severe/critical COVID-19 disease and triple risk of hospital mortality. (67)	
Hypertension		
Cerebrovascular disease		
Mental illness	Anxiety 25% and depression 28%, respectively. (69)	
Venous thromboembolism	The rate of thromboembolic complications in COVID-19 patients is 30%. (68)	
COPD		

Consequently, we will report in more detail the risk factors established in Table 5.

Acute renal failure (ARF)

The mortality of 5497 patients was studied through 26 studies of data meta-analysis, where the incidence of AKI was 8.4%. The data reflect that the incidence was higher in critically ill patients (19.9%) compared to hospitalized patients (7.3%). AKI is present in 8.3% of COVID-19 patients and 19.9% of critically ill patients. In conclusion, the presence of ARF is associated with an increase of 13 times the risk of mortality. (60)

Cardiovascular disease

The appearance of CVD was associated with a 3-fold increased probability of COVID-19 infection and an 11-fold increased risk of mortality. (61) In another study, Krittana Wong, *Chayakrit* et *al.* they concluded that patients at risk of pre-existing CVD, as well as DM and hypertension, were associated with an increased risk of developing severe disease. (62)

In the following study on metabolic diseases and severity by COVID-19, Li, *Bo* et *al.* they again found that the most frequent risk factors were hypertension, cardio-cerebrovascular diseases, and diabetes. The proportion of hypertension and cardio-cerebrovascular disease were both statistically more significant in ICU/severe patients compared to non-ICU/severe patients. They concluded that heart disease and diabetes increase the risk of death twice as much as other risk factors. (63)

In another study by C. Walker et *al.,* there was a significant association between elevated cardiac biomarkers and COVID-19 severeness, underscoring the increased risk of acute heart injury with more severe viral infection. The data showed that levels of cardiac biomarkers (TnI, CK-MB, NT-BNP, D-dimer and LDH) as well as inflammatory markers (CRP and IL-6) were significantly elevated in patients with severe COVID-19 infection compared to non-chronic infection. (64)

Another studio by G. Lippi et *al.* shows that cTnI values were significantly increased in patients with severe SARS-CoV-2 infection compared to milder forms of the disease. (65)

Diabetes mellitus (DM)

According to the study by A. Mantovani *et al.* on diabetes mellitus, the prevalence of diabetes was higher in non-Asian vs. Asian countries (23.34% [95% CI: 16.40 e30.28] vs. 11.06% [95% CI: 9.73e12.39]), and in patients aged over 60 years vs. those under 60 years (23.30% [95% CI 19.65e26.94] vs.8.79% [95% CI 7.56e10.02]). The data showed that pre-existing diabetes could be associated with a twofold increased risk of having severe/critical COVID-19 disease and triple risk of hospital mortality. (67) In a similar study, A. Kumar *et al*. showed that diabetes in COVID-19 patients had twice the mortality and severity compared to non-diabetics. (66)

The rate of venous thromboembolism

According to the study by Alessandro Di Minno *et al.* the hypercoagulable state in COVID-19 patients can lead to a high thrombotic risk. In conclusion, the rate of thromboembolic complications in patients with COVID-19 is high (30%.) (68)

Mental illness

As for mental illness, the meta-analysis by Xin Ren et *al.* showed that the combined prevalence of anxiety and depression was 25% and 28%, respectively. (69)

Treatment

The drugs that were studied to treat COVID-19 patients were those shown in Table 6.

Table 6. Medicines used for COVID-19. Source: Own elaboration

DRUGS	PATIENTS	DOSE	EFFECT
Systemic corticosteroids (73)	222/678 deaths among patients randomized to corticosteroids and 425/1025 deaths among patients randomized to usual care or placebo	- Dexamethasone: 20mg/d x 5d - Hydrocortisone: 200mg/d x7-14d - Methylprednisone: 40mg every 12h	Decreases mortality at 28 days.
IECA/AIIRA (74)	Critics (n = 4134) vs. non- critics (n = 20542)	It could not be established.	ACE inhibitors/AIIRA may be associated with a better prognosis of COVID-19.
Statins (75)	8990 COVID-19 patients	Atorvastatin. Average duration: 22 days. Average dose: 20.0 mg/d. 87 patients: 40mg	Reduces gravity by 30%
Remdesivir (76)	2290 patients with COVID-19. - 400 Remdesivir 5 days - 1090 Remdesivir 10 days. - 800 standard care.	It could not be established.	The rate of clinical improvement was significantly higher in the 5-day Remdesivir group compared to the 10-day Remdesivir group
HESC-IMRC (77)	27 patients. 7 discharged and 20 admitted.	The dose of this treatment was 3106 cells/kg intravenously.	In patients with pulmonary fibrosis, all showed clinical improvements in the 84 days after treatment with HESC-IMRC.
Tocilizumab (80)	42 patients.	1 single intravenous dose of 400mg	It can be effective in patients with severe or critical infection if started quickly during the severe stage. At day 28, a total of 7 patients died.
Azithromycin + hydroxychloroquine (HCQ) and Lopinavir/Ritonavir (LPV/r) (79)	A total of 55 patients in the control group who received hydroxychloroquine (HCQ) and Lopinavir/Ritonavir (LPV/r) were compared with 56 patients in the case group who, in addition to the same regimen, also received AZM	The case group received AZM 500mg/day, LPV/r 400/100mg twice daily and HCQ 400mg/ day orally. The control group received LPV/r 400/100mg twice daily and HCQ 400mg/day orally; All medications were given for 5 days.	Patients in the group that received the experimental treatment with AZM had a significantly shorter hospital stay, as well as significantly higher SpO2 and lower respiratory rate at discharge.
Drug combination: methylprednisolone + Tocilizumab. (78)	86 patients in the treatment group and 86 in the control group	Methylprednisone iv. for 5 days (250mg on day 1 and 80mg on days 2-5). If the respiratory condition did not improve, Tocilizumab (8mg/kg) was added on or after day 2.	Combination therapy of Methylprednisone and Tocilizumab may accelerate respiratory recovery, reduce in-hospital mortality, and reduce the likelihood of invasive mechanical ventilation

Systemic corticosteroids

It was concluded that the use of corticosteroids decreased mortality at 28 days. (73)

ACE inhibitor/AIIRA

Patients who had ACE inhibitors/AIIRA as a base for the treatment of arterial hypertension did not provide an increased risk. We compared patients with critical (n = 4134) vs. non-critical (n=20,542) outcomes and concluded that renin angiotensin aldosterone (RAAS) system inhibitors might be associated with a better prognosis of COVID-19. (74)

Statins

As for statins, their use in moderate or high interest was shown to reduce the severity of COVID-19 disease by 30%. (75)

Remdesivir

De 2290 COVID-19 patients who were studied, 400 were treated with Remdesivir for 5 days and 1090 for 10 days. The remaining 800 had standard care. As shown in figure 9, the rate of clinical improvement was significantly higher in the Remdesivir group at 5 days compared to the Remdesivir group at 10 days. (76)

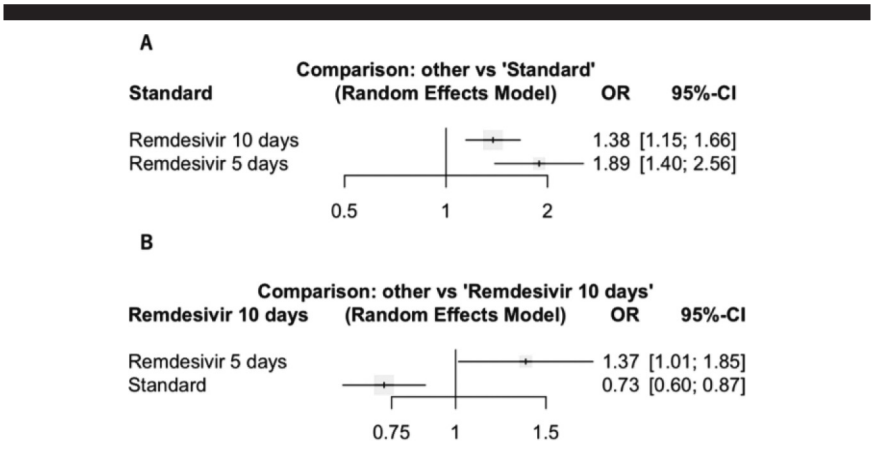

Figure 9. Prevention strategies for clinical improvement (random-effects model); a**:** vs. Standard care; b; Remdesivir of 10 days = confidence interval; or = odds ratio. Source: (76)

HESC-IMRC in pulmonary fibrosis

They identified 27 patients who had been COVID-19 positive for 3 consecutive weeks and who had pulmonary fibrosis pathology. All showed clinical improvements in the 84 days after treatment with HESC-IMRC. (77)

Tocilizumab

Of the 72 evaluated patients with severe or critical SARS-cov-2 infection, 42 were finally included in the study. Of these, 20 (48%) had the stage of severe infection and 22 (52%) were in the critical stage.

A single intravenous dose of 400mg of Tocilizumab was administered to all patients. After administration only 6 patients (14%) required invasive mechanical ventilation and 35 (83.33%) patients improved clinically. On the 28th day, 7 patients died. Primary outcomes therefore included changes in oxygenation support, need for invasive mechanical ventilation or death. And secondary outcomes included radiological changes, adverse drug reactions, neurological involvement, and changes in IL-6 and C-reactive protein levels. They concluded that Tocilizumab may be effective in patients with severe or critical infection if it is started rapidly during the severe stage. (80)

Drug combination: high doses of methylprednisolone + Tocilizumab

Of the 350 patients admitted between March 7 and 31, 2020, 86 patients from the treatment group and 86 from the control group were studied. Initially, all COVID-19 patients had symptoms of cytokine storm and acute respiratory failure, as well as high levels of C-reactive protein (>100 mg/L), ferritin (>900 μg/L) and D-dimer (>1500 μg/L). Patients in the treatment group received high doses of intravenous Methylprednisolone for 5 consecutive days (250 mg on day 1 followed by 80 mg on days 2-5). If the respiratory condition did not improve (43%) a single dose of Tocilizumab (8 mg/kg) was added on day 2. Of the treated patients, 79% improved satisfactorily, had 65% lower mortality and 71% did not need invasive mechanical ventilation.

In conclusion, the combined treatment of Methylprednisolone and Tocilizumab can accelerate respiratory recovery, reduce in-hospital mortality, and reduce the likelihood of invasive mechanical ventilation in patients with COVID-19-associated cytokine storm. (78)

Azithromycin

In a case-control study, patients in the control group (n=55) who received hydroxychloroquine (HCQ) and Lopinavir/Ritonavir (LPV/r) were compared with patients in the case group (n=56) who received Azithromycin and HCQ/LPVr. Patients in the case group, HCQ + AZM had a shorter hospital stay, higher SpO2 and lower respiratory rate.

Therefore, they concluded that the combined use of these drugs may be beneficial in patients at low risk of heart disease based on the ACC criteria. (79)

Diagnosis

As for the diagnosis, the results of the meta-analysis by Jieyun Zhu *et al.* in which 4121 patients were studied, they showed that the majority had bilateral lung involvement (73.8%), as well as multilobed involvement (67.3%). The most typical manifestation of chest CT was ground-glass opacities (68.1%). (84)

In another article Rami M. Elshazli *et al.* studied the diagnosis and prognosis of 6320 patients. The results of the cohorts showed that patients with high IL-6, CRP, D-dimer and neutrophils had a higher probability of mortality. (82)

Pathogeny

The results obtained in the COVID-19 inflammatory marker studies are shown in Table 7.

Table 7. Immunological parameters in COVID-19. Source: Own elaboration.

PARAMETERS	CHARACTERISTICS
IL-6	-The increase in IL-6 was significantly associated with severe disease, ICU admission and mortality. (85) (86) -Severe patients with COVID 19 had a higher IL 6/IFNγ ratio than moderate patients. (99)
IFN-γ	Patients' age and comorbidity were related to lower levels of IFN-γ (94)
CRP	- The non-severe group had lower levels of CRP. (86) - Severe patients had increased CRP. (89) -Elevated CRP was not associated with higher mortality, but was associated with increased risk of severe COVID-19, and the need for ICU care. (91) - CRP was above normal ranges in 100% of patients admitted to the ICU. (98)
PCT	Increased procalcitonin in severe COVID-19 patients. (91) (89)
ESR and SAA	The non-severe group had lower levels of ESR and SAA. (86)
Serum ferritin	Increased ferritin was associated with higher mortality. (91) and (98)
Creatinine	Severe illness and deaths higher creatinine count. (89)
White blood cell count.	Severe illness and deaths increased white blood cell count. (89)
CD4+/CD8+ T lymphocytes, B lymphocytes and NK cells	- Lymphocyte counts showed a statistically significant reduction in patients with severe/critical COVID-19 disease compared to mild/moderate disease.(93) - Low levels of lymphocytes were associated with severe CoV-2 infection. (89) (94) - The age and comorbidity of the patients was related to the increase in frequencies of CoV-2- specific TCD4+ cells. (94) - CD4+ T lymphocytes deteriorated qualitatively in critically ill patients. (95) - Convalescent patients had altered peripheral TCD4+ cells. (96)

PARAMETERS	CHARACTERISTICS
cTfh cells	Patients with COVID-19 had a higher frequency of memory-effecting cTfh cells. (96)
IL-2	The age and comorbidity of patients associated with higher levels of IL-2. (94)
ALT, AST	Severe disease and deaths increased ALT, AST counts.(89)
D-dimer	Severe illness and deaths increased D-dimer count. (89) (91) and (98)
Platelets	- Low platelet count increased risk of severe disease and mortality. (87) and (89)
LDH	LDH was above normal ranges in 100% of patients upon admission to the ICU. (98)
IgG	The response of the IgG antibody was remarkably strong in critically ill patients. (95)

In a meta-analysis by Peihua Zhang *et al.* in which 8752 COVID-19 positive patients were studied, the results indicated that increased IL-6 was significantly associated with severe illness, ICU admission, and mortality. (85)

The 3962 patients with COVID-19 that were studied in the meta-analysis by Furong Zeng *et al.*, were divided into severe and non-severe. The results showed that in the non-severe group they had lower levels of CRP, PCT, ESR, IL-6, SAA, and serum ferritin. Similarly, survivors had a lower level of IL-6 than non-survivors. Therefore, they concluded that these parameters were correlated with COVID-19 severity. (86)

In the following study, Giuseppe Lippi *et al.* revealed that low platelet counts were associated with an increased risk of severe disease and mortality. In addition, they observed that thrombocytopenia was associated with a 5-fold increased risk of severe COVID-19. (87)

The results of the metanalysis of *Mingchun Ou et al.* showed that patients with severe disease had a lower platelet and lymphocyte count, but higher CRP, lactate dehydrogenase, white blood cell count (WBC), PCT, D-dimer, ALT, AST, and Cr. (89)

For the study by Huang, Ian. *et al.* 5350 patients were pooled from 25 studies among which it was found that increased PCT, D-dimer and ferritin was association with higher mortality. In contrast, elevated CRP was not associated with higher mortality, but was associated with an increased risk of severe COVID-19, and the need for ICU care. The cut-off parameters were high CRP (10 mg/L), PCT (0.5 ng/mL) and D-dimer (>0.5 mg/L). Thus, this analysis showed that the association between elevated CRP, PCT, D-dimer and serum ferritin level was not significantly affected by gender, age, hypertension, cardiovascular disease, diabetes and COPD. (90) Similarly, the results of the analysis of *Lippi, Giuseppe et al*. showed an increase in procalcitonin in severe COVID-19 patients. (91)

The 20 publications selected for the meta-analysis by Wei Huang *et al.* included a total of 3017 subjects with CD4+ cell counts, where 2311 were classified as "Mild/Moderate" (76.6%) and 706 were classified as "Severe/Critical" (23.4%). All counts of CD4+ T cells, CD8+ T cells, CD19+B cells, CD16+CD56+ NK cells, and total lymphocyte cells showed a statistically significant reduction in patients with severe/critical COVID-19 disease compared to mild/moderate disease. Throughout these studies, CD4+ or CD8+ T cell counts were independently related to mortality, ICU admission, viral clearance, and recovery (see summary in Table 7). (93)

Results obtained by Arne Sattler *et al.* found that low lymphocyte levels were associated with severe CoV-2 infection. They showed that the specific response of CD4+ T cells was directed against the 3 M (membrane), N (nucleocapsid) and S (spike) proteins of the responding patients. Instead,

patients who died were more likely not to develop a cellular response to these proteins. On the other hand, the age and comorbidity of the patients was related to the increased frequencies of CoV-2- specific TCD4+ cells, harboring lower levels of IFN-γ and higher levels of IL-2. (94)

In Oja's *studio, Anna E. et al.* blood was collected from a total of 56 COVID-19 patients in whom CD4+ T cell responses were found to deteriorate qualitatively in critically ill patients (n=21). However, in these patients the specific response of the IgG antibody was remarkably strong. In addition, in the critically ill patients, a massive influx of circulating T cells into the lungs was observed, which intensified the local compartment of the T cells, and indicated vascular leakage. Finally, a significant correlation between the abundance of reactive CD4+ S T cells and the course of COVID-19 disease was observed for the mild group (n=21) and the ICU, but not for patients in the severe group (n=14). (95)

Fang Gong *et al.* did a CD4+ T cell analysis on 13 COVID-19 convalescent patients who had been confirmed SARS-CoV-2-free for 2 to 4 weeks. They showed that convalescent patients had altered peripheral TCD4+ cells compared to healthy patients. They showed that convalescent patients had a higher frequency of memory effector cTfh cells. The study demonstrated a close connection between CD4+ T cells and antibody production in convalescent COVID-19 patients. (96)

The study by Mazzoni, Alessio *et. al,* detected that T cells were reactive to sars-CoV-2 M, N and S proteins as well as IgM, IgA and IgG were specific to the serum virus, in almost all individuals infected with SARS-CoV-2, but not in healthy donors. More importantly, symptomatic patients showed a significantly greater magnitude of both cellular and humoral adaptation. (97)

In a longitudinal study by Didier Payen *et al.* on the immunity of 15 patients with COVID-19 in ICU, it was shown that mortality from this virus was related to the function of T cells. Nonspecific markers of systemic inflammation such as CRP, ferritin, D-dimer, fibrinogen, and LDH were largely above normal ranges in 100% of patients upon admission to the ICU. The lowest level of immunosuppression was observed in the initial phase between days 7-14 and tended to recover between days 15-23 and 24-35. A significant positive correlation was found in all periods between HLA-DR expansion and CD4/CD8 T cells. In conclusion, they showed that innate immunity as adaptative varied over time after SARS-CoV-2 infection. (98)

In the study of Lagunas-Rangel, F.A. *et al.* a meta-analysis was performed to investigate whether the IL-6/IFNγ ratio can help predict clinical severity in patients with COVID-19. They found that severe patients with COVID-19 had a higher IL 6/IFNγ ratio than moderate patients, which could be related to an increased cytokine storm that favors lung damage. (99)

Covid-19 in children

Rita Assaker *et al.* studied the symptoms of COVID-19 in children. For the diagnosis the CT was used in which typical changes were observed in only 55% of the patients so the study showed that the CT was of lower value in children than in adults. They also showed that the most effective test for detecting infected pediatric patients is CRP. Finally, this study conclusively confirmed that COVID-19 in children typically presents as a mild (37%) or moderate (45%) upper respiratory tract infection and is rarely severe or critical. (70)

According to the study by Linjie Zhang et *al.,* 551 children with laboratory-confirmed COVID-19 were hospitalized or treated in the emergency department (n=100), of which 18% were asymptomatic. The most common symptoms and signs were fever (53%), cough (39%) and sore throat (14%) but much less frequently than adults. Therefore, they concluded, children of all ages can contract COVID-19, although they appear to be affected less often than adults. (71)

In the case of children between 0 and 17.5 years old, the most characteristic of hematology was the decrease in neutrophil count (38%) (95% CI: 19-60%). Elevations in CRP levels were also observed in 18%, PCT in 26% and lactate dehydrogenase (LDH) in 28%. Creatine kinase-MB (CK- MB) was also elevated in 33% of patients. However, in the case of infants (< 1 year) hemoglobin and creatinine decreased significantly and they had significantly higher levels of leukocytes, lymphocytes, and platelets, along with elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT) and LDH, without any of these changes being significant. Regarding sex, males had significantly higher leukocytes. (92)

Following the results mentioned, I will proceed to discuss them.

DISCUSSION

The main objective of this systematic review was to study the immunological phenomenon or COVID- 19 disease.

The originality of this systematic review is based on the complete view of new developments on COVID-19, but it is also a limitation that there are not enough studies to determine the pathogenesis of SARS-CoV-2 and it is unknown how the cytokine storm affects each person individually.

In our results we appreciated how age and gender seemed to be related to COVID-19 as previous articles mentioned. (9) We therefore believe that one of the reasons why inflammatory factors increase may be age around 60 years and predominantly male sex.

Regarding genetics, the direct relationship of the mentioned studies with the severity of COVID-19 could not be concluded.

Regarding the clinic, it differed between the different phases of the disease. In the selected articles, most of the symptomatic patients had a respiratory clinic as we might think when it was a viral pneumonia. On the other hand, in children, the most frequent is that they were asymptomatic patients or with mild symptoms.

The comorbidities studied were diabetes, hypertension, respiratory, cardiac, or cerebrovascular diseases. In many of them mortality increased, or they progressed to severe disease, but we cannot confirm this because in the limits of some studies they did not consider the comorbidities of the patients.

On the other hand, cardiovascular disease, diabetes, and the presence of AKI are a highly progressive factor in mortality.

Likewise, Zheng, Mao *et al.* published in 2021 an article on diabetes showing that COVID-19 patients with elevated glucose levels promote cytokine profiles and immune response. (101)

The treatments used for COVID-19 patients in our review were corticosteroids, statins, Remdesivir, Tocilizumab, Azithromycin, and combination of Tocilizumab with corticosteroids. Similarly, we cannot affirm that these treatments reduce the mortality of patients, although in the selected articles

the time of hospital admission decreased, or the prognosis improved if they were used before progressing to serious disease.

Similarly, a study by Ferrara, Francesco and Vitiello, Antonio published in 2021, verify that a significant association between the use of statins and a reduction in mortality from COVID-19 could not be demonstrated. (103)

In a new January 2021 study on the use of Tocilizumab alone or in combination with corticosteroids, at the San Cecilio University Hospital in Granada, for patients with severe SARS- CoV-2 pneumonia, they said that the use of Tocilizumab would have to be limited to clinical trials as its use could increase hospital stay in the ICU without improving mortality. (104)

As *Attia's article, Youssef A.*et al. in February 2021 says, complete control of SARS-CoV-2 infection is likely only possible after full vaccination. (105)

Moreover, we believe that the long interval between infection and administration of these drugs may have played a role in reducing antiviral efficacy.

In terms of diagnosis, most articles suggested that CT was the best test of choice for COVID-19 disease progression as the images changed as the disease progressed. Almost all the articles presented the ground-glass opacities as the typical finding of lung disease and most presented multilobe involvement and bilateral pulmonary involvement. In our opinion, CT would be useful for the monitoring of the disease in critically ill patients or those admitted to the ICU, as well as to evaluate the severity of patients and the efficacy of treatment. In January 2021 *Rostad, Bradley S. et al.* published a study with the same results. (102)

On the other hand, inflammatory markers such as IL-6 or CRP could be useful for the diagnosis of the SARS-CoV-2 virus as seen in the results of our work.

Consequently, the results of this work mostly suggest a decrease in T lymphocytes in patients with severe disease and an increase in IL-6 compared to mild or asymptomatic patients. Based on the results, we believe that these alterations could be related to the massive influx of T lymphocytes into the lungs and subsequent vascular leakage causing a cytokine storm that favors lung damage. It was also seen that the specific response of CD4+ T cells was directed against the 3 proteins M (membrane), N (nucleocapsid) and S (spike) of the responding patients.

An article by *Jiang, Nan et al.* published in January 2021 verified these results showing that SARS-CoV-2 would induce lymphopenia and subsequently induce hyperinflammatory response and cytokine storm. (100)

In the same way, other parameters such as platelets, D-dimer, CRP, lactate dehydrogenase, white blood cell count (WBC), PCT, ALT, AST and Cr were studied. among others. We believe that these laboratory parameters could be related to COVID-19 severity as shown by some of the studies mentioned, although it is not clear that they increase mortality.

Other inflammatory biomarkers of importance in our work such as CRP and PCT also increased in severe disease in several studies which could be useful to assess the severity of the disease. In our study, we found higher ESR in the severe group, and one of the reasons it might increase is that severe patients had higher inflammation.

We believe our results may be useful in better understanding the progression of COVID-19 disease as well as the immunopathological phenomenon and cytokine storm of SARS-CoV-2.

However, the strength of this evidence is very weak as it comes from articles with various limitations. For example, the small sample size, the lack of a randomized control group, the limited time

to publish the articles, the incomplete data collection, or errors in reporting the laboratory markers units. In addition, many of the studies had not looked at comorbidities in cases of death or did not differentiate between age and sex.

Consequently, the limits of our study would be affected by the above limitations. In addition, the criteria of judgment for severe and non-severe patients were not uniform since they differed in each of the articles, which meant a limitation in the development of the work. Therefore, subsequent studies would be necessary to clarify the phases of the COVID-19 disease and specify the clinical and diagnostic associated with mild, moderate, or severe disease.

Although our study ends in 2020, due to the topicality of the topic to be discussed, they have added articles from 2021 to the discussion that provide more updated information and verify the results obtained in our study.

Finally, due to the limited quality and quantity of the included studies, more high-quality prospective studies, randomized clinical trials with a longer follow-up period and in more populations, are required to verify the conclusions.

CONCLUSION

The cytokine storm caused by the SARS-CoV-2 virus could be related to a decrease in T lymphocytes in symptomatic patients and an increase in IL-6. Other inflammatory markers also play an important role in the COVID-19 disease, such as CRP, PCT or INF-γ, among others. The study of these parameters could help to understand the progression of the disease and mortality from this cause.

Ground-glass opacities are characteristic of CT in critically ill patients which could be related to the spread of T lymphocytes to the lungs. Monitoring these patients by CT scan could help to understand the pulmonary fibrosis caused by the cytokine storm.

Age, gender, and comorbidities such as diabetes, hypertension or cardiovascular disease could increase the inflammatory phenomenon.

As for the treatment currently available, we cannot say that it improves the prognosis of patients.

Therefore, in the present project, the following conclusions were found.

- The immunological phenomenon of COVID-19 is characterized by lymphopenia and increased IL-6 in critically ill patients.
- CRP, PCT, IFN-γ and other inflammatory markers play an important role in the so-called cytokines storm. Monitoring these parameters could help to understand the progression of the COVID-19 disease.
- Symptomatic patients showed a greater magnitude of both cellular and humoral adaptation.

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