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SARS-CoV-2 infection and cognitive impairment in older adults at a family medicine unit in Mexico

Abstract

Introduction: It has been documented that SARS-CoV-2 infection can cause alterations in brain function, although the specific neurocognitive sequelae are not yet fully understood. Mechanisms involved include inflammation mediated by proinflammatory cytokines such as IL-4 and IL-6, generation of autoantibodies and an abnormal TH2-mediated immune response. In addition, other mechanisms such as reactivation of latent viruses, direct viral invasion into the central nervous system, disruption of the blood-brain barrier, hypercoagulation and the presence of microhaemorrhages have been proposed, all of which may contribute to the pathophysiology of neurological damage.

General objective: To determine the association between cognitive impairment and SARS-CoV-2 infection in mild post-COVID 19 older adults in the Family Medicine Unit No. 64 of the "Instituto Mexicano del Seguro Social" (Mexican Institute of Social Security (IMSS, for its acronym in Spanish)).

Material and methods: A cross-sectional and analytical study in older adults aged 60-65 years old with confirmed SARS-CoV-2 infection by rapid antigen test was carried out. Sixty-four subjects per group were included and selected by non-probabilistic convenience sampling. The association between infection and cognitive impairment was analysed with Pearson's chi-squared test, and multiple binary logistic regression was applied to control confounding factors.

Results: Out of a total of 128 subjects, 93.8% of participants were cognitively impaired. Of these, 59.6% had comorbidities, with systemic arterial hypertension being the most prevalent. In the multivariate analysis, SARS-CoV-2 infection was associated with cognitive impairment with an OR of 6.86 [95% CI p<0.05]. In contrast, T2D has an [OR 1.36 (95% CI) p .53], SAH (OR 1.25, 95% CI, p .651) and obesity (OR 1.14, 95% CI, p .810).

Conclusion: Cognitive impairment in older adults has been associated with SARS-CoV-2 positivity, highlighting the importance of neurocognitive assessment at the primary care level in Mexico.

Keywords: cognitive impairment, mild post-COVID-19, older adults, SARS-CoV-2 infection

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Abbreviations: FMU, family medicine unit; IMSS, "Instituto Mexicano del Seguro Social" (Mexican Institute of Social Security); OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IL-4, interleukin 4; IL-6, interleukin 6; Th2, T-helper 2 cells; COVID-19, coronavirus disease 2019; T2D, type 2 diabetes; SAH, systemic arterial hypertension; CI, confidence interval

Introduction

On March 11th 2022, the World Health Organisation (WHO) declared a pandemic due to a respiratory disease secondary to the SARS-CoV-2 virus "called COVID-19", which usually manifests itself between 4 and 5 days after exposure to the virus, with various symptoms, mainly fever, cough, fatigue, myalgia, arthralgia, odynophagia, chills, nasal congestion, anosmia, dysgeusia, and dyspnoea.[1]

Tests for SARS-CoV-2 are classified into those that detect active infection and those that confirm previous exposure. RT-PCR is the most reliable test, as it identifies viral RNA in biological samples, although it is slow to process. Rapid antigen tests give results in 15-30 minutes, but their sensitivity is low in asymptomatic individuals, increasing the risk of false negatives. Serological tests detect IgM, IgG, and IgA antibodies in blood; IgM antibodies appear from day 4 post-infection and decline after day 20, while IgG take longer to develop, but remain high for months.

The persistence of symptomatology for four weeks or longer that does not allow the patient to recover their baseline health status can be considered as long-term effects. Different studies have concluded that 80% of post-COVID-19 patients have at least one persistent symptom, usually in those who were severely ill, however, the presence of this symptomatology has also been documented in those with mild infection, these health conditions are known as sequelae and several terms have been implemented, including: long-COVID-19, post-COVID-19, persistent COVID-19, prolonged COVID-19, post-COVID-19 syndrome, and chronic COVID-19.[3]

In the post-COVID-19 phase, the presence of cognitive impairment in patients who did not develop acute neuro-COVID is noteworthy.

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This cognitive symptomatology has been documented up to 5 months after the acute infectious process.[4] According to a cohort study conducted by Hosp JA in 2021, the cognitive functions affected after SARS-CoV-2 infection involve the domains of visual construction, memory, executive ability and attention, leaving orientation and language functions intact.[5]

Several mechanisms influence the neuropathology of COVID-19 and may be overlapping, including direct viral infection, severe systemic inflammation, neuroinflammation, neurodegeneration, and microvascular thrombosis. These inflammatory processes, associated with immune activation, accumulation of memory T-cells and decreased responsiveness to new antigens, generate the cognitive-behavioural changes. Other pathological mechanisms related to neurocognitive alterations such as abnormal lymphatic drainage, viral invasion into extracellular spaces of the olfactory epithelium and the presence of elevated brain injury biomarkers such as neurofilament light chain, which is a protein component expressed by neurons and released into extracellular fluids in the presence of axonal damage, have also been proposed.[6]

These patients with a history of COVID-19 and cognitive symptoms demonstrated changes in metabolism at the level of the brainstem, hippocampus, limbic system and olfactory gyrus, when 18F-fluorodeoxyglucose Positron Emission Tomography studies were performed at brain level, which could later be classified with the support of other research, as a quantitative marker of brain involvement.[7]

A few publications have reported the presence of several receptors involved in the pathophysiology of SARS-CoV-2 neuroinfection, facilitating the entry and spread of the virus into brain cells. For example, angiotensin-converting enzyme 2 (ACE2) has been identified as playing a key role in the infection, acting as the main receptor for the binding of the S protein of the virus and allowing its entry into human cells. Importantly, this enzyme is not limited to lung tissue, but is also expressed in other organs, including the brain, which may be related to the neurological damage associated with SARS-CoV-2. Similarly, transmembrane serine protease 2 (TMPRSS2) plays a key role after virus penetration into the cell by cleaving protein S and promoting viral replication. Another receptor identified is CD147, which is present on host cells and widely expressed in brain tissue. Although its role is not yet fully understood, it has been suggested that it also facilitates the entry of SARS-CoV-2 into the central nervous system.[8]

As noted, several clinical investigations have explored the relationship between COVID-19 and cognitive impairment. Conversely, although theories on the association between SARS-CoV-2 positivity and the development of cognitive impairment have been proposed, the evidence available in the scientific literature remains limited. Most of the publications are cohort studies conducted in developed countries, focusing mainly on younger populations.[9–12] Therefore, there is insufficient scientific evidence of publications between post-COVID 19 cognitive impairments in the older adult population with mild disease and SARS-CoV-2 positivity. Furthermore, most of the studies have been conducted in the acute or immediate post-acute stage, in patients with a critical illness and who have required stay in intensive care units or ventilatory support.[13,14] For this reason, there is a need to extend the research on this condition. Therefore, the aim of the present study is to associate SARS-CoV-2 infection positivity and cognitive impairment in older adults.

Material and methods

Type of study and objective

An observational, cross-sectional, analytical design was conducted from September 2022 to December 2023. The main objective was to determine the association between SARS-CoV-2 infection and cognitive impairment in mild post-COVID 19 older adults[15] at the Family Medicine Unit No. 64 of the "Instituto Mexicano del Seguro Social" (Mexican Institute of Social Security (IMSS, for its acronym in Spanish)).

Subjects

Sample size was calculated by using the OpenEpi calculator version 3.01 with a 95% confidence interval and 80% power, with a prevalence of 7.3%[16] of cognitive impairment in older adults without COVID-19 infection and 25.8% of cognitive impairment in adults after COVID-19 infection,[13] resulting in a sample size of 128 subjects, with a 1:1 ratio. Non-probability convenience sampling was used.

Older adults aged 60-65 years old were included. Half of the sample included people with SARS-CoV-2 infection confirmed by a rapid antigen test recorded in their medical records at least 12 weeks previously. These cases corresponded to post-COVID-19 patients, according to the severity classification described by the WHO, with mild disease.

The selection of the diagnostic test in this study was based on resource availability within Family Medicine Units in Mexico, as well as on the clinical data documented in the institutional health information system. Although the SARS-CoV-2 antigen detection test is not regarded as the gold standard for diagnostic confirmation, it enables the identification of specific viral proteins, such as the nucleocapsid (N) protein and the S1 or S2 subunits of the spike (S) protein. This assay demonstrates an estimated sensitivity of approximately 95% and a specificity ranging between 95% and 99%, which entails a potential risk of false-negative or false-positive results. Therefore, it is essential to corroborate these findings through clinical evaluation and confirmatory reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2. Subjects with any type of dementia, established neurological or psychiatric disease and who consumed medications or substances that interfere with cognitive processes were excluded.

The MoCA test, designed to assess their cognitive status, and a socio-demographic questionnaire that collected information on personal history, such as age, sex, marital status, occupation, educational level, chronic diseases, medication use, history of SARS-CoV-2 infection, symptoms and management during the illness, were applied. In addition, they were also informed that a review of their medical records would be conducted to collect data such as weight, height, COVID-19 rapid test results, comorbidity, and treatments.

Ethical issues and consent

The research was carried out in the Family Medicine Unit No. 64 of the "Instituto Mexicano del Seguro Social" (Mexican Institute of Social Security) and obtained the registration number R-2023-1408-011 after being reviewed and approved by the Research Ethics Committee and the Local Health Research Committee.

Statistical analysis

Statistical analysis was performed with SPSS version 27. In the univariate analysis, for nominal qualitative variables (SARS-CoV-2

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infection, cognitive impairment, sex, marital status, occupation, type 2 diabetes, arterial hypertension, chronic obstructive disease (COPD), obesity, fever, cough, asthenia, anorexia, myalgia, odynophagia, nasal congestion, headache, diarrhoea, nausea, vomiting, anosmia, ageusia, and dyspnoea) and ordinal variables (schooling), frequencies and percentages were obtained.

In the case of the quantitative variable (age), the type of distribution was determined by using the Kolmogorov - Smirnov statistical test, considering a $p > 0.05$ as a Gaussian distribution. The variable was expressed with median and IQR (25.75) for assuming a free distribution.

The association between the variables of cognitive impairment and SARS-CoV-2 infection was determined by Pearson's Chi-square test. For multivariate analysis, a multiple binary logistic regression model was constructed. Simple and adjusted analyses were performed, including variables with clinical relevance and statistical significance, trying to create a parsimonious model. The following were included: history of SARS-CoV-2 infection, T2D, SAH, and obesity. We obtained betas, exponential betas (OR), 95% CI, p-values. The adjusted analysis was represented by a forest plot.

Results

Descriptive results

Out of a total of 128 subjects, the median age was 62.5 years (IQR 60.65). 71.1% were female, 61.7% of the participants had chronic diseases, among which type 2 diabetes was found in 61.7%, hypertension in 43.8% and obesity in 21.9%. 35.2% of the participants had primary education. Likewise, 54.9% of the older adults are married. And in 52.3% of the cases, they have their home as their occupation. Cognitive impairment was reported in 81.3 % and other symptoms in 48.4%. Headache came first, affecting 39.8% of the cases, followed by odynophagia with 34.4% and, in third place, cough with 32.9%. In addition, other non-respiratory symptoms were reported, such as diarrhoea in 6.3%, nausea in 6.3%, and vomiting in 1.6%. Although the study was conducted in patients with mild COVID-19, 8.6% reported experiencing dyspnoea (n=11) (Table 1).

Table 1 Sociodemographic and clinical characteristics of older adults aged 60 to 65 years old

General variable	n (%) = 128
Sex	Male 37 (28.9)
	Female 91 (71.1)
Age, Median, IQR (25,75), years	62.5 (60,65)
	No education 8 (6.3)
	Primary school 45 (35.2)
Education	Secondary school 42 (32.8)
	High school 31 (24.2)
	Bachelor's degree 2 (1.6)
	Single 14 (10.9)
	Married 70 (54.9)
Marital Status	Separated 13 (10.2)
	Divorced 11 (8.6)
	Widowed 20 (15.6)
	Employee 39 (30.5)
Occupation	Unemployed 2 (1.6)
	Retired 20 (15.6)
	Home 67(52.3)
	Yes 79 (61.7)
Chronic diseases	No 49 (38.3)
	Yes 79 (61.7)
Type 2 diabetes	No 49 (38.3)
Arterial hypertension	Yes 56 (43.8)
	No 72 (56.3)
COPD	If 3 (2.3)
	No 72 (56.3)
	Yes 28 (21.9)
Obesity	No 100 (28.1)
	Positive 64 (50)
SARS-CoV-2	Negative 64 (50)
	Yes 104 (81.3)
Cognitive impairment	No 24 (18.8)
Presence of symptoms	Yes 62 (48.4)
Fever	Yes 40 (31.3)
Cough	Yes 42 (32.8)
Asthenia	Yes 35 (27.3)
Anorexia	Yes 15 (11.7)
Myalgia	Yes 38 (29.7)
Odynophagia	Yes 44 (34.4)
Nasal congestion	Yes 34 (26.6)
Headache	Yes 51 (39.8)
Diarrhoea	Yes 8 (6.3)
Nausea	Yes 8 (6.3)
Vomiting	If 2 (1.6)
Ageusia	Yes 21 (16.4)
Anosmia	Yes 25 (19.5)
Dyspnoea	Yes 11 (8.6)

IQR: Interquartile Ranges; %: Percentage; n: Frequency

Bivariate results

Analysis of the association between cognitive impairment and SARS-CoV-2 infection resulted in a $p < .001$. Participants who presented post-COVID-19 cognitive impairment with a positive SARS-CoV-2 test on file accounted for 93.8% of cases (n= 60) (Table 2).

Table 2 Clinical and socio-demographic characteristics of older adults aged 60 to 65 years old with SARS-CoV-2 positivity

General variable	SARS-CoV-2 positive n= 62	SARS-CoV- 2 negative n= 62	p
Age	62 (61-64)	62 (61-64)	<.05[1]
Sex			
Man	18 (28.1)	19 (29.7)	
Woman	46 (71.9)	45 (79.3)	0.845[2]
Education			
No education	3 (4.7)	5 (7.8)	
Primary school	19 (29.7)	26(40.6)	
Secondary school	21 (32.8)	21 (32.8)	0.379[3]
High school	20 (31.2)	11 (17.2)	
Bachelor's degree	1 (1.6)	1 (1.6)	
Marital status			
Single	6 (9.4)	8 (12.5)	
Married	29 (45.3)	41(64.1)	
Separated	8 (12.5)	5 (7.8)	0.031[3]
Divorced	10 (15.6)	1 (1.6)	

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Table 2 Continued...

Widowed	11 (17.2)	9 (14.1)	
Occupation			
Employee	15 (23.4)	24 (37.5)	
Unemployed	1 (1.6)	1 (1.6)	
Retired	11 (17.2)	9 (14.1)	0.390[3]
Home	37 (57.8)	30 (46.9)	
Chronic diseases			
Yes	35 (54.7)	44 (68.8)	
No	29 (45.3)	20 (31.3)	0.102[2]
Type 2 diabetes			
Yes	22 (34.4)	26 (40.6)	
No	42 (65.6)	38 (59.4)	0.465[2]
Arterial Hypertension			
Yes	27 (42.2)	29 (45.3)	
No	37 (57.8)	35 (54.7)	0.722[2]
COPD			
Yes	1 (1.6)	2 (3.1)	
No	63 (98.4)	62 (96.9)	0.559[2]
Obesity			
Yes	10 (15.6)	18 (28.1)	
No	54 (84.4)	46 (71.9)	0.087[2]
Cognitive impairment post-COVID 19			
Yes	60 (93.8)	44 (68.8)	
No	4 (6.3)	20 (31.3)	<.05[2]
Memory loss			
Yes	60 (93.8)	44 (68.8)	
No	4 (6.3)	20(31.3)	<.05[2]
Trouble concentrating			
Yes	60(93.8)	44 (68.8)	
No	4(6.3)	20 (31.3)	<.05[2]
Trouble solving problems			
Yes	60 (93.8)	44 (68.8)	
No	4 (6.3)	20 (31.3)	<.05[2]
Trouble following instructions			
Yes	60 (93.8)	44 (68.8)	
No	4 (6.3)	20 (31.3)	<.05[2]
Symptoms			
Yes	62 (96.9)	0 (0)	
No	2 (3.1)	64 (100)	<.05[2]
Fever			
Yes	40 (62.5)	0 (0)	
No	24 (37.5)	64 (100)	<.05[2]
Cough			
Yes	42 (65.6)	0 (0)	
No	22 (34.4)	64 (100)	<.05[2]
Asthenia			
Yes	35 (54)	0 (0)	
No	29 (45.3)	64 (100)	<.05[2]
Anorexia			
Yes	15 (23.4)	0 (0)	
No	49 (76.6)	64 (100)	<.05[2]
Myalgia			
Yes	38 (59.4)	0 (0)	
No	26 (40.6)	64 (100)	<.05[2]
Odynophagia			
Yes	44 (68.8)	0 (0)	<.05[2]
No	20 (31.3)	64(100)	
Nasal congestion			
Yes	34 (53.1)	0 (0)	
No	30 (46.9)	64(100)	<.05[2]
Headache			
Yes	51 (79.7)	0 (0)	
No	13 (20.3)	64(100)	<.05[2]
Diarrhoea			
Yes	8 (12.5)	0 (0)	
No	56 (87.5)	64(100)	<.05[2]
Nausea			
Yes	8 (12.5)	0 (0)	
No	56 (87.5)	64(100	<.05[2]
Vomiting			
Yes	2 (3.1)	0 (0)	
No	62(96.9)	64(100	0.15[2]
Ageusia			
Yes	21 (32.8)	0 (0)	
No	43 (67.2)	64(100	<.05[2]
Anosmia			
Yes	25 (39.1)	0 (0)	
No	39 (60.9)	64(100)	<.05[2]
Dyspnoea			
Yes	11 (17.2)	0 (0)	
No	53 (82.8)	64(100)	<.05[2]

[1] Mann-Whitney U-test; [2] Pearson's chi-square; [3]Linear trend test

SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; COPD, chronic obstructive disease; COVID-19, coronavirus disease 2019

In the analysis of cognitive impairment and SARS-CoV-2 positive infection, an OR of 6.8 was obtained with a [95% CI (2.17-21.36), p< 0.05] (Table 3).

Table 3 SARS-CoV-2 positive infection and cognitive impairment in adults

General variable	Cognitive Impairment n=104	No Cognitive Impairment n=24	OR with 95% CI	p
Positive SARS-CoV-2 infection	60 (57.7)	4 (16.7)		
			6.81 (2,17-21,36)	< 0.01
Negative SARS-CoV-2 infection	44 (42.3)	20 (83.3)		

CI=Confidence Interval; OR=odds ratio; p=probability value

Clinical and socio-demographic characteristics were contrasted with the presence of cognitive impairment in this research and certain characteristics were present, among which 31.7% of the cases had primary education (p 0.09) and 74% (p 0.12) were female. The predominant marital status was marriage, accounting for 54.8% (p 0.45), and the main occupation was home-based, with 55.8% (p 0.33) of the people. In addition, 59.6% of cases were found to have comorbidities (p 0.30). Systemic arterial hypertension was the most prevalent, affecting 42.3% (p 0.49), followed by type 2 diabetes with 35.6% (p 0.35), and finally obesity with 21.2% (p 0.68) (Table 4).

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Table 4 Clinical and socio-demographic characteristics of older adults and cognitive impairment

General variable	Cognitive Impairment n=104	No Cognitive Impairment n=24	p
Sex			
Man	27 (26)	10(41.7)	
Woman	77 (74)	14 (58.3)	0.126[1]
Education			
No education	8 (7.7)	0 (0)	
Primary school	33 (31.7)	12 (50)	
Secondary school	32 (30.8)	10 (41.7)	
High school	29 (27.9)	2 (8.3)	0.094[2]
Bachelor's degree	2 (1.9)	0 (0)	
Marital status			
Single	13 (12.5)	1 (4.2)	
Married	57 (54.8)	13 (54.2)	
Separated	9 (8.7)	4 (16.7)	
Divorced	10 (9.6)	1 (4.2)	0.454[2]
Widowed	15 (14.4)	5 (20.8)	
Occupation			
Employee	29 (27.9)	10 (41.7)	
Unemployed	2 (1.9)	0 (0)	
Retired	15 (14.4)	5 (20.8)	0.330[2]
Home	58 (55.8)	9 (37.5)	
SARS-CoV-2			
Positive	60 (57.7)	4 (16.7)	<.001[1]
Negative	44 (42.3)	20 (83.3)	
Chronic diseases			
Yes			
No	62 (59.6)	17 (70.8)	
	42 (40.4)	7 (29.2)	0.308[1]
Type 2 diabetes			
Yes	37 (35.6)	11 (45.8)	
No	67 (64.4)	13 (54.2)	0.350[1]
Arterial Hypertension			
Yes	44 (42.3)	12 (50)	
No	60 (57.7)	12 (50)	0.494[1]
COPD			
Yes	3 (2.9)	0 (0)	
No	101 (97.1)	24 (100)	0.400[1]
Obesity			
Yes	22 (21.2)	6 (25)	
No	82 (78.8)	18(75)	0.681[1]
COVID-19 Management			
None	44 (42.3)	20 (83.3)	
Symptomatic at home (mild)	60 (57.7)	4 (16.7)	<.001[1]
Symptoms			
Yes	58 (55.8)	4 (16.7)	
No	46 (44.2)	20 (83.3)	<.001[1]
Fever			
Yes	37 (35.6)	3 (12.5)	
No	67 (64.4)	21 (87.5)	0.028[1]
Cough			
Yes	38 (36.5)	4 (16.7)	
No	66 (63.5)	20 (83.3)	0.062[1]
Asthenia			
Yes	31 (29.8)	4 (16.7)	0.193[1]
No	73 (70.2)	20 (83.3)	
Anorexia			
Yes	13 (12.5)	2 (8.3)	0.567[1]
No	91 (87.5)	22 (91.7)	
Myalgia			
Yes	34 (32.7)	4 (16.7)	
No	70 (67.3)	20 (83.3)	0.121[1]
Odynophagia			
Yes	41 (39.4)	3 (12.5)	
No	63(60.6)	21 (87.5)	0.012[1]
Nasal congestion			
Yes	32 (30.8)	2 (8.3)	
No	72 (69.2)	22 (91.7)	0.025[1]
Headache			
Yes	48 (46.2)	3 (12.5)	0.002[1]
No	56 (53.8)	21 (87.5)	
Diarrhoea			
Yes	7 (6.7)	1 (4.2)	0.640[1]
No	97 (93.3)	23 (95.8)	
Nausea			
Yes	8 (7.7)	0 (0)	0.161[1]
No	96 (92.3)	24 (100)	
Vomiting			
Yes	2 (1.9)	0 (0)	
No	102 (98.1)	24 (100)	0.494[1]
Ageusia			
Yes	20 (19.2)	1 (4.2)	0.072[1]
No	84 (80.8)	23 (95.8)	
Anosmia			
Yes	23 (22.1)	2 (8.3)	0.1251
No	81 (77.9)	22 (91.7)	
Dyspnoea			
Yes	9 (8.7)	2 (8.3)	0.960[1]
No	95 (91.3)	22 (91.7)	

[1]Pearson's chi-square;[2]Linear trend test

Multivariate results

Within the multivariate analysis, in the simple model an OR of 6.81 [95% CI (2.17-21.35), p<.01] and in the adjusted model an OR of 6.86 [95% CI (2.16-21.73), p<.05] were obtained between SARS-CoV-2 positive infection and development of cognitive impairment. In the analysis of the intervening variables, the presence of type 2 diabetes had an OR of 1.36 [95% CI (0.51-3.64), p .53], hypertension with an OR of 1.25 [95% CI (0.47-3.30), p 0.65] and obesity had an OR of 1.14 [95% CI (0.38-3.44) p 0.81] (Table 5 and Figure 1).

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Table 5 Multivariate analysis. Risk factors for cognitive impairment in subjects with SARS-CoV-2

General variable	Cognitive Impairment									
	Simple model					Adjusted model				
	OR[1]	95 % CI	p	B*	EE**	OR[2]	95 % CI	p	B*	EE**
SARS-CoV-2 positive	6.81	2,17-21,35	<.01	1.92	0.58	6.86	2,16-21,73	0.01	1,92	0.58
Type 2 diabetes	1.53	0.62-3,76	0.35	0.42	0.45	1.36	0.51-3,64	0.53	0.31	0.5
Arterial Hypertension	1.36	0.56-3,32	0.49	0.31	0.45	1.25	0.47-3,30	0.65	0.22	0.49
Obesity	1.24	0.44-3,50	0.68	0.21	0.52	1.14	0.38-3,44	0.81	0.13	0.56

[1] Simple logistic regression. [2] Multivariate logistic regression. *B= regression coefficient

**EE=Standard error; Overall percentage of the multiple model=81.3 %; Nagelkerke's R2 of the multivariate model=0.17; Hosmer-Lemeshow test =0.7

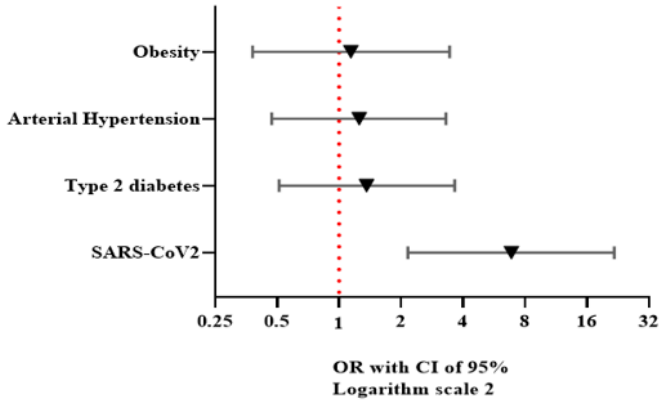

Figure 1 Multiple logistic regression. Risk factors for cognitive impairment.

Discussion

In the sociodemographic findings of patients who experienced cognitive impairment post-COVID-19 in this study, it is highlighted that the impairment was more prevalent in women. This is supported by literature reporting that women are more likely to experience and report somatic and cognitive symptoms, due to physiological and socialisation factors.[17] Furthermore, Francesca Bai et al.,[18] suggest that female hormones may influence the persistence of inflammation during COVID-19, and that increased IgG antibody production may prolong disease manifestations. These observations differ from the project by Checa et al., who identified in their research that the majority of those affected by SARS-CoV-2 and cognitive impairment were men. However, their study covered a smaller age range (18 to 65 years old) and included patients with moderate disease.[19]

In addition, the research revealed that most of the individuals who experienced cognitive impairment had completed only primary education. In view of this finding, it is pertinent to refer to the cognitive reserve theory, which states that factors such as lifestyle and educational level influence cognitive performance. In particular, people with higher educational attainment and mentally demanding jobs tend to maintain better cognitive performance over time.[20] This explains results obtained in our research; however, it contrasts with the results of Henneghan's study, in which cognitive impairment was observed in participants with a high level of education and proficiency in another language.[21]

This study identified a variety of symptoms in patients with COVID-19, the most common being headache, odynophagia and cough, together with non-respiratory manifestations such as diarrhoea, nausea, and vomiting. In relation to these data, the clinical presentations of SARS-CoV-2 disease are known to be diverse, with fever, dry cough, and fatigue being the most common presenting signs and symptoms according to the World Health Organisation.[22] In contrast to these observations, the results of the study by Almeria et al.,[23] reveal that, during COVID-19 disease, the most reported symptoms are fever, cough and myalgias. Nevertheless, it is important to note that their investigation excludes older adults and includes patients with varying degrees of severity and complications associated with COVID-19.[23]

Regarding the main objective of the study, an association was found between SARS-CoV-2 infection positivity and the development of cognitive impairment. This finding is supported by several publications documenting the neurological consequences following COVID-19, highlighting brain inflammation as a result of the immune response, as well as pathophysiological mechanisms such as direct viral involvement, neurovascular dysfunction, blood-brain barrier disruption, and neuronal death.[24] In addition, it is important to note that several factors can influence viral entry, including the function of newly identified receptors on the cell surface, cellular proteases that facilitate this process, and host-specific characteristics. These elements determine the ability of the virus to enter cells, leading to viral fusion and release of viral genetic material by endocytosis.[8] In contrast to the findings of this research, Carrillo-Garcia et al., found that 66% of COVID-19 survivors had sequelae, with depressive symptoms predominating in 51% of cases and cognitive impairment in 25.8%, a figure three times lower than that observed in our study. Conversely, their research was longitudinal, focusing on patients with a history of hospitalisation and using a variety of diagnostic criteria, including clinical assessments, imaging studies and laboratory tests.[13]

This project also documented those patients had several comorbidities, most notably systemic arterial hypertension, followed by type 2 diabetes and obesity. Given these findings, several studies agree that older adults, especially those with comorbidities such as hypertension, type 2 diabetes, cancer, renal or liver failure, and cardiovascular or cerebrovascular disease, are more vulnerable to COVID-19, which increases their frailty, susceptibility to infection, and morbidity and mortality rates.[25] This result is comparable to the findings of Vargas et al., who confirmed that these chronic degenerative diseases are associated with an increased risk of developing severe forms of COVID-19 and persistent post-COVID-19 syndrome.[26] In contrast, Graham et al., found that anxiety, depression, autoimmune diseases, and COPD were the most frequent conditions in patients seen at the Neuro COVID-19 Clinic at Northwestern Memorial Hospital.[27] Furthermore, Lui Yang identified that low educational level and episodes of delirium, adjusted for age and sex, also represent risk factors for post-COVID-19 cognitive impairment.

The instrument used only determined the presence or absence of cognitive impairment, without detailing the affected domains, thus

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restricting the neurocognitive assessment of the patients. Additional questionnaires and other diagnostic tools, such as imaging studies, are recommended to obtain a more accurate assessment of neurocognitive functions. A baseline assessment of participants' neurocognitive function is also considered essential, as in this study it was not possible to obtain information on their cognitive status prior to SARS-CoV-2 infection, which could have introduced a bias in the results, and being a cross-sectional study it was not possible to reliably establish the cause-effect relationship between SARS-CoV-2 infection positivity and cognitive impairment. It would also be pertinent to explore the possibility of using another diagnostic method for SARS-CoV-2 infection, as the test used in this study was selected based on available institutional resources and system records. Nonetheless, the rapid antigen test for the detection of SARS-CoV-2 infection is not considered the gold standard for confirmatory diagnosis of the virus, with a sensitivity of 95% and specificity of 95-99%, implying a risk of false positives and negatives.

Given that the design of this study is cross-sectional, it is essential to conduct prospective and longitudinal studies that monitor the cognitive function of patients after SARS-CoV-2 infection, especially in those with greater symptomatology, to assess the evolution of cognitive impairment and its impact on quality of life, functionality and work performance. This follow-up will make it possible to identify the progression or improvement of the deterioration and even analyse the response to neurocognitive rehabilitation.

The results of this study can be extrapolated to men and women with clinical and socio-demographic characteristics included in the study in the context of the IMSS and the Mexican population. As a strength of the research, a binary logistic regression model was used to control confounding factors, which showed that the presence of type 2 diabetes, systemic arterial hypertension or obesity are not statistically significant variables as risk factors for the development of cognitive impairment.

Finally, it is concluded that SARS-CoV-2 infection positivity represents a risk factor linked to the development of cognitive impairment. Therefore, these findings highlight the need for further study of post-COVID-19 neurocognitive complications and emphasise the importance of early surveillance by family physicians at the primary care level to ensure timely neurocognitive diagnosis and treatment.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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