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Personal and vaccinal history as factors associated with SARS-CoV-2 infection.

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RESUMEN

Background and objective: SARS-CoV-2 has been a major public health challenge. Since the beginning of the pandemic, different comorbidities have been postulated to be associated with higher severity and mortality spectra. The objectives of the present investigation are: 1) to analyze the factors associated with SARS-CoV-2 infection (COVID-19) in a health area of northern Spain; 2) to know the possible role of influenza and pneumococcal vaccination in the development of COVID-19.
Materials and methods: A negative test case-control study was carried out. Variables related to personal and vaccination history were taken into account. Although the epidemiological definition of case varied over time, we used as reference the one corresponding to January 31, 2020 in Spain. A bivariate and multivariate analysis was performed.
Results: The sample included 188 patients, of whom 63 were cases and 125 controls. The results show that obesity increases the risk of suffering this infection 2.4 times (95% CI 1,301 to 4,521) and angiotensin II receptor antagonists (ARA-2) increase it 2.2 times (95% CI 1,256 to 6,982). On the other hand, pneumococcal conjugate vaccination with 13 serotypes showed results close to statistical significance (OR = 0.4; 95% CI 0.170 to 1,006).
Conclusions: Obesity and the use of ARA-2 drugs increase the risk of COVID-19. Scientific knowledge on the factors associated with COVID-19 should be further expanded. The present investigation raises the need to further investigate the role of vaccines on this infection and their possible heterologous properties.

Personal and vaccination history as factors associated with SARS-CoV-2 infection

Keywords:
SARS-CoV-2
COVID-19
Risk factors
Vaccine
Vaccination

ABSTRACT

Background and objective: SARS-CoV-2 has been and is a major global Public Health challenge. Since the beginning of the pandemic, different comorbidities have been postulated and associated with spectra of increased severity and mortality. The objectives of this research are: 1) to analyze the factors associated with SARS-CoV-2 infection (COVID-19) in a health area in northern Spain; 2) to understand the possible role of influenza vaccination and pneumococcal vaccination in the development of COVID-19.
Materials and method: A test-negative case-control study was conducted. Variables related to personal and vaccination history were considered. Although the epidemiological definition of the case varied over time, the reference definition was that corresponding to 31/01/2020 in Spain. A bivariate and multivariate analysis was performed.

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Results: The sample included 188 patients, of which 63 were cases and 125 controls. The results show that obesity increases the risk 2.4-fold of suffering this infection (95% CI 1,301-4,521) and ARA-2 increases it 2.2-fold (95% CI 1,256-6,982). On the other hand, anti-pneumococcal vaccination of 13 serotypes showed results close to statistical significance (OR = 0.4; 95% CI 0.170-1,006).
Conclusion: Obesity and the use of ARA-2 increases the risk of COVID-19. Scientific knowledge about factors associated with COVID-19 should be expanded. The authors consider that the present research raises the need further investigate the role of vaccines in this infection and their possible heterologous properties.

Introduction

Most of the pandemics described in recent decades have originated from viruses of animal origin1 . 1 Coronaviruses represent a family of viruses with a high capacity for recombination of genetic material between the genomes of different coronaviruses. In 2003, severe acute respiratory syndrome (SARS) was described in Asia and, in 2012, Middle East respiratory syndrome (MERS-CoV), both originating from previously unknown variants of coronaviruses2. In January 2020, the World Health Organization (WHO) declared an international public health emergency3 due to the appearance in China, a month earlier, of a new variant of coronavirus called SARS-CoV-2.
118,000 cases4.

SARS-CoV-2 has posed a major public health challenge to the world and has challenged the capacity of the health care system. At the clinical level, SARS-CoV-2 (COVID-19) infection leads to a wide range of clinical presentations and courses, from asymptomatic or paucisymptomatic cases, mild symptoms compatible with the common cold or flu-like illness, to its most severe manifestation in the form of severe acute respiratory syndrome with pneumonia and multiorgan involvement and finally letha15 .

As with other infectious diseases, clinical variability is largely explained by the intrinsic characteristics of the host6. Thus, since the beginning of the pandemic, different comorbidities or risk factors have been postulated that have been associated with spectra of greater severity and mortality. In general, everything suggests that this virus affects, as a priority, elderly, multi-pathological and possibly also polymedicated populations7. 7 In this regard, with the data available to date, there is a certain consensus on the role of age, obesity, dyslipidemia, cardiovascular disease, diabetes mellitus, arterial hypertension (AHT) and chronic pulmonary, hepatic or neurological disease, among others, as risk factors 8,9 However, since the beginning of the pandemic, the effect of some antihypertensive treatments has been under discussion due to the penetration of the virus into the cell through the angiotensin-converting enzyme receptor 2 (ACE-2), which is mainly present in the kidney, lungs and heart.

The major limitation for the global approach to SARS-CoV-2 is the scarce natural immunity of the population, as well as the absence of preventive tools linked to vaccination. For this reason, an important scientific race is currently underway to obtain an effective vaccine13 , while at the same time exploring whether any of the vaccines available for the pre-exposure prophylaxis of SARS-CoV-2 can be used as a preventive tool.
The BCG vaccine against severe forms of tuberculosis may have heterologous properties on the prevention of SARS-CoV-214.

Therefore, and taking into account all of the above, the objectives of the present research are: 1) to analyze the factors associated with to SARS-CoV-2 infection in a health area of northern Spain; 2) to know the possible role of influenza and pneumococcal vaccination in the development of SARS-CoV-2 infection.

Material and methods

Scope of study

The study was carried out in a regional hospital in northern Spain with a reference population of 61,267 inhabitants, which has shown a progressive downward trend in recent years (loss of approximately 750 to 1,000 inhabitants/year). It is an aging, multi-pathological and polymedicated population with more than 26% of the population over 65 years of age. The hospital is equipped with more than 120 beds and has a Maternal-Child Unit and a Psychiatry Unit15,16.

Type of study

A negative test case-control study was performed.

Case definition

Patients who from February 28, 2020 (date of the start of epidemiological surveillance of SARS-CoV-2 in the health area in which the research is being conducted) until May 8, 2020 met the *case definition of infection by the new SARS-CoV-2 corona virus* and, after performing the polymerase chain reaction (PCR) test for this virus, the result was positive.

It is important to note that the *definition of a case of infection by the new SARS-CoV-2 coronavirus* was modified in accordance with the updates published by the Epidemiological Surveillance Service of the Health Department of the Autonomous Community of reference, in line with the information published by the Center for Coordination of Alerts and Health Emergencies of the Ministry of Health, Consumer Affairs and Social Welfare, with the initial definition corresponding to January 31, 2020.

This definition has been as follows:

Cases will be investigated for 2019-nCoV infection if they meet at least one epidemiological criterion and the clinical criteria below.

A. Epidemiological criteria

A.1 Any person with a history of travel to Hubei Province, China, within 14 days prior to the onset of symptoms, or
A.2 any person who, in the 14 days prior to the onset of symptoms, has been in close contact with a probable or confirmed case.

It is defined as close contact:

- Any person who has provided care to a probable or confirmed case*: health care workers who have not provided care to a probable or confirmed case.

The following persons, family members or friends, as well as persons who have had other similar types of physical contact, have used appropriate protective measures.
- Any person who was in the same location as a probable or confirmed case* at a distance < 2 m (e.g., con- vivants, visitors).
- Close contact in an aircraft is defined as passengers within a two-seat radius of a probable or confirmed case* and crew who have had contact with such cases.

* At this time, and following the recommendations of WHO and the European Centre for Disease Prevention and Control (ECDC), until further epidemiological information is available, contact will be considered with probable or confirmed cases in a period between 14 days before and 14 days after the onset of symptoms of such cases.

B. Clinical criteria

Any person with clinical symptoms compatible with an acute respiratory infection, of any severity, presenting fever and any of the following symptoms: dyspnea, cough or general malaise.

Selection of controls

Two controls were selected for each case. Patients were considered who from February 28, 2020 through May 08, 2020 met the *case definition for infection with the new SARS-CoV-2 coronavirus* and, after PCR testing for this virus, the result was negative.

In order to minimize possible selection bias, negative test controls were matched to each case based on the variables "sex" (male/female), "age" (age at years) and "severity" (hospital admission/domicile).

Selection and definition of variables

A literature search was carried out in the PubMed database to identify articles written in English published in the last three months related to coronavirus. The variables included in the meta-analysis published by Yang et al.[17] were mainly taken into account. In addition, others were added that, although not widely explored, were considered relevant from the clinical point of view. Finally, the variables selected were:

- Age (years)
- Sex (male/female)
- Viral ribonucleic acid (RNA) copies at the time of diagnosis (copies/1,000 cells)
- Severity (domicile/entry)
- Final denouement (*exitus/alta*)
- Diabetes (yes/no)
- Diabetes type (1/2)
- Diabetes treatment (oral antidiabetics/insulin)
- Obesity (yes/no)
- Dyslipemia (yes/no)
- Arterial hypertension (yes/no)
- Treatment of arterial hypertension (angiotensin-converting enzyme inhibitors [ACE inhibitors]/angiotensin II receptor blockers [ARA-2]).
- Metabolic syndrome[18] (yes/no)
- Chronic liver disease (yes/no)
- Chronic kidney disease (yes/no)
- Immunodeficiency/immunosuppression (yes/no)
- Cardiovascular disease (yes/no)
- Chronic lung disease (yes/no)
- Neurological or neuromuscular disease (yes/no)
- Chronic disease 1 (yes/no)
- Chronic disease 2 (number of chronic diseases)
- Pluripathology[19] (yes/no)
- Polypharmacy[20] (yes/no)
- Hospitalization in the previous three months (yes/no)
- Stay (number of days)
- Complications (intensive care unit [ICU]/exitus/other complications)
- Flu vaccine 2019/20 (Y/N)
- Pneumococcal conjugate vaccine 13 v (Y/N)
- Pneumococcal polysaccharide vaccine 23 v (Y/N)
- Sequential schedule of pneumococcal conjugate vaccine 13 v + polysaccharide 23 v (Y/N)
- Influenza vaccine 2019/20 + pneumococcal conjugate vaccine 13 v (Y/N)
- Influenza vaccine 2019/20 + pneumococcal polysaccharide vaccine 23 v (Y/N)
- Flu vaccine 2019/20 + pneumococcal conjugate vaccine 13v + pneumococcal polysaccharide vaccine 23v (yes/no)

Statistical analysis

A descriptive statistical analysis was performed for each variable (univariate analysis), calculating absolute and relative frequencies for qualitative variables, and means and standard deviations (SD), as measures of central tendency and dispersion, for quantitative variables. Secondary variables were created from the initial variables, mainly to organize them into ranges ("age" and "sex").
"viral RNA copies at diagnosis") or combine them ("metabolic syndrome", "influenza vaccine 2019/20", "pneumococcal conjugate vaccine 13 v" and "pneumococcal polysaccharide vaccine 23 v"). A bivariate analysis was performed to assess the association between the selected variables. For dichotomous qualitative variables, the X test was used^2 . For the quantitative variables studied, Student's t test was used. On the other hand, the Pearson correlation coefficient was calculated to measure the statistical relationship between the continuous variables "number of days of stay", "number of copies of viral RNA" and "number of chronic diseases".

The analysis was performed with *Statistical Package for the Social Sciences* version 23.0 and EPIDAT version 3.1.

Ethical aspects

The present research was approved by the Research Ethics Committee of the Autonomous Community (reference 2020.260).

Results

General description of the sample

The sample consisted of 188 patients, of whom 63 were cases and 125 controls. Of these, 52.1% were women and the mean age was 64.66 years (SD ± 19.97). No statistically significant differences were observed between the variable age (95% CI -5.75 to 6.44), sex (95% CI 0.53 to 1.80) and patient location (95% CI 0.48 to 1.74) between cases and controls.

Description of cases

Of the 63 cases registered, 47.6% were men. The most

frequent age group was ≥ 65 years (55.6%), followed by the age of

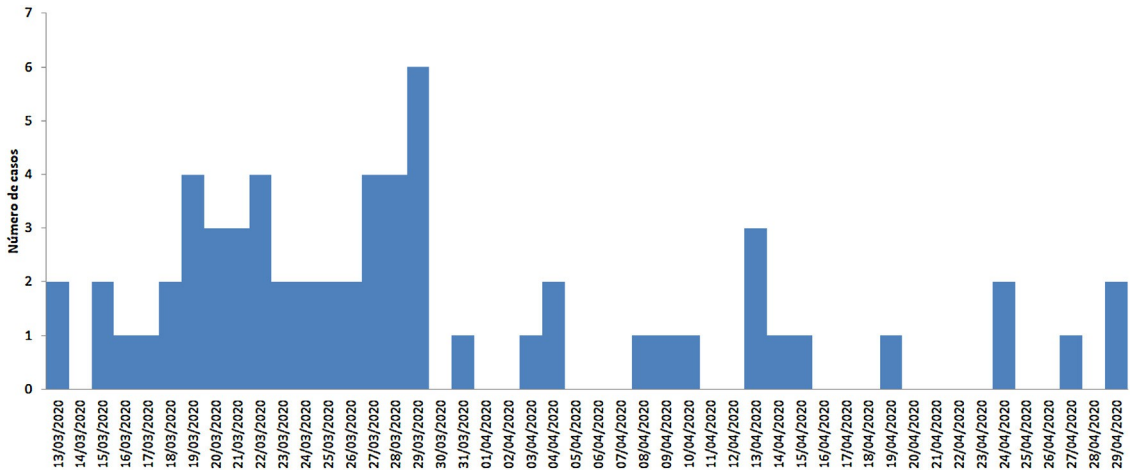

Figure 1. Epidemic curve according to date of diagnosis. Each unit represents a patient diagnosed with SARS-CoV-2 infection.

15 to 49 years (23.8%), 50 to 64 years (17.5%) and 0 to 14 years (3.2%). The mean age was 64.89 years (SD ± 20.13). Figure 1 shows the epidemic curve according to the date of diagnosis. Regarding the need for hospital admission, 42 patients (66.7%) required hospitalization. The mean hospital stay in this group was 13.05 days (SD ± 9.326 days). As for the number of viral RNA copies at the time of diagnosis, 69.8% were above 50,000 copies/mL. Finally, the overall case fatality was 14.28%, while for admitted patients it amounted to 21.42%.

Table 1 shows the distribution of the main personal antecedents of the patients with COVID-19, as well as the vaccination history (against influenza and pneumococcus) in those aged ≥ 65 years or chronic patients. In general, obesity was found to be the most frequent history (52.4%) followed by dyslipidemia (47.6%). A total of 49.2% of the patients met the definition of
The "polypharmacy" and, overall, 52.4% had some chronic disease.
.

No statistically significant differences were observed between the number of days of hospital stay and the presence of any of the personal and vaccination history.

Regarding the link between continuous variables, a positive relationship was found between the number of chronic diseases and the number of days of hospital stay (r = 0.251; 95% CI -0.05 to 0.51), however, no such relationship was observed between the number of chronic diseases and the number of viral RNA copies at diagnosis (r = 0.128; 95% CI -0.12 to 0.36) or between the number of viral RNA copies and days of hospital stay (r = 0.032; 95% CI -0.27 to 0.33).

Personal and vaccination history

The main risk factors associated with coronavirus infection were obesity and active treatment with anti-hypertensive drugs ARA-2. Thus, bivariate analysis showed that being obese increased the risk of developing this infection 2.4-fold (95% CI 1,301 to 4,521) and that ARA-2 increased it 2.2-fold (95% CI 1,256 to 6,982). At the same time, it was found that both obesity and polypharmacy were identified as risk factors for clinical complications such as referral to the ICU and *exitus,* with an *odds ratio* (OR) = 3.1 (95% CI 1.4 to 7.2) for obesity and an OR of 3.1 (95% CI 1.4 to 7.2) for obesity and an OR of 3.1 (95% CI 1.4 to 7.2) for polypharmacy.
= 2.3 (95% CI 1.004 to 5.249) for polypharmacy. Table 2 shows the rest of the results.

With respect to vaccination history, pneumococcal conjugate vaccination of 13 serotypes showed results close to statistical significance with an OR = 0.4 (95% CI 0.170 to 1.006) (Table 2).

Discussion

SARS-CoV-2 infection in the present study population has been shown to affect older age groups more, as has been reported in other similar investigations21,22 published on other types of coronavirus such as SARS and MERS. 23-26 Furthermore, on most occasions, this situation is linked to the increase in the number of chronic diseases and, therefore, to polymedication which, although it has not been found to be a risk factor for COVID-19 as it is with other types of infections,[27] the results point to an association between polymedication and complications, including *exitus*. These findings are consistent with those of other authors who relate polypharmacy with increased mortality in persons over 65 years [28] although this could also be explained by the high prevalence of chronic diseases in the study sample (52.4%) and polymedication (49.2%), the latter being much higher than that described in national studies where it does not exceed 30% for the year 201729.

In recent months, obesity has been a variable that numerous authors have explored in their research related to COVID-19 and it seems logical to think that it may have a relevant role in the development of this infection. It is known that obese patients present alterations in pulmonary function, a decrease in thoraco-pulmonary distensibility and, as a consequence, an increase in respiratory work. Likewise, a decrease in maximal inspiratory pressure is observed. As a consequence of both phenomena, there is an increase in respiratory work and greater muscle fatigue. Furthermore, in patients with obesity, a diminished response has been observed.
of the respiratory center to hypercapnia30,31. 30,31 On the other hand, the obe-
sity is associated with a low degree of chronic inflammation, as well as with a greater risk of thrombosis32 that can be increased by SARS-CoV-2, and with a worse immune response and poor prognosis of respiratory infections with a greater risk of hospitalization and death, as has been demonstrated in the case of influenza virus infection33-35. In the case of the present study, and as indicated by the results of authors such as Simonnet et al.[36], Richardson et al.[37] or Caussy et al.[38] in different parts of the world, bivariate analysis indicates that obesity is an important risk factor for the development of SARS-CoV-2 infection (OR = 2.4; 95% CI 1.30 to 4.52), in addition to producing a significant increase in the risk of complications (OR = 4.1; 95% CI 1.81 to 9.46).

The effect of antihypertensives on the development of COVID-19, as well as its complications, has also been subjected

Table 1
Distribution of the main personal and vaccination history of patients with SARS-CoV-2 infection.

	n	%
Diabetes		
Yes	13	20,6
No	50	79,4
Diabetes treatment (n = 13)		
ADOs	8	61,5
Insulin	2	15,3
ADOs + insulin	1	7,6
It does not take	2	15,3
Obesity		
Yes	33	52,4
No	30	47,6
Dyslipemia		
Yes	30	47,6
No	33	52,4
HTA		
Yes	29	46
No	34	54
HTA treatment (n = 29)		
ACE inhibitors	7	24,1
ARA-2	14	48,2
It does not take	8	27,5
HTA treatment (ACE inhibitors)		
Yes	8	12,7
No	55	87,3
Treatment of hypertension (ARA-2)		
Yes	14	22,2
No	49	77,8
Metabolic syndrome		
Yes	16	25,4
No	47	74,5
Polypharmacy		
Yes	31	49,2
No	32	50,8
Liver disease		
Yes	4	6,3
No	59	93,7
Renal disease		
Yes	9	14,3
No	54	85,7
Immunodeficiency		
Yes	4	6,3
No	59	93,7
Cardiovascular disease		
Yes	18	28,6
No	45	74,4
Pulmonary disease		
Yes	18	28,6
No	45	71,4
Neurological disease		
Yes	11	17,5
No	52	82,5
Chronic disease		
Yes	41	65,1
No	22	34,9
Pluripathology		
Yes	19	30,2
No	44	69,8
Hospitalization 3 months prior		
Yes	7	11,1
No	56	88,9
Complications		
Yes	18	28,6
No	45	71,4
Influenza 2019/20		
Yes	33	52,4
No	30	47,6
VNC13		
Yes	7	11,1
No	56	88,9
VNP23		
Yes	6	9,5
No	57	90,5
VNC13 + VNP23		
Yes	2	3,2
No	61	96,8
Influenza 2019/20 + VNC13		
Yes	7	11,1
No	56	88,9
Influenza 2019/20 + VNP23		
Yes	6	9,5
No	57	90,5
Influenza 2019/20 + CNV13 + NPV23		
Yes	2	3,2
No	61	96,8

ACE inhibitors, angiotensin-converting enzyme inhibitors; ARA-2, angiotensin II receptor blockers; AHT, arterial hypertension; ACE inhibitors, angiotensin-converting enzyme; PCV13, 13-valent pneumococcal conjugate vaccine; PCV23, 23-valent pneumococcal polysaccharide vaccine; OADs, oral antidiabetic drugs; Pneumococcal conjugate vaccine, 13 serotypes.

Theories supporting a detrimental effect and others in the opposite direction advocating a beneficial effect have been postulated. There have been theories supporting a detrimental effect and others in the opposite direction advocating a beneficial effect. The hypothetical detrimental effect of these drugs supported by the present investigation is based on the fact that chronic treatment with ARA-2 would produce an overexpression of angiotensin-converting enzyme 2 (ACE-2), an enzyme used by the virus for endocytosis. This situation would favor the entry of the virus into the pulmonary cells, aggravating the infection39,[40]. 39,40 On the contrary, the hypothetical beneficial effect is postulated through the fact that the ARA-2, binding to the angiotensin II type 1 (AT1) receptor, would avoid the profibrotic and proinflammatory effects that would lead to the stimulation of this receptor, and the overexpression of ACE-2 would degrade angiotensin II into peptides with anti-inflammatory and anti-fibrotic properties12,[41].

Contrary to what might be expected, having been hospitalized for any cause in the last three months was identified as a possible protective factor for SARS-CoV-2 (OR = 0.4; 95% CI 0.170 to 1.006). Although, so far, no publications have been found that evaluate this specific situation in the context of the current pandemic, it is known that SARS-CoV-2 affects, like other infectious diseases, most significantly peri-

In the case of patients belonging to vulnerable groups and groups with high social [interaction42-44] , these results could be interpreted as the need for home recovery after such hospitalization and, therefore, less exposure to meetings or social activities involving contact with other people.

The study of the possible effect of influenza and pneumococcal vaccination on SARS-CoV-2 infection brings a novelty to this research since, so far, except for some specific reference on the possible inverse relationship between influenza vaccination coverage and COVID- 19 mortality in [Italy45] , there seems to be no study in the literature on the possible inverse relationship between influenza vaccination coverage and COVID-19 mortality in Italy45.

field on the subject. Knowing that no benefit or detriment is expected to be found from these vaccines on the development of COVID-19, it is surprising to note that the 13-serotype pneumococcal conjugate vaccine is proposed as a possible protective factor for the development of COVID-19 (OR = 0.4; 95% CI 0.170 to 1.006). In recent years, the heterologous or nonspecific effects of some live attenuated vaccines have been investigated in depth through numerous investigations, beyond the target microorganisms for each of [them46]. These studies were have focused mainly on BCG and measles vaccines47,[48].

It must be said that what was found in the present investigation

may be a chance finding that should in no way suggest a true heterologous effect of this vaccine on SARS-CoV-2 infection, but that, at this time, it raises the need to

Table 2
Factors Associated with SARS-CoV-2 Infection

	Cases		Controls		OR 95% CI
	n	%	n	%	
Diabetes					
Yes	13	20,6	29	23,2	0,8
No	50	79,4	96	76,8	0,411-1.801
Obesity					
Yes	33	52,4	39	31,2	2,4
No	30	47,6	86	68,8	1.301-4.521
Dyslipemia					
Yes	30	47,6	46	36,8	1,5
No	33	52,4	79	63,2	0,845-2.884
HTA					
Yes	30	47,6	55	44	1,1
No	33	52,4	70	56	0,651-2.203
HTA treatment (ACE inhibitors)					
Yes	8	12,7	13	10,4	1,2
No	55	87,3	112	89,6	0,490-3.202
Treatment of hypertension (ARA-2)					
Yes	14	22,2	11	8,8	2,2
No	49	77,8	114	91,2	1.256-6.982
Metabolic syndrome					
Yes	16	25,4	35	28	0,8
No	47	74,5	90	72	0,440-1.743
Polypharmacy					
Yes	31	49,2	60	48	1,05
No	32	50,8	65	52	0,573-1.924
Liver disease					
Yes	4	6,3	4	3,2	2,05
No	59	93,7	121	96,8	0,496-8.488
Renal disease					
Yes	9	14,3	14	11,2	1,3
No	54	85,7	111	88,8	0,538-3.245
Immunodeficiency					
Yes	4	6,3	3	2,4	2,7
No	59	93,7	122	97,6	0,598-12.178
Cardiovascular disease					
Yes	18	28,6	45	36	0,7
No	45	74,4	80	64	0,368-1.372
Pulmonary disease					
Yes	18	28,6	39	31,2	0,8
No	45	71,4	86	68,8	0,454-1.715
Neurological disease					
Yes	11	17,5	19	15,2	1,2
No	52	82,5	106	84,8	0,523-2.662
Chronic disease					
Yes	41	65,1	85	68	0,8
No	22	34,9	40	32	0,462-1.663
Pluripathology					
Yes	19	30,2	42	33,9	0,8
No	44	69,8	82	66,1	0,438-1.622
Hospitalization 3 months prior					
Yes	7	11,1	29	23,2	0,4
No	56	88,9	96	76,8	0,170-1.006
Complications					
Yes	18	28,6	11	8,8	4,1
No	45	71,4	114	91,2	1.815-9.466
Influenza 2019/20					
Yes	33	52,4	48	38,4	1,7
No	30	47,6	77	61,6	0,957-3.254
VNC13					
Yes	7	11,1	29	23,2	0,4
No	56	88,9	96	76,8	0,170-1.006
VNP23					
Yes	6	9,5	14	12	0,7
No	57	90,5	110	88	0,284-2.097
VNC13 + VNP23					
Yes	2	3,2	14	11,2	0,2
No	61	96,8	111	88,8	0,057-1.182
Influenza 2019/20 + VNC13					
Yes	7	11,1	20	17,6	0,5
No	56	88,9	103	82,4	0,235-1.455
Influenza 2019/20 + VNP23					
Yes	6	9,5	9	7,2	1,3
No	57	90,5	116	92,8	0,460-3.997
Influenza 2019/20 + CNV13 + NPV23	2	3,2	11	8,8	0,3
Yes					
No	61	96,8	114	91,2	0,073-1.582

ARA-2, angiotensin II receptor antagonists; AHT, arterial hypertension; ACE inhibitors, angiotensin-converting enzyme inhibitors; PCV13, 13-valent pneumococcal conjugate vaccine; PCV23, 23-valent pneumococcal polysaccharide vaccine.

further larger studies should be carried out to specifically exploit the role of this preventive tool. Thus, the authors do not know whether these results could be related to the recently published data on co-infection of SARS-CoV-2 with other viruses and bacteria where, in an investigation carried out in China, 94.2% of patients were co-infected with one or more pathogens, the most frequently identified being *Streptococcus pneumoniae*[49] . Based on these results and also considering a scenario in which the influenza virus and SARS-CoV-2 may co-circulate in the coming autumn-winter in the northern hemisphere, some independent authors as well as the WHO are in favor of generalized vaccination against influenza and intensification of pneumococcal vaccination in especially vulnerable groups such as those institutionalized in social and health centers. The aim of these interventions is to be capable of combating and minimizing the possible overload on the health care system, given that these vaccines protect against infections that make a significant contribution to mortality from respiratory causes in the elderly50[,51].

The present work is not free of limitations. On the one hand, although the epidemiological design (case-control study with negative test design) implies certain methodological biases, it is currently the most commonly used design in observational studies on the effectiveness of vaccines,[52-54] which is the main reason for its choice. Ade-

Moreover, this is a local study whose sample may not be representative of the general population. As a future prospec- tive, it seems necessary to further study the risk and protective factors for the development of this infection and, until effective and safe vaccines against SARS-CoV-2 itself are available, the role that other known vaccines can play against it.

Conclusions

Treatment with ARA-2 antihypertensive drugs and obe- sity are identified as risk factors, while hospitalization in the previous three months for any cause and, possibly, 13-serotype pneumococcal conjugate vaccination are postulated as protective factors.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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