Clinical presentation and factors associated to COVID-19 disease in Mexican patients.

Short title: COVID-19 disease in Mexican patients.

Abstract

Objective The objective was determining the clinical presentation and factors strongest associated to COVID-19 by age group.

Material and Methods A case-control study was performed. A total of 196,640 patients with laboratory-confirm SARS-CoV-2 infection and 196,640 persons without SARS-CoV-2 infection were included.

Results The strongest signs and symptoms associated with SARS-CoV-2 infection were: in children fever (OR=1.31, CI95% 1.15-1.492), and headache (OR=1.208, CI95% 1.056-1.381). In adolescents, rhinorrhoea (OR=1.314, CI95% 1.218-1.419), myalgia (OR=1.142, CI95% 1.032-1.264), odynophagia (OR=1.151, CI95% 1.069-1.240), cough (OR=1.109, CI95% 1.032-1.192), and fever (OR=1.617, CI95% 1.501-1.742). In young-adults, rhinorrhoea (OR=1.224, CI95% 1.192-1.257), and chest pain (OR=1.076, CI95% 1.044-1.108). In older adults, polypnea (OR=1.088, CI95% 1.027-1.154), and diarrhea (OR=1.138, CI95% 1.086-1.193), and in both adults' groups, cyanosis, malaise, arthralgia, myalgia, chills, dyspnoea, cough, and fever.

Conclusion Clinical presentation associated with SARS-CoV-2 infection was different in each group. The strongest associated factors to predict SARS-CoV-2 infection are: smoking, obesity and diabetes.

Keywords

2019-nCoV Disease; SARS-CoV-2 Case Control Studies

Introduction

Novel recently emerged Coronaviruse (CoV) at 2019 (2019-nCoV, a.k.a. SARS-CoV-2) causes an acute respiratory illness, which has been named Coronavirus Disease 2019 (COVID-19).[1-4] The four so-called common Human CoV: 229E (Alphacoronavirus), NL63 (Alphacoronavirus), OC43 (Betacoronavirus), and HKU1 (Betacoronavirus) commonly cause mild to moderate respiratory diseases, and contribute to 15–30% of cases of common colds in human adults (although severe and life-threatening lower respiratory tract infections can sometimes occur in infants, older adults, or immunocompromised patients).[3] While Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV), often cause serious illness.[1] COVID-19 leads to primarily respiratory symptoms.[4-5] The cost of health care, epidemiologic surveillance, and infection spread are greater than the capacity of the health care systems. Hitherto, a wide range of clinical spectrum has been reported from complete lack of symptoms, mild symptoms, influenza-like to severe lower respiratory disease with dyspnoea, pneumonia and life- threatening multiple organ failure.[4-30] Moreover, patients with comorbidities including cardiovascular diseases, chronic respiratory disease, hypertension, diabetes, chronic obstructive pulmonary disease, chronic kidney disease, cerebrovascular disease, malignancy, obesity, having more than one comorbidity, or levels of creatine kinase ≥180 U/L or counts of CD4+ T-cell <300 cells/μL, have a higher risk for COVID-19 disease or severe COVID-19 complications.[4, 26-30] Other factors associated to COVID-19 disease are age, sex (male gender), place of residence, and to be indigenous.[4, 28-30] While, male gender, older age, having one or more comorbidities, chronic kidney disease, diabetes, obesity, chronic obstructive pulmonary disease, immunosuppression, and hypertension also were associated with higher hospital admision.[22, 29-32] Even the symptoms

to predict COVID-19 are dissimilar by geographic region.[33-44] Therefore, it is important to delimit or specify the symptoms or combination of them to guide the identification of subjects with COVID-19 and prevent a severe or fatal illness or its complications. The objective of the present study was determining the clinical presentation and factors strongest associated to COVID-19 by age group.

Materials and methods

Study design, setting and participants.

A *population-based case-control study* using a cross-sectional secondary dataset of patients whom undergoing both COVID-19 symptom screening and nasopharyngeal SARS-CoV-2 assays at medical facilities in Mexico was performed.[45] The publicly available dataset included patients classified as 'suspected cases of viral respiratory disease' using an epidemiological study form.[45] The data used was that data released by the Mexican Health Ministry on November 16, 2020. This database included sociodemographic, and clinical information of 656,827 patients during the period, January 1—November 10, 2020. The dataset was compiled by the General Directorate of Epidemiology (DGE by its acronyms in Spanish Dirección General de Epidemiología,) through the Epidemiological Surveillance System for Viral Respiratory Diseases.[45] Risk set sampling was used because the controls were selected from the at-risk source population at the same time as cases occur.[46] In these case-control studies, the odds ratio estimates the rate ratio, without assuming that the disease is rare in the source population.[46] Moreover, due to it is possible, that a control selected at a later time point could become a case during the remaining time that the registry of the dataset is running.[46-47] "This differs from case-control studies that use cumulative density sampling or survivor sampling, which select their controls after the

conclusion of the study from among those individuals remaining at risk".[46] Selecting controls in a risk set sampling manner provides two advantages: 1) a direct estimate of the rate ratio is possible, and 2) the estimates are not biased by differential loss to follow up among the exposed vs. unexposed controls.[46] Population controls were used. Sampling randomly from the registry of the secondary dataset was the way to find and recruit population-based controls. In addition, case–control studies with incident cases can be conducted in two contexts—dynamic populations and cohorts—of which the first is the most commonly used because it comes naturally, and the resulting odds ratio directly estimates the rate ratio from this dynamic population, provided that the control subjects represent the source population's distribution of person-time of exposure over the risk period.[47] "This can be achieved either by matching on time or by selecting control subjects more loosely from the same period, if the population is judged to be in steady state for the exposure(s) and other variables of interest".[47]

Database and data sources.

Open data comes from the 475 Viral Respiratory Disease Monitoring Health Units (Unidades de Salud Monitoras de Enfermedad Respiratoria Viral, USMER by its acronyms in Spanish) throughout the country.[45] In these units, viral respiratory disease syndrome is monitored, and various respiratory viruses are studied: SARSCoV-2, the four variants of influenza that circulate each season, *Adenovirus, Bocavirus, Coronavirus, Enterovirus, Rhinovirus, Metapneumovirus, Parainfluenza* and *Respiratory Syncytial Virus*.[45]

Additionally, data also is provided by units that had been adapted to screen suspected COVID-19 cases that do not belong to "USMER" units (Non-USMER).[45] This dataset is

continuously updated. Upon admission at medical facilities in Mexico patients were screened by healthcare professionals.[45] All units (USMER and Non-USMER) fill the same forms and sent the information using an online platform (SISVER platform).[45] In all cases, a diagnostic testing for COVID-19 (RT-PCR) was performed to patients with serious symptoms.[45] For cases with mild symptoms (classified as ambulatory cases), USMER units perform COVID-19 diagnostic testing on at least 10% of these cases whereas for Non-USMER units depend on their resource capacity.[45] After the case was evaluated and confirmed at the district, the state and national level surveillance system, it was added to the dataset and classified as negative or positive COVID-19 case or pending case.[45]

A laboratory testing to confirm SARS-CoV-2 infection was performed according to Wordl Health Organization interim guidance.[46] Combined nasopharyngeal and oropharyngeal swabs were obtained for its analysis.[45] The swabs were placed in a container.[45] The samples were sent to the nearest Laboratory of Respiratory Virus (InDRE) for testing by RT-PCR test.[45] For intubated patients, bronchoalveolar lavage was obtained.[45] In case of death, lung biopsies were obtained during autopsy, from an area visibly affected by disease.[45] In the current study only confirmed case as negative or positive to SARS-CoV-2 were included.

Study variables.

All information was included in a database. The database includes information on COVID-19 testing results, as well as sociodemographic information, clinical characteristics and medical units' specifications. Sociodemographic information included patients' age, gender and nationality (Mexican or not). Clinical characteristics included existing comorbidities, sign and symptoms. The comorbidities were defined as dichotomous variables: diabetes,

chronic obstructive lung disease (COPD), asthma, immunosuppression, hypertension, HIV-AIDS, cardiovascular disease, obesity, chronic renal disease and other comorbidities (not defined). The smoking variable was classified as smokers or nonsmokers. Also, the number of comorbidities were included. The sign and symptoms included as dichotomous variables were fever, cough, odynophagia, dyspnoea, irritability, diarrhea, chest pain, chills, headache, myalgia, arthralgia, malaise, rhinorrhoea, polypnea, vomit, abdominal pain, conjunctivitis, cyanosis, sudden onset symptoms. As well, patient's information, such as if there was previous contact with someone who was viral infection were involved, and if the same patient was vaccinated. All the information was recorded on a specific "Respiratory Triage form by the attending physicians.[45, 47] For patients with laboratory-confirmed SARS-CoV-2 infection, additional information associated to admission of patient into an intensive care unit or if she/he was intubated, or died were included. Medical units' specifications included if the healthcare unit was part of the USMER or Non-USMER network, and the type of facility where the patient was diagnosed.

Outcomes, subject's selection, and statistical analysis.

The main outcome variable is COVID-19 diagnosis established through SARS-CoV-2 infection, and defined as a dichotomous indicator (presence or absence). Patients with diagnosis of COVID-19 were defined as person with laboratory-confirm SARS-CoV-2 infection. To reduce the effect of selection bias, one person of the same sex and age without SARS-CoV-2 infection was included for each patient diagnosed with COVID-19. The selection of the records was made using random numbers. Descriptive analyses of all patients to characterize the overall study population were performed. Categorical variables were expressed as absolute and relative frequencies (with their corresponding 95%

confidence intervals [95% CI]) and were compared using chi-square test. All 95% CI were obtained using bootstrap sample of 1000 replications. Numerical variables were compared by non-parametric Mann Whitney U test. To estimate the association of all the independent variables with the main outcome variable a multivariate logistic regression was conducted. The first model included clinical comorbidities and sign and symptoms as dichotomous indicators, while the second included the number of clinical diagnoses (comorbidities), and number of sign and symptoms, due to multicollinearity, as the later was derived from the clinical diagnoses and clinical presentation.

Ethical considerations.

This study was conducted according to good clinical practices, as defined by Mexican law, and the Helsinki Declaration for research using human beings. The database designed used anonymized dataset of patients that is publicly available and accessible to anyone through the Mexican Health Ministry. The principles that emerge from the United Nations General Assembly, 1989, were used. Principle of legality and loyalty (the information was obtained in a lawful manner), principle of accuracy (the relevance of the data was verified), principle of purpose (the database is specific, legitimate and public before its creation), principle of non-discrimination and principle of security.

Results

Characteristics of study population.

From the total of 656,827 records in the database corresponding to the period from January 1 to November 10, 2020, a total of 393,280 records were selected. 196,640 patients with laboratory-confirm SARS-CoV-2 infection (cases) and 196,640 persons of the same sex,

and age without SARS-CoV-2 infection (controls, supplemental material Figure 1). Similar percentage of females and males were included (Table 1).

Table 1. General characteristics of the study population.

Variables	Total population	Control group	SARS-CoV-2 infection group	p value
Male	197108; (50.12)	98554; (50.12)	98554; (50.12)	1.000
Female	196172; (49.88)	98086; (49.88)	98086; (49.88)	
Older adult	69584; (17.69)	34792; (17.69)	34792; (17.69)	1.000
Non-USMER	313383; (79.68)	160582; (81.66)	152801; (77.71)	<0.001
USMER	79897; (20.32)	36058; (18.34)	43839; (22.29)	
Red Cross	123; (0.03)	80; (0.04)	43; (0.02)	<0.001[b]
DIF	1; (0.0003)	1; (0.001)		
Estatal	270; (0.07)	121; (0.06)	149; (0.08)	
IMSS	64869; (16.49)	22573; (11.48)	42296; (21.51)	
IMSS-Oportunidades	15; (0.004)	12; (0.01)	3; (0.002)	
ISSSTE	7041; (1.79)	2905; (1.48)	4136; (2.1)	
PEMEX	4029; (1.02)	1670; (0.85)	2359; (1.2)	
Private	7186; (1.83)	3043; (1.55)	4143; (2.11)	
SEDENA	1871; (0.48)	417; (0.21)	1454; (0.74)	
SEMAR	1832; (0.47)	20; (0.01)	1812; (0.92)	
SSA	306029; (77.81)	165792; (84.31)	140237; (71.32)	
University	14; (0.004)	6; (0.003)	8; (0.004)	
Ambulatory patient	347193; (88.28)	183330; (93.23)	163863; (83.33)	<0.001
Hospitalized patient	46087; (11.72)	13310; (6.77)	32777; (16.67)	
Foreign	1905; (0.48)	1044; (0.53)	861; (0.44)	<0.001
Mexican	391375; (99.52)	195596; (99.47)	195779; (99.56)	
Pregnant	2058; (0.52)	1212; (0.62)	846; (0.43)	<0.001[b]
Indigenous	1904; (0.48)	963; (0.49)	941; (0.48)	0.613
Farmers	789; (0.2)	399; (0.2)	390; (0.2)	<0.001[b]
Drivers	8806; (2.24)	3697; (1.88)	5109; (2.6)	
Stationary or itinerant market traders	20302; (5.16)	10136; (5.15)	10166; (5.17)	
Dentists	909; (0.23)	569; (0.29)	340; (0.17)	
Unemployed	16865; (4.29)	9225; (4.69)	7640; (3.89)	
Employees	124731; (31.72)	66139; (33.63)	58592; (29.8)	
Nurses	16174; (4.11)	8321; (4.23)	7853; (3.99)	
Students	28479; (7.24)	13722; (6.98)	14757; (7.5)	
Managers or owners of companies or businesses	1003; (0.26)	370; (0.19)	633; (0.32)	
Home	56834; (14.45)	25784; (13.11)	31050; (15.79)	
Retiree / pensioner	14361; (3.65)	6740; (3.43)	7621; (3.88)	
Laboratory workers	983; (0.25)	476; (0.24)	507; (0.26)	
Teachers	3289; (0.84)	1603; (0.82)	1686; (0.86)	
Physicians	13766; (3.5)	7855; (3.99)	5911; (3.01)	
Workers	4897; (1.25)	2284; (1.16)	2613; (1.33)	
Others	53109; (13.5)	24987; (12.71)	28122; (14.3)	
Other professionals	13789; (3.51)	6921; (3.52)	6868; (3.49)	
Other health workers	14194; (3.61)	7412; (3.77)	6782; (3.45)	
Outpatient consultation	316795; (80.55)	170773; (86.85)	146022; (74.26)	<0.001[b]
Infectology	1714; (0.44)	328; (0.17)	1386; (0.7)	
Internal Medicine	17356; (4.41)	4915; (2.5)	12441; (6.33)	
Pneumology	1136; (0.29)	236; (0.12)	900; (0.46)	
Observation of Emergencies	30448; (7.74)	12559; (6.39)	17889; (9.1)	
Intensive care unit	1065; (0.27)	359; (0.18)	706; (0.36)	
Neonatal Intensive Care Unit	199; (0.05)	91; (0.05)	108; (0.05)	
Adult Emergencies	22570; (5.74)	6094; (3.1)	16476; (8.38)	
Emergency Surgery	664; (0.17)	308; (0.16)	356; (0.18)	
Paediatrics Emergencies	1268; (0.32)	942; (0.48)	326; (0.17)	
Paediatrics Intensive Therapy Unit	65; (0.02)	35; (0.02)	30; (0.02)	
Fever	169548; (43.11)	59985; (30.5)	109563; (55.72)	<0.001
Cough	222150; (56.49)	90223; (45.88)	131927; (67.09)	<0.001
Odynophagia	145837; (37.08)	62875; (31.97)	82962; (42.19)	<0.001

Dyspnoea	88038; (22.39)	32480; (16.52)	55558; (28.25)	<0.001
Irritability	56834; (14.45)	24868; (12.65)	31966; (16.26)	<0.001
Diarrhea	72833; (18.52)	31089; (15.81)	41744; (21.23)	<0.001
Chest pain	81036; (20.61)	31586; (16.06)	49450; (25.15)	<0.001
Chills	105882; (26.92)	39641; (20.16)	66241; (33.69)	<0.001
Headache	236323; (60.09)	105425; (53.61)	130898; (66.57)	<0.001
Myalgia	156255; (39.73)	59901; (30.46)	96354; (49)	<0.001
Arthralgia	139230; (35.4)	52331; (26.61)	86899; (44.19)	<0.001
Malaise	132245; (33.63)	49817; (25.33)	82428; (41.92)	<0.001
Rhinorrhoea	95601; (24.31)	39624; (20.15)	55977; (28.47)	<0.001
Polypnea	30523; (7.76)	10527; (5.35)	19996; (10.17)	<0.001
Vomiting	22145; (5.63)	8996; (4.57)	13149; (6.69)	<0.001
Abdominal pain	39953; (10.16)	17428; (8.86)	22525; (11.45)	<0.001
Conjunctivitis	42045; (10.69)	18464; (9.39)	23581; (11.99)	<0.001
Cyanosis	11355; (2.89)	3901; (1.98)	7454; (3.79)	<0.001
Sudden onset symptoms	111274; (28.29)	47699; (24.26)	63575; (32.33)	<0.001
At least one symptom	329347; (83.74)	148593; (75.57)	180754; (91.92)	<0.001
Diabetes	44249; (11.25)	19482; (9.91)	24767; (12.6)	<0.001
Chronic obstructive pulmonary disease	4220; (1.07)	1977; (1.01)	2243; (1.14)	<0.001
Asthma	9136; (2.32)	4757; (2.42)	4379; (2.23)	<0.001
Immunosuppressive	4890; (1.24)	2606; (1.33)	2284; (1.16)	<0.001
Hypertension	57808; (14.7)	27154; (13.81)	30654; (15.59)	<0.001
HIV-AIDS	1760; (0.45)	926; (0.47)	834; (0.42)	0.028
Other condition	6711; (1.71)	3127; (1.59)	3584; (1.82)	<0.001
Heart disease	7301; (1.86)	3679; (1.87)	3622; (1.84)	0.501
Obesity	56324; (14.32)	24237; (12.33)	32087; (16.32)	<0.001
Chronic kidney disease	5035; (1.28)	2303; (1.17)	2732; (1.39)	<0.001
Smoking	48347; (12.29)	26550; (13.5)	21797; (11.08)	<0.001
Contact with someone with viral infection	221305; (56.27)	117039; (59.52)	104266; (53.02)	<0.001[b]
Vaccinated	82578; (21)	44715; (22.74)	37863; (19.25)	<0.001

Source: Prepared by the authors with the records of the database. P Value was calculated by chi squared.

Average of age was 43.5 years (SD 16.8, range 120 y, minimum 0 y, maximum 120 y, median= 43 y, IQR= 31-55 y). Most of the dataset comes from Non-USMER units. The units belonging to the Ministry of Health and the Mexican Institute of Social Security are the ones who cared for more than 90% of the people with suspected viral respiratory disease. More than 85% are ambulatory patients. Less than 0.5% are foreign, and indigenous, respectively. More than 40% are employees and are dedicated to household. 80 percent of subjects derive from the outpatient consultation. All signs and symptoms, and factors are more prevalent in COVID-19 patients, except to heart disease (Table 1). The order of sign and symptoms is different between groups of age. In children from 0 to 9 years old, the first five most frequently observed signs and symptoms were fever, cough, headache, rhinorrhoea, and irritability. In teenagers and adults, the most prevalent sign and symptoms are headache, cough, and fever, followed by odynophagia, and myalgia, but in different order. However, in older adults' the cough, headache, fever, myalgia, and malaise were the main signs and symptoms observed (Table 2).

Table 2. Order of sign and symptoms adjusted by group of age.

Order	0-9 years	%	10-19 years	%	20-59 years	%	60 or more years	%
1	Fever	43.2	Headache	52.3	Headache	62.4	Cough	58.3
2	Cough	43.0	Cough	47.4	Cough	56.9	Headache	54.6
3	Headache	33.1	Fever	34.4	Fever	43.0	Fever	45.9
4	Rhinorrhoea	25.7	Odynophagia	31.1	Myalgia	40.8	Myalgia	40.8
5	Irritability	23.9	Myalgia	25.8	Odynophagia	38.8	Attack on the general state	38.4
6	Attack on the general state	22.6	Rhinorrhoea	25.2	Arthralgia	36.1	Arthralgia	38.0
7	Odynophagia	21.8	Attack on the general state	23.0	Attack on the general state	33.4	Dyspnoea	34.8
8	Myalgia	17.1	Arthralgia	21.0	Chills	27.8	Odynophagia	32.6
9	Diarrhea	14.5	Chills	19.6	Rhinorrhoea	25.3	Chills	26.0
10	Arthralgia	13.9	Diarrhea	13.5	Chest pain	21.0	Chest pain	22.0
11	Chills	13.5	Dyspnoea	12.6	Dyspnoea	20.3	Rhinorrhoea	19.7
12	Dyspnoea	12.6	Chest pain	12.5	Diarrhea	19.4	Diarrhea	16.6
13	Abdominal pain	11.7	Irritability	12.4	Irritability	14.5	Irritability	13.8
14	Vomiting	9.3	Abdominal pain	9.3	Conjunctivitis	11.4	Polypnea	11.9
15	Conjunctivitis	9.1	Conjunctivitis	9.0	Abdominal pain	10.2	Abdominal pain	10.1
16	Polypnea	7.9	Vomiting	5.4	Polypnea	7.0	Conjunctivitis	8.0
17	Chest pain	7.1	Polypnea	4.9	Vomiting	5.4	Vomiting	6.2
18	Cyanosis	3.1	Cyanosis	1.9	Cyanosis	2.5	Cyanosis	4.6

Source: Prepared by the authors with the records of the database.

Models of regression to predict SARS-CoV-2 infection.

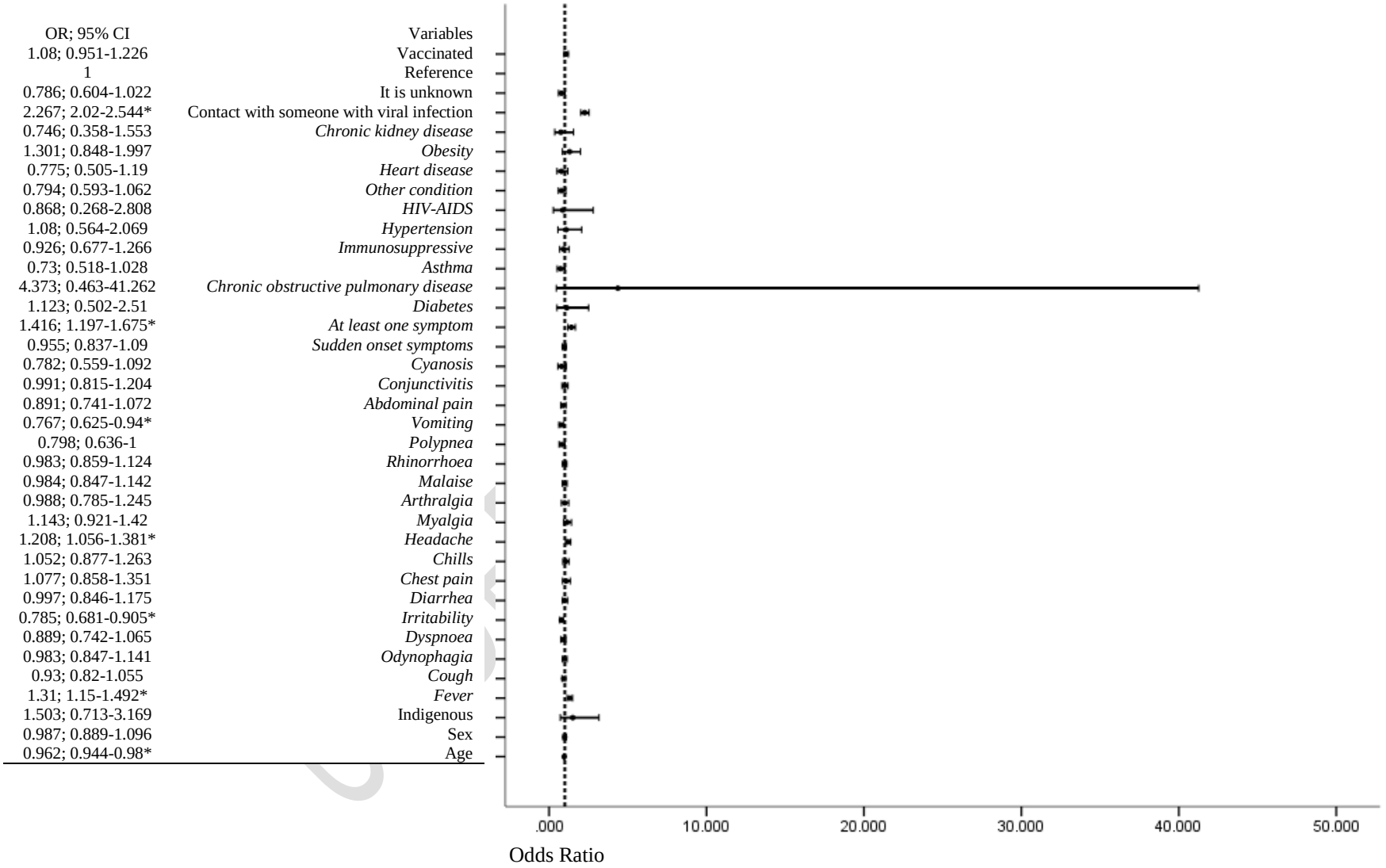
A multivariable logistic regression using the database of Mexican Health Ministry, by randomly dividing it into two arms adjusted by age, and sex (ratio: 1:1) was performed to identify independent signs and symptoms most strongly correlated with COVID-19 disease. In this cohort, children (0-9 y) who tested positive for SARS-CoV-2, the main signs and symptoms reported were fever, cough, headache, sudden onset symptoms, and rhinorrhoea (Table 3), whereas adolescents, adults, and older adults reported fever, cough, headache, and myalgia as main signs and symptoms but in different order (Table 3).

Table 3. Sign and symptoms adjusted by group of age in people with and without SARS-CoV-2 infection.								
	0-9 years		10-19 years		20-59 years		62 or more	
Variables	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
Fever	1231 (40.6)	1388 (45.8)	2482 (27.5)	3730 (41.3)	45460 (30.3)	83296 (55.6)	10812 (31.1)	21149 (60.8)
Cough	1251 (41.2)	1357 (44.7)	3715 (41.2)	4837 (53.6)	69639 (46.5)	100799 (67.3)	15618 (44.9)	24934 (71.7)
Odynophagia	613 (20.2)	707 (23.3)	2363 (26.2)	3255 (36.1)	50649 (33.8)	65546 (43.8)	9250 (26.6)	13454 (38.7)
Dyspnoea	433 (14.3)	331 (10.9)	1085 (12)	1197 (13.3)	22844 (15.3)	37903 (25.3)	8118 (23.3)	16127 (46.4)
Irritability	777 (25.6)	670 (22.1)	1019 (11.3)	1223 (13.5)	19110 (12.8)	24451 (16.3)	3962 (11.4)	5622 (16.2)
*Diarrhea**	431 (14.2)	449 (14.8)	1173 (13)	1269 (14.1)	25043 (16.7)	32932 (22)	4442 (12.8)	7094 (20.4)
*Chest pain**	214 (7.1)	216 (7.1)	1015 (11.2)	1248 (13.8)	24758 (16.5)	38264 (25.5)	5599 (16.1)	9722 (27.9)
*Chills**	394 (13)	424 (14)	1515 (16.8)	2028 (22.5)	31387 (21)	52045 (34.7)	6345 (18.2)	11744 (33.8)
Headache	899 (29.6)	1106 (36.5)	4261 (47.2)	5188 (57.5)	84055 (56.1)	102843 (68.7)	16210 (46.6)	21761 (62.5)
Myalgia	472 (15.6)	563 (18.6)	1909 (21.2)	2753 (30.5)	47217 (31.5)	74938 (50)	10303 (29.6)	18100 (52)
Arthralgia	389 (12.8)	456 (15)	1541 (17.1)	2253 (25)	40914 (27.3)	67253 (44.9)	9487 (27.3)	16937 (48.7)
*Attack on the general state**	694 (22.9)	674 (22.2)	1803 (20)	2357 (26.1)	37796 (25.2)	62228 (41.5)	9524 (27.4)	17169 (49.3)
*Rhinorrhoea**	749 (24.7)	807 (26.6)	1843 (20.4)	2714 (30.1)	31329 (20.9)	44453 (29.7)	5703 (16.4)	8003 (23)
Polypnea	292 (9.6)	186 (6.1)	412 (4.6)	481 (5.3)	7225 (4.8)	13650 (9.1)	2598 (7.5)	5679 (16.3)
*Vomiting***	332 (10.9)	230 (7.6)	501 (5.6)	480 (5.3)	6536 (4.4)	9743 (6.5)	1627 (4.7)	2696 (7.7)
*Abdominal pain***	380 (12.5)	328 (10.8)	851 (9.4)	827 (9.2)	13380 (8.9)	17173 (11.5)	2817 (8.1)	4197 (12.1)
*Conjunctivitis**	284 (9.4)	267 (8.8)	710 (7.9)	916 (10.1)	15014 (10)	19267 (12.9)	2456 (7.1)	3131 (9)
*Cyanosis***	121 (4)	68 (2.2)	157 (1.7)	191 (2.1)	2625 (1.8)	4974 (3.3)	998 (2.9)	2221 (6.4)
*Sudden onset symptoms**	892 (29.4)	885 (29.2)	2150 (23.8)	2562 (28.4)	36613 (24.4)	48746 (32.5)	8044 (23.1)	11382 (32.7)

Source: Prepared by the authors with the records of the database.

The regression analysis shows that fever, headache, and contact with someone with viral infection resulted the most strongly clinical presentation associated with SARS-CoV-2 infection in children group (figure 1).

Figure 1. Regression model to predict SARS-CoV-2 infection in population from 0 to 9 years old. Signs, symptoms and factors associated.

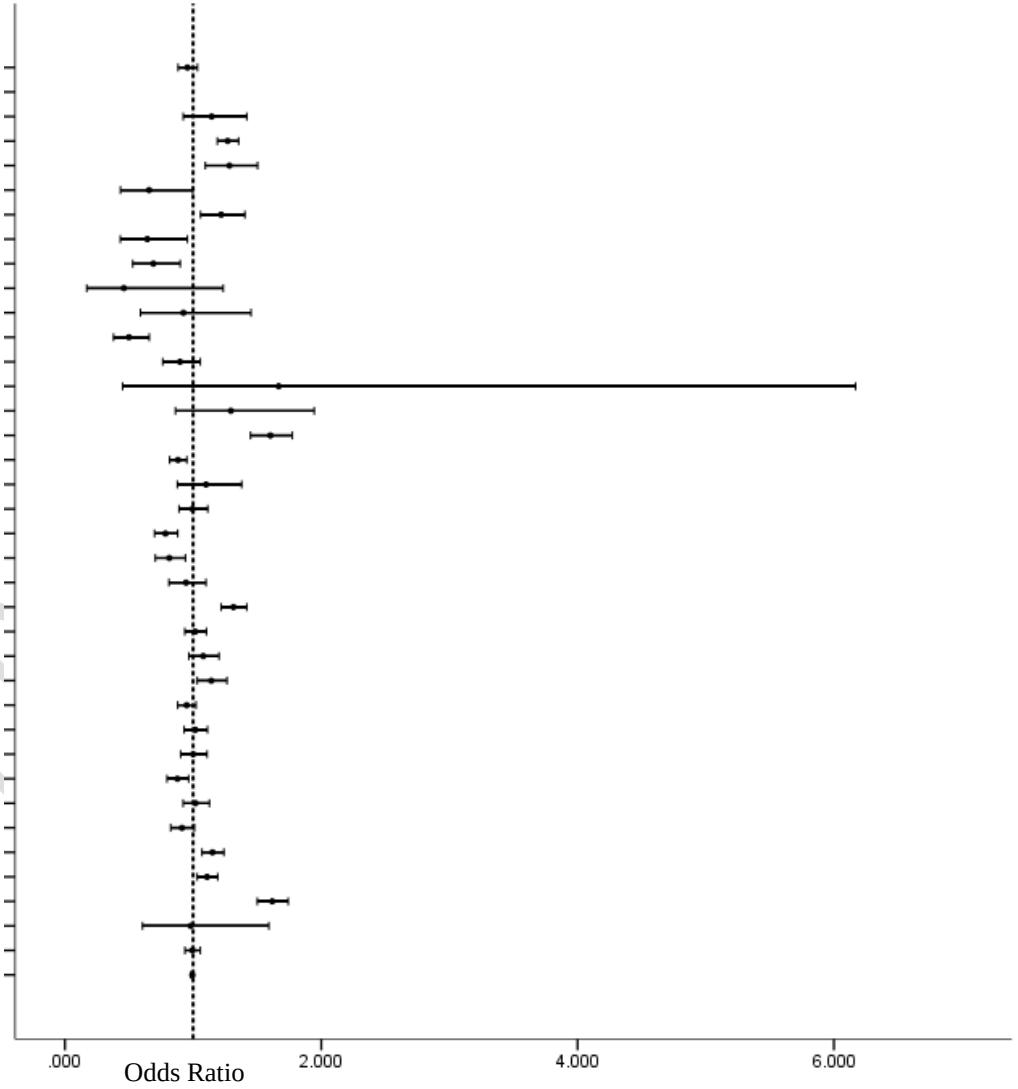


Similarly, in teenagers the clinical presentation associated with SARSCoV-2 infection are rhinorrhoea, myalgia, odynophagia, cough, fever and contact with someone with viral infection. Moreover, smoking, and obesity are also associated with SARS-CoV-2 infection (figure 2).

Figure 2. Regression model to predict SARS-CoV-2 infection in young population (from 10-19 years old). Signs, symptoms and factors associated.

OR; 95% CI	Variables
0.956; 0.883-1.034	Vaccinated
1	Reference
1.144; 0.923-1.419	It is unknown
1.269; 1.189-1.355*	Contact with someone with viral infection
1.283; 1.095-1.503*	*Smoking*
0.657; 0.433-0.997*	*Chronic kidney disease*
1.219; 1.058-1.404*	*Obesity*
0.642; 0.432-0.955*	*Heart disease*
0.69; 0.529-0.899*	*Other condition*
0.459; 0.17-1.235	*HIV-AIDS*
0.924; 0.589-1.452	*Hypertension*
0.499; 0.379-0.658*	*Immunosuppressive*
0.898; 0.763-1.056	*Asthma*
1.667; 0.45-6.169	*Chronic obstructive pulmonary disease*
1.295; 0.862-1.945	*Diabetes*
1.603; 1.448-1.774*	*At least one symptom*
0.881; 0.817-0.951*	*Sudden onset symptoms*
1.1; 0.877-1.379	*Cyanosis*
0.995; 0.89-1.114	*Conjunctivitis*
0.784; 0.699-0.88*	*Abdominal pain*
0.814; 0.705-0.94*	*Vomiting*
0.944; 0.811-1.1	*Polypnea*
1.314; 1.218-1.419*	*Rhinorrhoea*
1.016; 0.935-1.104	*Malaise*
1.078; 0.967-1.202	*Arthralgia*
1.142; 1.032-1.264*	*Myalgia*
0.949; 0.88-1.023	*Headache*
1.017; 0.93-1.112	*Chills*
1; 0.903-1.109	*Chest pain*
0.877; 0.796-0.965*	*Diarrhea*
1.019; 0.922-1.127	*Irritability*
0.913; 0.825-1.01	*Dyspnoea*
1.151; 1.069-1.24*	*Odynophagia*
1.109; 1.032-1.192*	*Cough*
1.617; 1.501-1.742*	*Fever*
0.981; 0.605-1.591	Indigenous
0.994; 0.936-1.056	Sex
0.994; 0.983-1.005	Age

*p Value <0.05



In the same way, the clinical presentation that predicts SARS-CoV-2 infection, in adults is: cyanosis, rhinorrhoea, malaise, arthralgia, myalgia, chills, chest pain, dyspnoea, cough, and fever (but only in adults aged 40-59 years polypnea was associated with infection). Likewise, smoking, obesity, and diabetes are associated with SARS-CoV-2 infection. While, the personal history of vaccination and to know if a person has a viral infection are associated with protection (figures 3-4).

Figure 3. Regression model to predict SARS-CoV-2 infection in adult population from 20 to 39 years old. Signs, symptoms and factors associated.

OR; 95% CI	Variables
0.873; 0.85-0.896*	Vaccinated
1	Reference
1.211; 1.148-1.277*	It is unknown
0.898; 0.877-0.919*	Contact with someone with viral infection
1.295; 1.256-1.335*	Smoking
0.98; 0.843-1.14	Chronic kidney disease
1.196; 1.157-1.236*	Obesity
0.773; 0.671-0.891*	Heart disease
1.032; 0.929-1.145	Other condition
0.761; 0.654-0.886*	HIV-AIDS
0.981; 0.919-1.048	Hypertension
0.745; 0.648-0.858*	Immunosuppressive
0.733; 0.685-0.783*	Asthma
1.011; 0.774-1.321	Chronic obstructive pulmonary disease
1.269; 1.174-1.371*	Diabetes
1.747; 1.675-1.822*	At least one symptom
0.898; 0.876-0.922*	Sudden onset symptoms
1.137; 1.053-1.228*	Cyanosis
0.968; 0.935-1.003	Conjunctivitis
0.799; 0.769-0.831*	Abdominal pain
0.962; 0.915-1.012	Vomiting
1.046; 0.996-1.099	Polypnea
1.224; 1.192-1.257*	Rhinorrhoea
1.218; 1.186-1.251*	Malaise
1.142; 1.104-1.181*	Arthralgia
1.212; 1.173-1.253*	Myalgia
0.851; 0.828-0.875*	Headache
1.141; 1.11-1.174*	Chills
1.076; 1.044-1.108*	Chest pain
0.93; 0.903-0.957*	Diarrhea
0.886; 0.857-0.915*	Irritability
1.067; 1.034-1.1*	Dyspnoea
0.963; 0.939-0.987*	Odynophagia
1.316; 1.283-1.35*	Cough
1.808; 1.764-1.854*	Fever
0.941; 0.793-1.117	Indigenous
0.991; 0.969-1.013	Sex
0.992; 0.99-0.994*	Age

*p Value <0.05

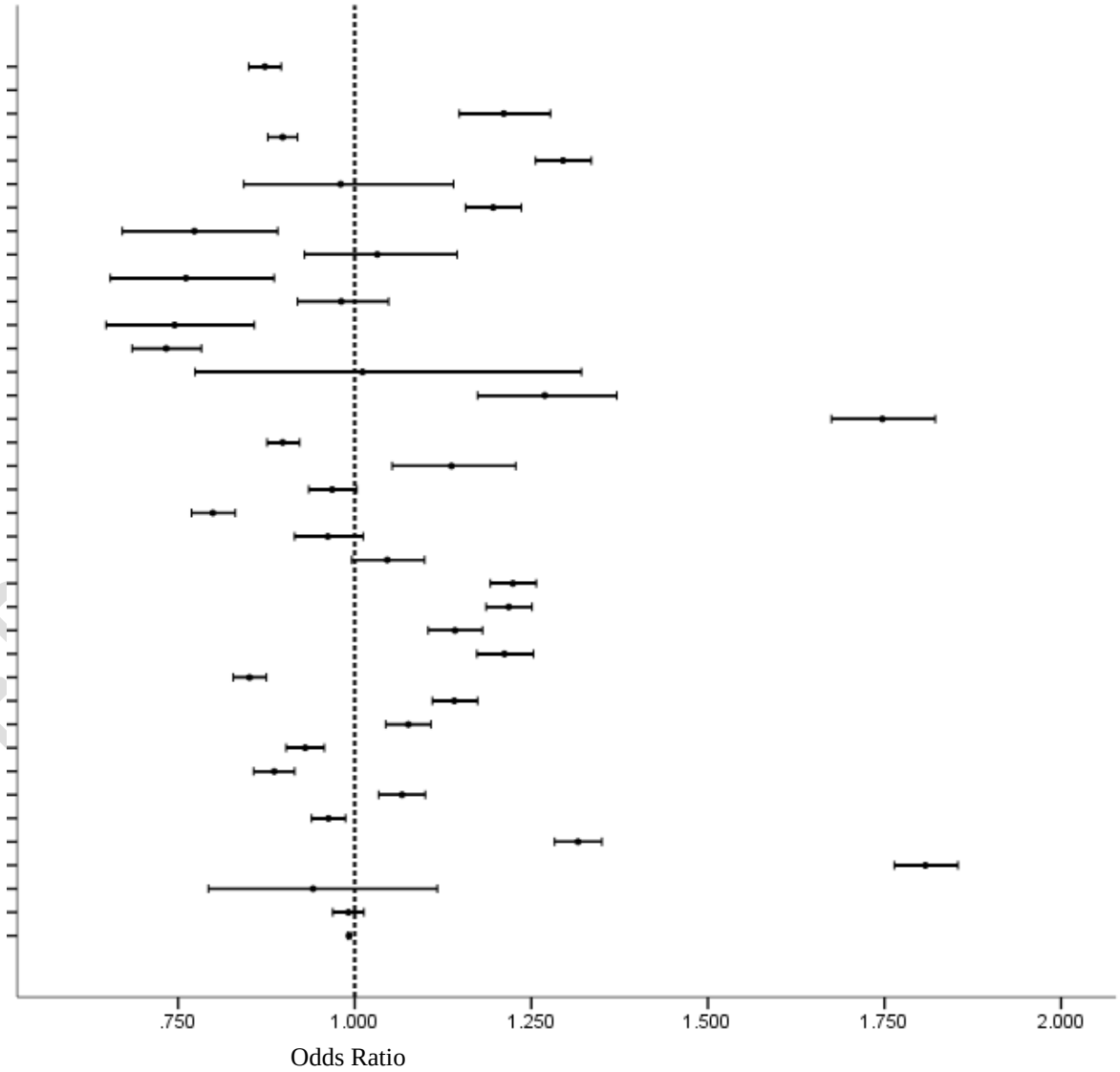
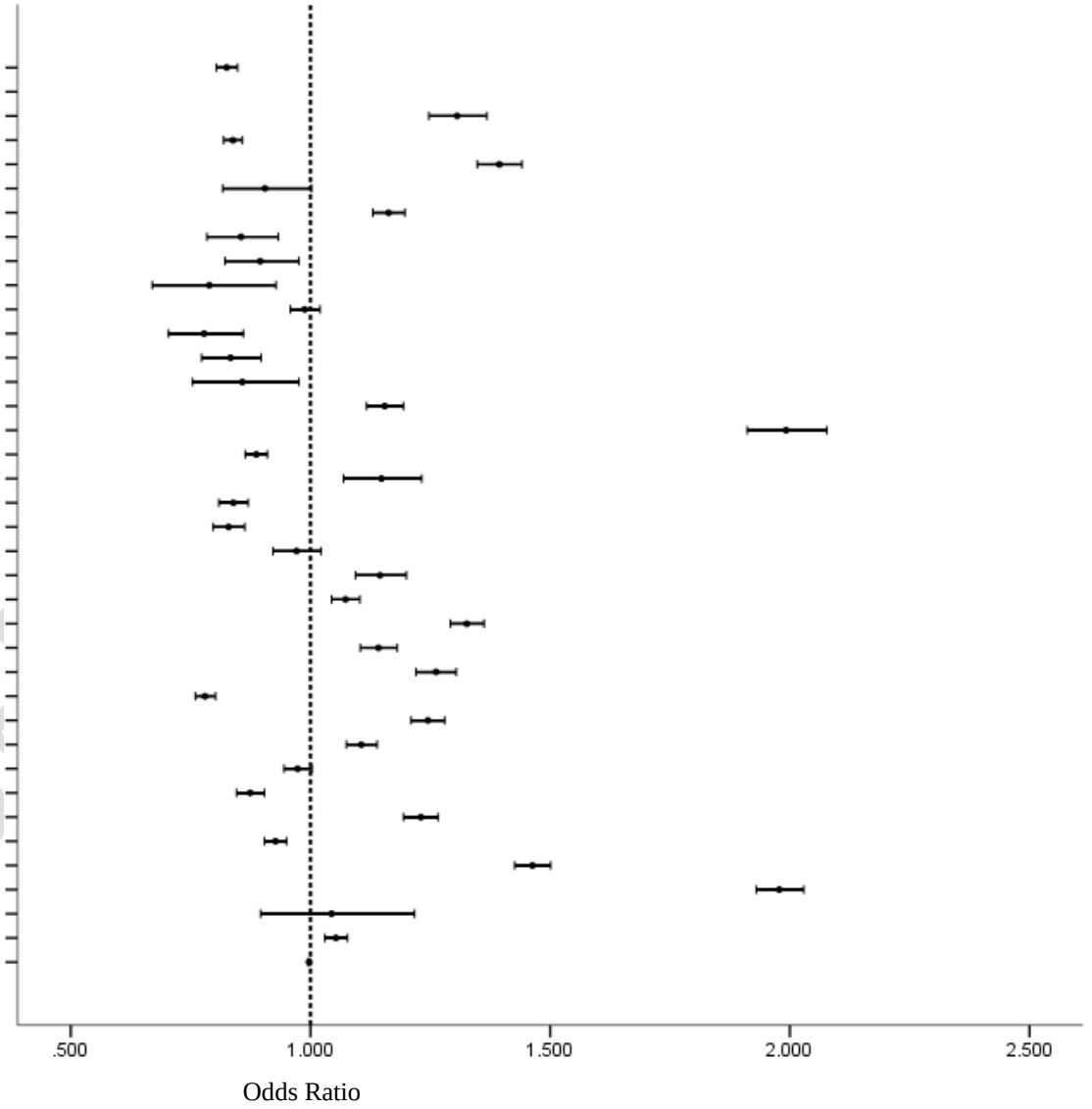


Figure 4. Regression model to predict SARS-CoV-2 infection in adult population from 40 to 59 years old. Signs, symptoms and factors associated.

OR; 95% CI	Variables
0.825; 0.804-0.848*	Vaccinated
1	Reference
1.306; 1.247-1.368*	It is unknown
0.838; 0.819-0.858*	Contact with someone with viral infection
1.394; 1.348-1.441*	Smoking
0.905; 0.817-1.002	Chronic kidney disease
1.163; 1.13-1.197*	Obesity
0.855; 0.784-0.933*	Heart disease
0.895; 0.822-0.976*	Other condition
0.789; 0.67-0.928*	HIV-AIDS
0.988; 0.958-1.02	Hypertension
0.778; 0.704-0.86*	Immunosuppressive
0.833; 0.773-0.897*	Asthma
0.858; 0.754-0.976*	Chronic obstructive pulmonary disease
1.155; 1.117-1.194*	Diabetes
1.992; 1.911-2.077*	At least one symptom
0.887; 0.864-0.91*	Sudden onset symptoms
1.148; 1.069-1.232*	Cyanosis
0.839; 0.809-0.87*	Conjunctivitis
0.829; 0.797-0.863*	Abdominal pain
0.971; 0.922-1.022	Vomiting
1.145; 1.094-1.2*	Polypnea
1.073; 1.044-1.103*	Rhinorrhoea
1.326; 1.292-1.362*	Malaise
1.142; 1.104-1.181*	Arthralgia
1.262; 1.22-1.304*	Myalgia
0.78; 0.76-0.802*	Headache
1.245; 1.21-1.28*	Chills
1.106; 1.075-1.139*	Chest pain
0.973; 0.945-1.003	Diarrhea
0.874; 0.846-0.904*	Irritability
1.23; 1.194-1.266*	Dyspnoea
0.927; 0.904-0.95*	Odynophagia
1.463; 1.426-1.501*	Cough
1.978; 1.93-2.029*	Fever
1.044; 0.896-1.217	Indigenous
1.053; 1.03-1.077*	Sex
0.997; 0.995-0.999*	Age

*p Value <0.05

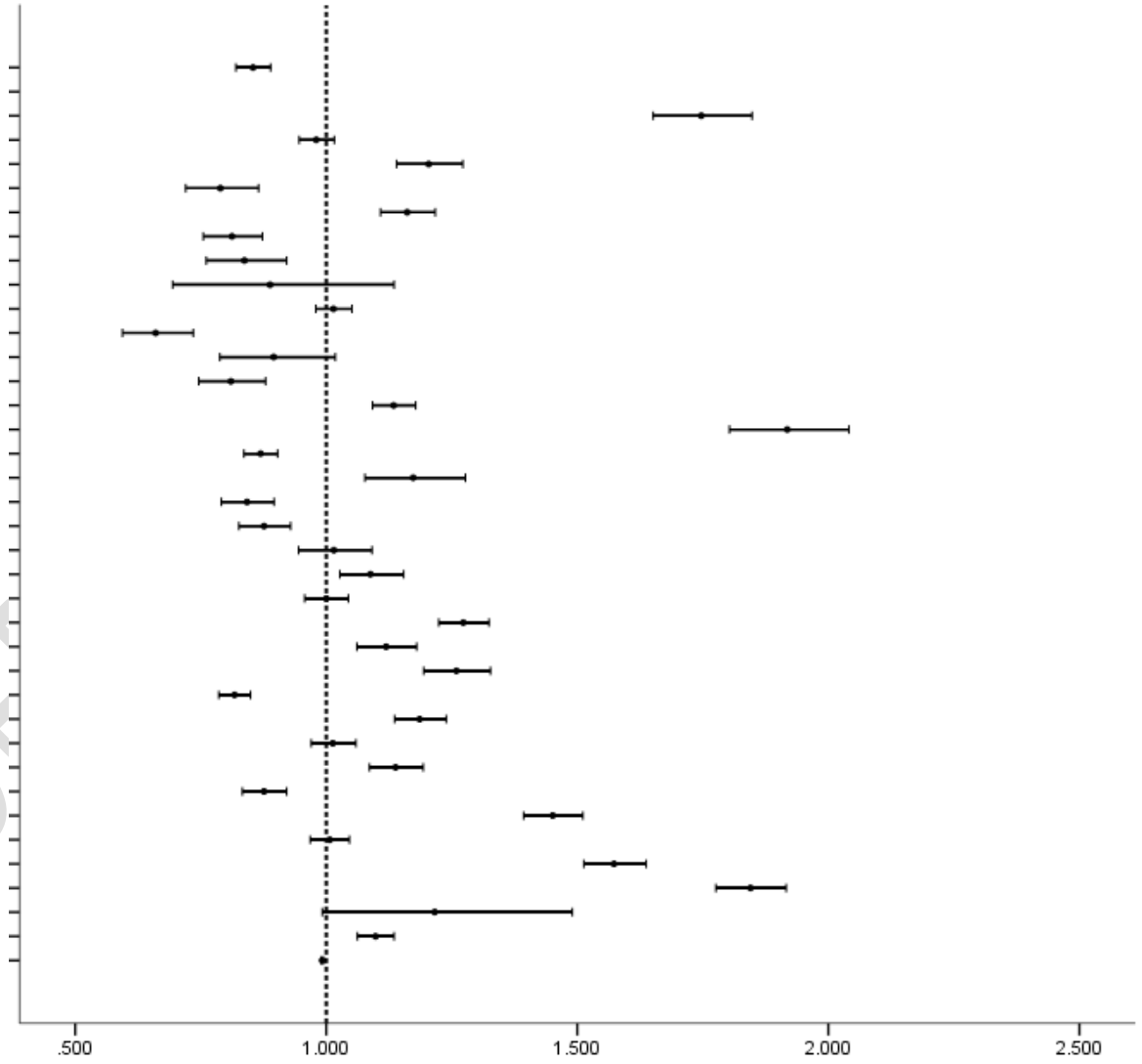


On the other hand, in older adults (60 or more y) smoking, obesity, diabetes, cyanosis, polypnea, malaise, arthralgia, myalgia, chills, diarrhea, dyspnoea, cough, fever, and gender (females) predict most strongly SARS-CoV-2 infection. Likewise, the personal history of vaccination is associated with protection to SARS-CoV-2 infection (figure 5). According to multivariate analysis the most relevance triad of symptoms for children between 0 to 9 years old are fever, headache, and diarrhea, or fever, headache, and rhinorrhoea.

Figure 5. Regression model to predict SARS-CoV-2 infection in older adult population (60 or more years old). Signs, symptoms and factors associated.

OR; 95% CI	Variables
0.854; 0.82-0.889*	Vaccinated
1	Reference
1.747; 1.651-1.848*	It is unknown
0.98; 0.946-1.016	Contact with someone with viral infection
1.204; 1.14-1.272*	*Smoking*
0.789; 0.72-0.865*	*Chronic kidney disease*
1.161; 1.108-1.217*	*Obesity*
0.812; 0.755-0.873*	*Heart disease*
0.837; 0.761-0.921*	*Other condition*
0.888; 0.694-1.135	*HIV-AIDS*
1.014; 0.979-1.051	*Hypertension*
0.66; 0.594-0.735*	*Immunosuppressive*
0.895; 0.788-1.018	*Asthma*
0.81; 0.746-0.879*	*Chronic obstructive pulmonary disease*
1.134; 1.092-1.178*	*Diabetes*
1.918; 1.803-2.041*	*At least one symptom*
0.869; 0.836-0.903*	*Sudden onset symptoms*
1.173; 1.077-1.277*	*Cyanosis*
0.842; 0.791-0.896*	*Conjunctivitis*
0.876; 0.826-0.929*	*Abdominal pain*
1.015; 0.945-1.091	*Vomiting*
1.088; 1.027-1.154*	*Polypnea*
1; 0.957-1.044	*Rhinorrhoea*
1.273; 1.224-1.324*	*Attack on the general state*
1.119; 1.061-1.18*	*Arthralgia*
1.259; 1.194-1.327*	*Myalgia*
0.817; 0.786-0.849*	*Headache*
1.186; 1.136-1.239*	*Chills*
1.013; 0.97-1.059	*Chest pain*
1.138; 1.086-1.193*	*Diarrhea*
0.876; 0.833-0.921*	*Irritability*
1.451; 1.393-1.511*	*Dyspnoea*
1.007; 0.968-1.046	*Odynophagia*
1.573; 1.513-1.637*	*Cough*
1.845; 1.776-1.916*	*Fever*
1.216; 0.992-1.49	Indigenous
1.098; 1.062-1.135*	Sex
0.992; 0.99-0.994*	Age

*p Value <0.05



Discussion

The spread of COVID-19 disease is multifactorial, and decreased through a set of measures that include personal hygiene (as frequently clean your hands with soap and water, or use an alcohol-based hand rub), keeping a safe distance between people, avoiding overcrowding, stay in environments with adequate ventilation (where aerosol formation is avoided) and where people are not in close contact (more than 1 meter apart), preventing contact with polluted surfaces (due to people may become infected by touching these polluted surfaces, then touching their eyes, nose or mouth without having cleaned their hands first), cleaning surfaces regularly with standard disinfectants, and using a mask when going out.

On other hand, this investigation describes the symptoms and their associations with positive SARS-CoV-2 assays among a sample of 393 280 people tested between January 1st and November 10th, 2020. According to results obtained the strongest independent predictors for infection of SARS-CoV-2 (SARS-CoV-2 positive assays) in Mexican population are different by age group. In people between 0 to 9 years the strongest predictors were: fever, and headache. While in young people (10 to 19 y) these predictors were: rhinorrhoea, myalgia, odynophagia, cough, and fever. In contrast, in adults from 20 years old and more the predictors were: cyanosis, malaise, arthralgia, myalgia, chills, dyspnoea, cough, and fever. However, in adults aged 20- and 59-years old rhinorrhoea, and chest pain were also independent predictors. But in people from 40 years old or more polypnea, and gender (female) were predictors for SARS-Cov-2 infection too. Although, diarrhea was an independent predictor only in older adults. Regarding age it was useful to compare results, which were similar with reported average ages (42–43 years-old) by other

authors.[26, 34, 48] Several studies support varying clinical manifestations among COVID-19 patients and their different proportion.[12-14, 34] Similarly to others large studies in the United States population, the three most common reported manifestations in adult's population in the current study were cough, fever, and myalgia, but with different proportions, and accompanied by other symptoms. Other authors in different scenarios reported fever (temperature ≥ 38°C), cough and/or shortness of breath, accompanied by tachypnoea, [34, 49] or fever with non-specific symptoms, such as cough and sore throat, or the presence of anosmia, and ageusia.[13, 34] Regarding to fever and myalgia findings in adult population, they are according to results reported by other investigations, which reported that both symptoms are predictors for SARS-CoV-2 infection or COVID-19 disease.[34] Moreover, anosmia/ageusia also were strong independent predictors for SARS-CoV-2 infection (positive assays), however, in the present study for the presence of anosmia and ageusia the model cannot be tested. [34, 50]

Unlike the findings found in the present study, Menni et al reported that loss of smell and taste, fever, and persistent cough are potential predictors of COVID-19.[33] In addition, they also identify a combination of symptoms, including anosmia, fatigue, persistent cough and loss of appetite, that together might identify individuals with COVID-19.[33] Even they suggest that a detailed and broader study on the natural history of COVID-19 symptoms, especially according to timing and frequency, will help us to understand the usefulness of symptom tracking and modelling, and to identify probable clusters of infection.[33] However, in the United States population the absence of symptoms or symptoms limited to nasal congestion, and sore throat were associated with negative assays to SARS-CoV-2 infection, while, in our adult population from 20 to 59 years old rhinorrhoea was a predictor

symptom. [34] Similarly to the results reported by Lan et al (nasal symptoms: runny, sneezing, congestion, sinus: OR= 0.51; CI 95% 0.31-0.82)[34] there are several signs and symptoms that are significantly associated with having negative SARS-CoV-2 assays, demonstrating that there are non-specific signs and symptoms to predict COVID-19 disease and that the presence of these clinical presentation associated with lower probability of clinical COVID-19 diagnosis. The signs and symptoms were vomit and irritability in population between 0 to 9 years old. Vomit, abdominal pain, and diarrhea in population from 10 to 19 years old. Irritability, abdominal pain, diarrhea, headache, and odynophagia in adult population from 20 to 39 years old. Irritability, abdominal pain, headache, odynophagia, and conjunctivitis in adult population from 40 to 59 years old. Finally, irritability, abdominal pain, headache, and conjunctivitis in older adult population (60 or more years old).

Also, there are comorbidities that significantly associated with SARS-CoV-2 infection. Similarly, to the results reported by Giannouchos's et al both obesity (population from 10 years old) and diabetes (adult population from 20 years old) increase the risk of SARSCoV-2 infection. While, the results described by these authors smoking indicated that is associated with having negative SARS-CoV-2 assays; the results in the present study showed that smoking increases the risk of SARS-CoV-2 infection from 10 years old, probably due to the authors did not analyze the dataset by different groups of age. In the same way, there were comorbidities that significantly associated with having negative SARS-CoV-2 assays, such as chronic kidney disease (in young people 10-19 years, and older adults), heart disease (from 10 years old), HIV-AIDS (adults from 20 to 59 years old), immunosuppression (from 10 years old), asthma (adults from 20 to 59 years old) and

chronic obstructive pulmonary disease (adults from 40 years), demonstrating a low probability of a positive test of RT-PCR and COVID-19, however, the probability is different by each group of age. In most studies, several investigators observed an association between COVID-19 and hearth disease. However, the results show in the present study are not consistent with other studies. Probably, due to the cardiovascular disease continues to be the main cause of death in Mexican population before and during current pandemic.[48]

The probability of having a positive SARS-CoV-2 RT-PCR test ranged from 23.7-31.8% for people with asthma, between 24.1-30.8% for people with heart disease, between 24.2-71.5% for people with COPD, between 20.6 -34.7% for people with immunosuppression, between 25.1-34.4% for people with chronic kidney disease and between 19.2-33.3% for people with HIV-AIDS. In addition, the probability of having positive assays for SARS-CoV-2 infection increased 3.7% by each additional sign or symptom reported.

Limitations

The current study does have some limitations. First, the dataset tested were random and matched with a relation 1:1, adjusted by gender and age. Thus, the results do not necessarily reflect total cumulative incidence of COVID-19 in our national healthcare system. Second, the test performance characteristics of the RT-PCR are limited at the time of sampling after the onset of symptoms. Finally, no data about the duration and evolution of comorbidities, or pharmacotherapy or permission for biopsy for dead patients of SARS-CoV-2 were available (lack of follow-up); that enables to evaluate their effect on the regression models.

The findings have potential implications for COVID-19 surveillance. First, subjects without symptoms or with symptoms limited to vomit, irritability, abdominal pain, diarrhea, headache, odynophagia, and conjunctivitis (which are non-specific symptoms) accompanied with the antecedent of sudden onset show a low probability to have a positive assay for SARS-CoV-2 infection, and therefore, it will be difficult to establish the diagnosis of COVID-19 disease (for each specific group of age). Vomiting is a non-specific symptom in teenagers and people with less than 9 years old. Irritability is unspecific for people between 0 to 9 years, and adults from 20 or more age. Abdominal pain is an unspecific symptom for people from 10 years old. Diarrhea is a non-specific symptom for teenagers and young adults (from 10 to 39 years). Headache is unspecific for adults from 20 years old. Odynophagia is an unspecific symptom for adults from 20 to 59 years old. Finally, conjunctivitis is a non-specific symptom in adult's population from 40 age or more. Thus, many subjects with symptoms more compatible with gastrointestinal disease, allergy or common cold may not be diagnosed with COVID-19 disease. In contrast, fever is the only predictive of possible clinical COVID-19 in all population. This result supports expert guidelines for temperature monitoring.[34]

However, the current study also has several strengths. First, the triage and testing process were conducted according to expert guidelines. Second, the adjustments to sample decreases the possible selection bias, and therefore, the results can inform other healthcare systems employing comparable protocols. Third, people generally reported their symptoms at triage before their SARS-CoV-2 PCR test results were available, eliminating recall bias. Fourth, all symptoms' reports were collected by physicians, strengthening their accuracy.

Fifth, all selected records of dataset had complete symptoms and testing data. Sixth, the dataset included all groups of age, people with different occupations, ethnic origin and place of residence. Therefore, results may be generalized to other similar populations. In addition, a collinearity diagnosis for all variables was performed. No collinearity or multicollinearity was observed. In conclusion, the clinical presentation associated with SARS-CoV-2 infection was different in each group of age. The present study showed evidence in population between 0-9 years old the strongest signs and symptoms associated with SARS-CoV-2 infection were: fever, and headache. Moreover, the clinical presentation associated with SARSCoV-2 infection in adolescents was: rhinorrhoea, myalgia, odynophagia, cough, and fever. While, in adults from 20 to 59 years old the signs and symptoms associated included: cyanosis, rhinorrhoea, malaise, arthralgia, myalgia, chills, chest pain, dyspnoea, cough, and fever (but only in adults from 40 to 59 years, polypnea was associated with SARS-CoV-2 infection). Finally, in older adults the clinical presentation associated were: cyanosis, polypnea, malaise, arthralgia, myalgia, chills, diarrhea, dyspnoea, cough, and fever. Subjects with symptoms more compatible with gastrointestinal disease, allergy or common cold may not be diagnosed with COVID-19 disease. Smoking, obesity and diabetes are the strongest associated factors to predict SARS-CoV-2 infection.

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