ANALYSIS OF FACTORS ASSOCIATES A THE PRESENCE OF SYMPTOMS PERSISTENT IN PEOPLE WITH DIAGNOSIS OF COVID-19 (Aralongcov STUDY): STUDY OF CASES-CONTROL.

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1. Introduction

A measure that the pandemic get moving, we go knowing plus of is illness Y their consequences in the medium and/or long term, making it evident that it is much more complex in its evolution, demonstrations clinics, mutations, bases biochemical etc., of it that in a beginning I know thought.

Most patients who have had a Covid infection recover within a short period of time. greater than one month. Many patients have developed nonspecific symptoms after passing the disease, even after negative PCR and development of antibodies. The symptoms that They present with extensive, both physical and neurological, that last for weeks and, a often, months. Symptoms such What: fatigue severe, difficulty for breathe, pains muscle cramps, joint pain, "brain fog", memory loss, lack of concentration, as well as depression and problems of Health mental.

The infection by SARS-CoV-2 (Covid19) entails a response either waterfall hyperinflammatory inthe guest. This hyperinflammatory response includes vascular damage and infection as has been checked with the studies of autopsies of the deceased patients.

Therefore, in general terms the control of systemic inflammation and its resolution is as important What the eradication of own self virus.

Resolution of the inflammatory response is an active biochemical process regulated by mediators lipid natural autoacoids pro-resolution Y specialized, No immunosuppressants, called SPMs, such as resolvins. Both the resolvins and other SPMs stimulate the removal by macrophages of cell debris and clots, decreasing production of cytokines proinflammatory (inflammation).

It should be noted that currently the treatment of inflammation/pain is carried out with therapies immunosuppressive (anti-inflammatories), that a the dessert cause effects secondary, Y do not resolve the causes that generate the symptoms of the disease, so they cannot be considerate What a unique therapy.

On the other hand, the symptoms and sequelae in persistent COVID add to the psychosocial impact of interruption of access to medical care (such as Arrangements for get medication regular), basic personal routines (such as walking to local stores), social interactions (such as meeting friends) and support networks. Support should be personalized with input from the equipment multiprofessional (by example, medical of attention primary, worker Social, equipment rehabilitation).

The majority of the publications about covid-19 and health mental they have emphasized reactions individual a the pandemic, What anxiety, stress Y conditions related with routines broken, loneliness and isolation. It has been suggested that persistent Covid is often associated with a condition of cheer up bass, hopelessness, elderly anxiety and difficulty for sleep.

These aspects social also are included in the approach of the patients with covid persistent and in the protocols, Present Project.

Therefore, with this working hypothesis, it is necessary to accurately characterize both the disease, like to the patient, Y the hypothesis of work raised.

2. Aims

2.1. Principal aim

The general objective of this study is to characterize sociodemographically, clinically and biologically the patients that present symptomatology persistent front a the that No present persistent symptomatology after the diagnosis of covid-19 and analyze the factors associated with persistence of the symptomatology of covid-19.

2.2. Specific aims

The objectives specific of **Aralongcov** study are:

- describe the features sociodemographic of the patients with symptomatology persistent of Covid-19 and the no present symptomatology persistent.
- Investigate the lack of resolution and adequate level of SPMs in patients with Covid persistent and the no have persistent symptoms.
- To identify the existence of different clinical phenotypes among patients with Covid-19 persistent and that No present symptoms persistent.
- Evaluate the substratum organic genetic, inflammatory, immunological either of dysfunction endothelial in the patients with Covid-19 persistent Y the that No present symptomatology persistent.
- Measure the degree of disability and psychological impact and alteration of quality of life of the patients with Covid-19 persistent Y the that No present symptomatology persistent.
- To study the evolution of symptoms and the organic substrate in patients with Covid-19 to it length weather for identify sequelae and characterize them.

3. Design

Study of control cases, with inclusion consecutive with a tracing of a year.
Scope : Community Autonomous of Aragon

4. Patients

Size sample

All patients who meet the inclusion criteria and who accept take part in the same Y that assume that they can to have that commute voluntarily Y without compensation, a a care center outside of your residence.
Aragon a date of 24 of May of 2021 have a population of 124,000 patients with diagnosis of Covid-19. In the absence of rigorous clinical studies, a prevalence of covid persistent of 10% of everybody the patients that suffer either they have suffered Covid-19 (rajan, s. et to the In the Wake of the pandemic: preparing for Length covid - Policy Brief 39).
In base a these data, for a test unilateral, with a level of confidence of 95% Y with a statistical power of 80%, assuming empirically that in the control group they can persist laboratory abnormalities in up to 30% and that in the intervention group there may be up to the fifty% (considering single a difference Come in both of them of twenty%) you would need a 73 in each group for find that difference.

Criteria of inclusion

Patients in the intervention group must meet the diagnostic criteria of the Guideline (1) in which we base the study, Persistent Covid or Long COVID (CP/LP): Symptomatic complex multiorgan system that affects those patients who have suffered from COVID-19 (diagnosed confirmed with or without laboratory tests) and who remains symptomatic after considered

acute phase of the disease, after 4 or even 12 weeks, persisting symptom in the weather.
The criterion of inclusion of cluster control will be infection by covid Already pass through RT-PCR, test antigenic either serology, of a duration No higher a 4 weeks, without symptom later.
For both groups, it will be necessary to sign the informed consent document of stake in the study. In the that I know will specify that Yes someone wants backing out of study, You can ask for it the destruction of their data.
In addition, the patients with persistent covid a include in the cluster of intervention should comply the following Criteria: Persistence of symptom plus there of the 12 weeks since the diagnosis of the infection by SARS-CoV-2 No presents previously a the same.

Criterion of exclusion:

- The symptom / symptom Already existed before of the infection acute by SARS-Cov-2
- Refusal to take part

5. Variables

So much for the cluster control What for the cluster intervention, I know they will pick up the following variables :

5.1. Variables sociodemographic and Determinants

Sex, age, place of residence, life habits, perceived quality of life (SF-12), occupation, habitability, ethnicity, source
Variable lifestyles:

- Diet measured using the MEDAS Scale
- Sedentary lifestyle measured using the International Physical Activity Questionnaire
- Sleeping habits measured using Pittsburgh
- Consumption measured using a battery of questions

5.2. Comorbidity

Medical history previous: including illness cardiovascular previous (illness chronic heart disease, heart failure, myocardial infarction, peripheral vascular disease, illness stroke), hypertension, dyslipidemia, diseases respiratory previous (COPD, asthma, bronchitis chronicle), diseases renal Chronicles, diseases liverworts
Chronicles, disorders neurological chronic, immunosuppression / transplant previous, diseases hematological Chronicles (leukemias, lymphomas, myelomas), cancer / neoplasm, HIV Y others immunodeficiencies, obesity, malnutrition, diabetes, diseases dermatological, diseases rheumatologic, disorders mental Y dementia, pathologythyroid, autoimmune pathology.
Charlson index
Use of pharmacotherapy, nutritional supplements, and probiotics measured using a battery of questions (active ingredient, dose, medication schedule, approximate date from the beginning).

5.3. Clinics

5.3.1. Related with the episode initial

Elaboration of Map of symptom, first symptom, symptom plus relevant in theepisode and graduation of the themselves.

- **Date approximate of beginning of symptom**
- **BP, Sat O_2 %, body mass index (BMI) and temperature**
- **CRP** : positive/negative / Nope done. Yes positive, specify **date**
- **Test antigenic** : Positive / Negative / Nope done. Yes positive specify **date**
- **Serology:** Positive / Negative / Nope done. Yes positive specify **date**
- **Hospitalization:** Yes / Nope. Yes Yes, specify: **Date of income** , **Date of high** Y Yes **accurateentry in ICU** (Yes / Nope)

- **Gravity episode initial:** Mild / Moderate / Serious / Critical. Date Classification SEMI
- **Pneumonia:** Yes / Nope / NA
- **Onset symptoms in the acute phase**
- **Predominant symptom in the acute phase**
- **Treatment steroidal systemic:** Yes / Nope / NA
- **Negativization time and/or appearance of antibodies**
- **Case source**

5.3.2. Related with the symptom of covid persistent

COVID-19 persistent symptoms measured with a battery of questions at baseline that include:

- **Approximate date of the beginning of symptoms**
- **Duration**
- **Intensity of symptoms**
- **Frequency of each symptom**
- **Eg dysgeusia, dyspnea, neuromuscular conditions** ; measured at baseline, and revised with symptomatology

Emotional affective variable measured using the Patient Health Questionnaire-9 (PHQ-9) scale
Functional ability:

- **Functional status post-COVID 19 measured using Post-COVID-19 Functional Status (PCFS) at baseline**
- **Functional physical skills measured using 1-min stand-sit test and 6-minute walk test at baseline**
- **Respiratory function measured using spirometry at baseline**

Cognitive ability:

- **Attention capacity measured using the Stroop test and Symbol Digit Modalities Test (SDMT) at baseline**
- **Long-term memory measured using the Rey–Osterrieth complex figure test (ROCF) at baseline**

Other variables:

- **Pain measured using the Pain Catastrophizing Scale (PCS) at baseline**
- **Fatigue severity measured using the Fatigue Severity Scale (FSS) at baseline**

5.4. Analytics

Myoglobin (ng/mL)	Uric Acid (mg/dL)
Creatine kinase (ng/mL)	Magnesium (mg/dL)
B-type natriuretic peptide (pg/mL)	Triglycerides (mg/dL)
Thyrotropin Tsh (µIU/mL)	Total cholesterol (mg/dL)
Thyroxine Free T4	HDL cholesterol (mg/dL)
Thyroid peroxidase antibodies	LDL cholesterol (mg/dL)
Iron (µg/dL)	Total Cholesterol / HDL Cholesterol
Ferritin (ng/mL)	Non-HDL cholesterol in serum (mg/dL)
Transferrin (mg/mL)	Bilirubin (mg/dL)
Transferrin saturation (%)	Total protein (g/dL)
Haptoglobin (mg/mL)	Albumin (g/dL)
Folic acid (ng/mL)	Sodium (mEq/L)
Vitamin B12 (Pg/mL)	Potassium (mEq/L)
Anti-intrinsic factor antibodies (AU/mL)	Glomerular Filtration Rate (mL/min*1.73m^2)
C-Reactive Protein (mg/dL)	Aldolase (U/L)
Glucose (mg/dL)	Phosphatase (U/L)
Creatinine (mg/dL)	GGT Gammaglutamyl Transferase (U/L)

AST Aspartate aminotransferase (U/L)	Red blood cell count (10^6/µL)
ALT Alanine Transaminase (U/L)	Hemoglobin (g/dL)
Lactate Dehydrogenase (U/L)	Hematocrit %
Streptococcus ASLO antistreptolysins (IU/mL)	Mean Corpuscular Volume (fL)
Rheumatic factor (IU/mL)	Mean Corpuscular Hemoglobin (pg)
Anti-cyclic citrullinated peptide (anti-CCP) antibodies (IU/mL)	Mean Corpuscular Hb Concentration (g/dL)
Alpha-1 Antitrypsin (mg/dL)	Erythrocyte Distribution Width %
Beta-2 Microglobulin (mg/dL)	Platelet count (10^3/µL)
Total IgE (IU/mL)	Mean Platelet Volume (fL)
IgG (mg/dL)	Erythrocyte sedimentation rate (mm/hour)
IgA (mg/dL)	Ac. anti nuclear
IgM (mg/dL)	Ac. antimitochondrial
IgD (mg/dL)	Ac. anti-smooth muscle
Complement C1 Inhibitor (mg/dL)	Ac. anti parietal cells
Complement C3 (mg/dL)	Ac. anti-nDNA (IU/mL)
C4 complement (mg/dL)	Screening Ac. anti-ENA
C-peptide (ng/mL)	Ac. aniendomysium
Anti-GAD antibodies (U/mL)	Ac. antineutrophils (PR3) - (C-ANCA) (u)
IGFBP-3 Insulin-like growth factor type 1 (µg/mL)	Ac. antineutrophils (MPO) - (P-ANCA) (u)
Ig A tissue anti-transglutaminase antibodies (U/mL)	Ac. anticardiolipin IgG (U/mL)
Glycosylated hemoglobin (%)	Ac. anticardiolipin IgM (U/mL)
25-hydroxyvitamin D (nmol/L)	INR
Leukocyte count (10^3/µL)	Cephalin Time (TTP) (sec)
Neutrophil count (10^3/µL)	APTT ratio
Eosinophil count (10^3/µL)	Prothrombin time (sec)
Basophil count (10^3/µL)	Prothrombin activity %
Monocyte count (10^3/µL)	Derived Fibrinogen (g/L)
Lymphocyte count (10^3/µL)	D-dimer (µg/L)
antithrombin %	Observations on the proteinogram
Lymphocyte population total lymphocytes *1000/mm^3	IgG1 immunoproteins (mg/dL)
B lymphocytes (CD19) %	IgG2 immunoproteins (mg/dL)
T lymphocytes (CD3) %	IgG3 immunoproteins (mg/dL)
NK cells (CD56) %	IgG4 immunoproteins (mg/dL)
Helper lymphocytes (CD4) %	% Cryoglobulins
Cytotoxic/Suppressive Lymphocytes (CD8)%	Electroimmunofixation of cryoglobulins
B lymphocyte count (CD19)	Ig M Cytomegalovirus
T lymphocyte count (CD3)	Ig G Varicella Herpes Zoster
NK Lymphocyte Count (CD56)	Ig G Epstein Barr
Helper Lymphocyte Count (CD4)	IgG Herpes virus
Cytotoxic/Suppressive Lymphocyte Count (CD8)	CMV or EBNA Eipstein Barr or H6
CD4/CD8 ratio	Anti-spicule antibodies
Alpha-1 Globulin %	antinuclear antibodies
Alpha-2 Globulin %	Total antibodies serology
Beta Globulin %	Cytokines
Gamma Globulin %	

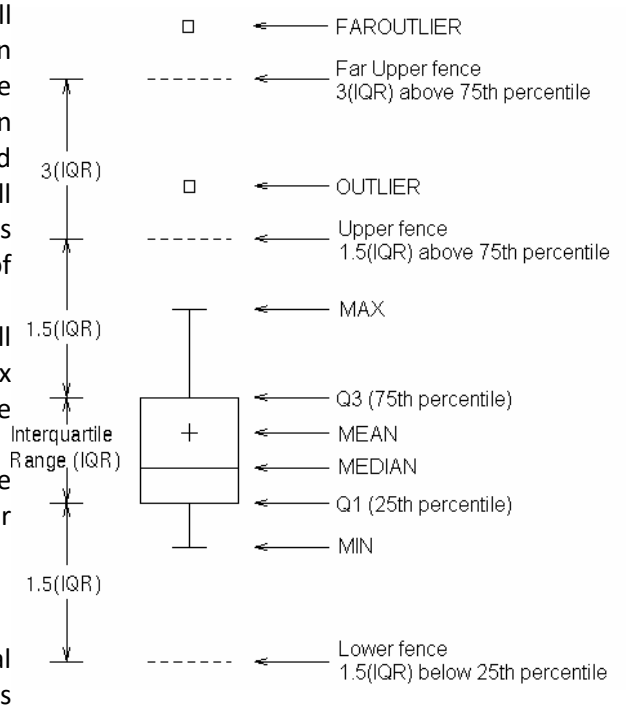
ANALYSIS STATISTICAL

Analysis Descriptive

The description of the variables quantitative I know will perform through the statistics descriptions of the mean and standard deviation. Since it is possible that the distributions of the data do not follow a Gaussian distribution, other robust statistics will also be indicated such as the median, and the interquartile range, as well as the maximum and minimum values. The distributions of categorical variables will be described by means of absolute frequencies and relative of the distribution.

The graphic description of the quantitative variables will be done by means of graphs of boxes and whiskers (Box plot graphics), indicating the information shown in the figure to the side.

On the other hand, the graphic description of the categorical variables will be done through the use of bar graphs or sector graphs.



Inferential Analysis

First , the incidence of residual symptoms of global COVID and according to diagnostic groups with its 95% confidence interval will be estimated.

The main sociodemographic and clinical variables of the patients will be described again, disaggregating by residual symptomatology, making associations between them. To analyze the relationship between qualitative variables we will use the chi-square test or Fisher's exact test, as appropriate. In the case of quantitative variables, we will use the T-Student test if the variable assumes a normal distribution or the Mann-Whitney U test if it does not, performing the normality test using the Shapiro Wilks test. In case of associating with more than two groups, we will use the one-factor ANOVA test, performing post-hoc contrasts if said contrast turns out to be significant, with the aim of delving into which group or groups show different behaviors. In the event that the variable does not have a normal distribution, we will carry out the non-parametric Kruskal Wallis test, supported by tables and box-plots to identify heterogeneous groups.

Analysis multivariate

The analysis multivariate I know will perform with the objective of analyze in depth the aftermath of the illness. The analysis multivariable se carry a cape through regression binary logistics, with the forward conditional method, introducing as dependent variable each of the diagnoses of the possible sequelae and as independent variables those that obtained statistical significance in the univariate analysis or could have an implication clinically plausible. The analysis of the calibration of model I know made through the Hosmer-Lemeshow statistic. The discriminatory power of the model was evaluated using the area under the ROC curve (receiver-operator characteristics) obtained by analyzing the probability of the value predicted by the multivariate model. The results of the multivariate model are present adjusted Y in form of odds ratio (interval of confidence [CI] of 95%)

6. Flow of patients. Integration with the practice clinic. Visits.

6.1. Patient flow. Integration with clinical practice.Ambit

Cluster of intervention:

The patients with Covid-19 persistent in Aragon are catered mostly in the Service Aragonese of Health, on all in Attention Primary, being presumably scattered by all the net assistance. It is probable that Some patients with Covid-19 persistent be catered also by Attention specialized Y that is patients catered within of others Models assistance (MUFACE).

For all of the above, the scope of the Aralongcov study is the patients in the intervention group with persistent Covid-19 treated by Primary Care within the HEALTH care network. We will also have the collaboration of Specialized Attention in what affects the patients that they can be taken care of in the two levels assistance

We are collaborating with the Collective of patients with persistent covid in Aragón, so also I know has its support for Y your participation in the study.

Cluster control

As has already been defined, the control group will be made up of patients with already overcome covid. They will be selected from the EHR database, grouping them by age and sex to the group of intervention .

Integration with the practice clinic

Persistent Covid-19 is a new entity for which many aspects of its nature are unknown. etiopathogenesis, presentation and natural history. However, it is already a healthcare reality, It is necessary to standardize diagnostic evaluation and management procedures, as well as how to train health professionals in them. This will be achieved by performingof a guide Clinic, target but priority from the Point of view assistance.

Flow of patients

When a patient with persistent Covid-19 is identified, they will be informed of the existence of theAralongcov study and you will offer the possibility to participate in the same.

The **process of inclusion / shunt** has several options:

1. **The family doctor obtains informed consent** and fills out a form specific in IMO / EHR indicating that the patient has been included. said form would checked daily by the Aralongcov team, that I know would order of quote to the patient.
2. **The family doctor reports the existence of the study Aralongcov** and in case of interest by the patient indicates it in a specific form in OMI / EHR indicating that the patient wishes to participate. This form would be reviewed daily by the Aralongcov team, which would be in charge of quoting the patient and obtaining consent informed.

Once the patient has given their consent, they are transferred to the Research Units of Persistent Covid and future pandemics (UICp) that are implemented in the project, where I know carry a cape the different phases of Project.

The process identification of patients candidates:

- Information / awareness a the doctors of family
- Information a the associations / groups of patients
- Search active of cases using criteria defaults:

I know could pose the inclusion on the intervention nutritional a leave of the visit basal.

7. Put in March of study

the sunset in March this subject to:

- Definition of a protocol assistance of Covid-19 persistent in Aragon. In this In this sense, meetings have been held with the General Directorate of Planning and the managementof HEALTH, from the PC SSCC in which this research group participates to adapt the published persistent covid protocol (1). At these meetings, it was decided that this protocol is in a position to be applied to the Autonomous Community of Aragon and by so much will be the referent for East study.

- Training a the doctors of family:
- Developing of the forms necessary in EHR / IMO
- Design of the structure of support for the visits (definition of the meansnecessary, Location, etc.)
- Design of tools of self registration for the patients (Apps)

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