Clinical Signs and Symptoms Associated with COVID-19: A Cross Sectional Study

Norma Samanta Romero Castro¹; Israel Colin Hernández²; Maria Estela Godoy Reyes³; Margarita Hernández Hernández⁴; Alicia García Verónica⁵; Sergio Paredes-Solís⁵ & Salvador Reyes Fernández¹,⁶

ABSTRACT: Covid-19 is a viral disease that has spread throughout the world, becoming a pandemic. Dysgeusia and anosmia are some of its most frequent symptoms. The aim of the study was to determine the frequent signs and symptoms associated with COVID-19 patients. A cross-sectional study from 370 patients with acute respiratory illness admitted by emergency services of a hospital in Acapulco. An institutional survey was applied to all patients as a data collection instrument, and a SARS-CoV-2 test, by RT-PCR processed by a certified laboratory. Statistical analysis was performed using the STATA V13 program. The numerical variables without normality were reported in medians, 25th and 75th percentiles, and the Mann Withney U test was performed for differences between groups. The categorical variables were presented in percentages and differences between groups with Chi-square test. A generalized linear models (GLM) analysis was carried out to determine the most frequent symptoms and signs associated with COVID-19. Clinical signs and symptoms associated to COVID-19 in the bivariate analysis were dysgeusia, odynophagia, anosmia, arthralgia, myalgia, conjunctivitis, and age older than 40 years. In the final multivariate model only age older than 40 years (OR) 2.2; CI 95 % 1.3,3.8) and dysgeusia (OR 2.1; CI95 % 1.2,3.6) kept significance. Dysgeusia, odynophagia, anosmia, arthralgia, myalgia and conjunctivitis are clinical signs and symptoms that can appear in the early stages of the disease, so they could be important for an early diagnosis.

KEY WORDS: COVID-19. dysgeusia. odynophagia. anosmia. arthralgia. myalgia.

INTRODUCTION

The pandemic that is currently being faced throughout the world has its origin in the Chinese city of Wuhan in the Hubei province. At the end of December 2019 (Meng et al., 2020), a group of people who had in common being workers or frequent consumers of a market in this city where wild animal meat is sold (Odeh et al., 2020), including bats, developed acute respiratory syndrome (Gaitán Cepeda et al., 2020). These patients were diagnosed with atypical pneumonia of possible viral origin. Subsequently, a type of coronavirus was isolated from the material obtained from bronchial washes of these patients (Gaitán Cepeda et al.). Authors suggest that it is a zoonosis and that this coronavirus comes from the bat (Sabino-Silva et al., 2020). In January 2020, the World Health Organization (WHO) determined that it was a global public health emergency (Meng et al.,) and in March of this year declared it a true pandemic (Saddik et al., 2020). At the end of February 2020, it was officially announced by the Chinese Center for Disease Control and Prevention that the causative agent of this emerging...
disease called COVID-19 was a new coronavirus called SARS-CoV-2 for its acronym in English (Severe acute respiratory syndrome coronavirus-2) and in the same month it had already expanded to 34 countries, reaching more than 80,000 laboratory-confirmed cases and more than 2,500 deaths (Meng et al.).

Human coronaviruses (HCoV) were for a long time considered harmless pathogens that cause the common cold, however in 2003 (Smales & Samaranyake, 2003; Saddik et al.) and 2012 (Kharma et al., 2015), two variants of coronavirus emerged that caused major epidemics. The severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) respectively (Saddik et al.).

Recent research concludes that this virus is zoonotic from some species of bat, and that the transmission initially took place from animal to human, to later be transmitted from human to human by drops of saliva and direct contact. The virus is currently known to be present in the feces, urine, and saliva of infected people (Smales & Samaranyake; Meng et al.). Its incubation period ranges from 5 to 6 days and it can last up to 14 days (Meng et al.).

Fortunately, most people who become infected with this virus are asymptomatic or develop mild signs or symptoms such as fever, dry cough, fatigue, muscle pain, diarrhea, and vomiting. Still others develop acute respiratory failure, arrhythmias, and shock, for which they must be transferred to an intensive care unit. These serious and sometimes fatal conditions tend to occur in older people or those with pre-existing systemic diseases such as diabetes mellitus, high blood pressure and other cardiovascular diseases, which worsens the prognosis (Meng et al.).

The diagnosis is based on four aspects: The history of contact with potentially infected people, signs and symptoms, imaging studies, and laboratory tests.

The main way to control the spread of COVID-19 is to prevent person-to-person transmission, which can be achieved through a combination of public health measures, including the rapid identification and isolation of infected people (Pissurno et al., 2020).

Hand hygiene remains the most appropriate measure to reduce the risk of transmission. SARS-CoV-2 can remain active on surfaces from a few hours to several days, depending on the type of surface, temperature or humidity of the environment.

The recommended measures for dental clinical practice are aimed at different infection control methods such as physical barriers, area management and general asepsis, antisepsis and sterilization measures (Meng et al.).

Angiotensin-converting enzyme 2 (ACE2) has been reported to be the major host cell receptor for 2019-nCoV and plays a crucial role in virus entry into the cell to cause eventual infection. Recent work has shown that ACE2 is expressed in the oral mucosa, especially in the mucus of the tongue, so the oral cavity may be a high-risk site for infectious susceptibility to COVID-19 (Dos Santos et al., 2020). The genome of the COVID-19 virus has been detected in saliva in most patients with this disease, indicating possible infection of the salivary glands (To et al., 2020).

Because Covid-19 is an emerging disease, there are not many publications of an association of oral lesions to the disease. One of those publications is the one that reported the case of a 45-year-old female who presented an irregular ulceration in the oral mucosal, however, the authors concluded that it is only a possible incidental finding (Chaux-Bodard et al., 2020). Another article reports three cases of oral mucosal ulcerations and blisters in one positive and two COVID-19 suspects but they suppose that many intraoral findings can often go unnoticed due to the lack of an intraoral examination during hospital admission (Sinadinos & Shelswell, 2020). Other researchers have published isolated cases of lesions of the oral mucosa in patients with the disease (Dos Santos et al.). Olfactory and gustatory disorders have also been reported as prevalent symptoms in COVID-19 (Barón-Sánchez et al., 2020; Abalo-Lojo et al., 2020; Levinson et al., 2020; Russell et al., 2020).

The objective of this research was to determine the frequent signs and symptoms associated with COVID-19 positive patients.

MATERIAL AND METHOD

We carried out a cross-sectional study from 370 patients with acute respiratory illness admitted by emergency services of a hospital in Acapulco, Mexico, from April 13th to August 29th, 2020. All patients had a SARS-CoV-2 test, by real-time polymerase chain reaction processed by a certified laboratory, 227 tested positive, 135 negative and 8 cases had unsuitable
samples, leaving 362 useful observations. From patients
clinical files we collected clinical signs and symptoms
related to acute respiratory illness. Clinical signs and
symptoms included in analysis were age, fever,
headache, dry cough, fatigue, dysgeusia, odynophagia,
anosmia, rhinorrhea, conjunctivitis, polypnea, dyspnea,
perioral cyanosis, chest pain, arthralgia, myalgia, gene-
ral discomfort, diarrhea, and abdominal pain.

The statistical analysis of the data was carried
out in the STATA V13 program, simple frequencies of
the data are presented, the numerical variable age when
not having normality was reported in medians, 25th and
75th percentiles and the Mann Withney U test was
applied for difference between groups. The categorical
variables were presented in percentages and the
differences between groups with the Chi-square test. An
generalized linear models (GLM) analysis was carried
out to determine the most frequent symptoms and signs
associated with COVID-19.

RESULTS

Patients average age was 45 years old (range
33-61); 226 (62 %) were male and 136(38 %) female,
the sociodemographic variables are shown in Table I.

Table I. Sociodemographic characteristics of the study population.

| Characteristic                | Population | COVID-19 positive | COVID-19 negative | p value |
|------------------------------|------------|-------------------|-------------------|---------|
| Age, years                  | 45 (33-61) | 46 (34-62)        | 41 (31-58)        | 0.01    |
| Sex                         |            |                   |                   |         |
| Female                      | 136 (38)   | 85 (37)           | 52 (38)           | 0.95    |
| Male                        | 226 (62)   | 142 (63)          | 84 (62)           |         |
| Total n (%)                 | 362 (100)  | 227 (100)         | 135 (100)         |         |
| Occupation                  |            |                   |                   |         |
| Employees from other areas  | 193 (53)   | 114 (50)          | 79 (58)           |         |
| Health area employees       | 57 (16)    | 41 (18)           | 16 (12)           |         |
| Merchant                    | 12 (3)     | 9 (4)             | 3 (2)             |         |
| Home                        | 70 (19)    | 45 (20)           | 25 (19)           | 0.12    |
| Retired                     | 20 (6)     | 15 (6.5)          | 5 (4)             |         |
| Unemployed                  | 3 (1)      | 1 (0.5)           | 2 (1)             |         |
| Students                    | 7 (2)      | 2 (1)             | 5 (4)             |         |
| Total n (%)                 | 362 (100)  | 227 (100)         | 135 (100)         |         |

*Median is shown (p25-p75), p value calculated by Mann Whitney statistical test; *n(%) are shown for
categorical variables, p value calculated by Chi-Square statistical test.
Table II. Frequent clinical signs and symptoms of the study population (n(%)) are shown for categorical variables; p value calculated by Chi Square statistical test.

| Characteristic | Population n = 362 (100%) | COVID-19 positive n = 227 (63%) | COVID-19 negative n = 135 (37%) | p value |
|----------------|---------------------------|---------------------------------|---------------------------------|---------|
| Fever          |                           |                                 |                                 | 0.35    |
| Yes            | 325 (90)                  | 201 (89)                        | 124 (92)                        |         |
| No             | 37 (10)                   | 26 (11)                         | 11 (8)                          |         |
| Total          | 362 (100)                 | 227 (100)                       | 135 (100)                       |         |
| Cough          |                           |                                 |                                 | 0.38    |
| Yes            | 318 (88)                  | 202 (89)                        | 116 (86)                        |         |
| No             | 44 (12)                   | 25 (11)                         | 19 (14)                         |         |
| Total          | 362 (100)                 | 227 (100)                       | 135 (100)                       |         |
| Headache       |                           |                                 |                                 | 0.91    |
| Yes            | 304 (84)                  | 191 (84)                        | 113 (84)                        |         |
| No             | 58 (16)                   | 36 (16)                         | 22 (16)                         |         |
| Total          | 362 (100)                 | 227 (100)                       | 135 (100)                       |         |
| General        |                           |                                 |                                 | 0.32    |
| Yes            | 255 (70)                  | 165 (73)                        | 90 (67)                         |         |
| No             | 106 (29)                  | 61 (26)                         | 45 (33)                         |         |
| Total          | 361 (99)                  | 226 (100)                       | 135 (100)                       |         |

Table III. Study population systemic condition.

| Characteristic | Population n = 362 (100%) | COVID-19 positive n = 227 (63%) | COVID-19 negative n = 135 (37%) | p value |
|----------------|---------------------------|---------------------------------|---------------------------------|---------|
| Hypertension   |                           |                                 |                                 | 0.69    |
| Yes            | 65 (18)                   | 42 (20)                         | 23 (17)                         |         |
| No             | 296 (82)                  | 184 (80)                        | 112 (83)                        |         |
| Total          | 361 (100)                 | 226 (100)                       | 135 (100)                       |         |
| Obesity        |                           |                                 |                                 | 0.79    |
| Yes            | 33 (9)                    | 20 (9)                          | 13 (10)                         |         |
| No             | 329 (91)                  | 207 (91)                        | 122 (90)                        |         |
| Total          | 362 (100)                 | 227 (100)                       | 135 (100)                       |         |
| Diabetes       |                           |                                 |                                 | 0.00    |
| Yes            | 68 (19)                   | 52 (23)                         | 16 (12)                         |         |
| No             | 294 (81)                  | 175 (77)                        | 119 (88)                        |         |
| Total          | 362 (100)                 | 227 (100)                       | 135 (100)                       |         |
| Smoking        |                           |                                 |                                 | 0.18    |
| Yes            | 3 (1)                     | 3 (1)                           | 0 (0)                           |         |
| No             | 359 (99)                  | 224 (99)                        | 135 (100)                       |         |
| Total          | 362 (100)                 | 227 (100)                       | 135 (100)                       |         |

n(%) are shown for categorical variables; P value calculated by Chi Square statistical test.

52 COVID-19 positive patients with diabetes mellitus, 15.4 % (8) died during their hospital stay.

Table IV shows the results of the analysis of bivariate generalized linear models (GLM) of clinical signs and symptoms associated to COVID-19. In the final multivariate model only age older than 40 years (OR 2.2; CI95 % 1.2,3.6) and dysgeusia (OR 2.1; CI95 % 1.3,3.8) kept statistical significance.

Table IV. Clinical signs and symptoms associated to COVID-19

| Characteristic | OR     | 95%CI   | p value |
|----------------|--------|---------|---------|
| Age older than 40 years | 1.6    | 1.1,2.5 | 0.03    |
| Arthralgia      | 2.4    | 1.6,3.7 | 0.00    |
| Conjunctivitis  | 1.9    | 1.1,3.6 | 0.03    |
| Myalgia         | 1.9    | 1.3,3.1 | 0.00    |
| Odynophagia     | 1.6    | 1.1,2.4 | 0.04    |
| Anosmia         | 1.9    | 1.1,3.4 | 0.01    |
| Dysgeusia       | 2.2    | 1.2,3.8 | 0.00    |

Generalized linear models bivariate analysis (GLM); OR = odds ratio.
This cross-sectional study carried out in patients with COVID-19 at a hospital in Acapulco, México, shows important results regarding the most frequent signs and symptoms that were found in the institutional admission COVID-19 format, such as dysgeusia, odynophagia, anosmia, arthralgia, myalgia, conjunctivitis, age older than 40 years and comorbidity with diabetes mellitus. Two of the symptoms that showed significant differences between positive for COVID-19 and those negative were dysgeusia and anosmia (Table V). Of the patients who tested positive for COVID-19, 46% had dysgeusia, 44% had anosmia, and 40% had both. This agrees with Abalo-Lojo et al. who reported high percentages of these signs. Of their total sample, 58.8% had anosmia, and 56.5% had dysgeusia. Other authors such as Lozada-Nur et al. in a sample of 42 patients with COVID-19 reported 35.7% anosmia and 33.3% dysgeusia.

However, there are reports of much higher percentages of presentation of these disorders in COVID-19 patients such as that of Ormianer, who reported that 67% of their patients had olfactory disorders and 52% taste alteration (Biadsee et al., 2020).

Other authors report different percentages of anosmia in their COVID-19 patients, such as Klopfenstein et al. (2020) who found 47% of this disorder.

Salmon et al. (2020) reported in their study of 55 patients, that 92% of all patients with olfactory alterations were positive for SARS-CoV-2.

Although the cause of these taste and olfactory alterations is not clear, it is thought that the virus damages the taste and olfactory cells by binding to the angiotensin-converting enzyme 2 receptor, which is expressed both in the mucosa of the tongue and in the olfactory mucosa (Abalo-Lojo et al.; Lozada-Nur et al., 2020).

Patients often find it difficult to distinguish between smell and taste disturbances. Therefore, in patients who refer to these alterations in a combined way in COVID-19, there is the possibility of an underlying olfactory alteration being the primary etiology. The perceived taste disturbance could be secondary to anosmia, rather than any actual disturbance with the taste system. We must pay attention to the cases of

### Table V. Signs and symptoms with significant differences between groups.

| Characteristic | Population | COVID-19 positive | COVID-19 negative | p value |
|---------------|------------|-------------------|-------------------|---------|
|               | n = 362   | n = 227           | n = 135           |         |
|               | (100%)    | (63%)             | (37%)             |         |
| Arthralgia    |           |                   |                   | 0.00    |
| Yes           | 205 (57)  | 147 (65)          | 58 (43)           |         |
| No            | 156 (43)  | 80 (35)           | 76 (57)           |         |
| Total         | 361 (100) | 227 (100)         | 134 (100)         |         |
| Myalgia       |           |                   |                   | 0.00    |
| Yes           | 237 (65)  | 162 (71)          | 75 (56)           |         |
| No            | 125 (35)  | 65 (29)           | 60 (44)           |         |
| Total         | 362 (100) | 227 (100)         | 135 (100)         |         |
| Odynophagia   |           |                   |                   | 0.04    |
| Yes           | 225 (62)  | 150 (66)          | 75 (56)           |         |
| No            | 137 (38)  | 77 (34)           | 60 (44)           |         |
| Total         | 362 (100) | 227 (100)         | 135 (100)         |         |
| Anosmia       |           |                   |                   | 0.01    |
| Yes           | 89 (38)   | 62 (44)           | 27 (28)           |         |
| No            | 148 (62)  | 80 (56)           | 68 (72)           |         |
| Total         | 237 (100) | 142 (100)         | 95 (100)          |         |
| Dysgeusia     |           |                   |                   | 0.00    |
| Yes           | 93 (39)   | 66 (46)           | 27 (28)           |         |
| No            | 145 (61)  | 77 (54)           | 68 (72)           |         |
| Total         | 238 (100) | 143 (100)         | 95 (100)          |         |

n (%) are shown for categorical variables; P value calculated by Chi Square statistical test.
patients who reported having taste alterations without alterations in smell. This could be the first report of any oral manifestation associated with COVID-19 (Vinayachandran & Balasubramanian, 2021).

Our results lead us to affirm, like Abalo-Lojo et al., that these two symptoms are essential for the early diagnosis of COVID-19 because they usually appear in the first days of the disease.

In this regard, Levinson et al. reported that both symptoms began approximately on the third day after the onset of the disease, and that most of these patients recovered both senses about a week after being detected. Another relevant data reported by Ormianer is that within their studied patients, 38.3 % presented smell alterations and 38.2 % presented taste alterations as initial symptoms (Biadsee et al.).

With the data obtained in this research on taste and smell alterations, we intend to contribute to the evidence that Russell et al. consider necessary to affirm this association.

Our patients presented other signs and symptoms similar to those reported by most authors, such as fever, cough, headache and general attack, chest pain, rhinorrhea, polypnea, dyspnea, perioral cyanosis, and some gastrointestinal symptoms such as diarrhea, pain abdominal pain and vomiting (Meng et al.; Abalo-Lojo et al.; Biadsee et al.; Klopfenstein et al.). However, none of the aforementioned signs or symptoms showed significant differences between the groups that were positive and negative for COVID-19.

Other symptoms frequently associated with COVID-19, such as odynophagia, arthralgia and myalgia, also showed significant differences between the groups that were positive and negative for COVID-19. In our studies we found 66 % percentage of odynophagia, against 30 % of Abalo-Lojo et al., 43 % of Klopfenstein et al. and 26 % of Ormianer (Biadsee et al.).

Regarding arthralgia, we found 75 %, against 72 % reported by Klopfestein et al., and Myalgias with 71 % in our study, against 74 %, 46.6 % and 47 % reported by Klopfestein et al., Abalo-Lojo et al. and Ormianer respectively (Biadsee et al.).

Within the systemic conditions presented by the patients, only diabetes mellitus showed significant differences between the groups, with a greater number of diabetics in proportion among the positive than among the negative cases, being 23 % of the total COVID-19 positive patients diabetics. These data coincide with the global consensus regarding the association between COVID-19 and diabetes mellitus (Rubino et al., 2020). This association is bidirectional as stated by Rubino et al., who afirm that diabetes increased risk of getting COVID-19, and that COVID-19 can lead to new-onset diabetes and/or serious metabolic complications of pre-existing diabetes. In our study 8 patients (15.4 %) of the total diabetic and COVID-19 positive patients (52 patients) died during their hospital stay.

The sample size was determined by the number of patients who came to the study hospital for consultation with respiratory disorders, until the moment when the cases of covid-19 decreased significantly in this hospital and throughout Mexico. We waited until then, in order to achieve the largest possible sample size. It is evident that this study can be expanded and reconsidered with a much larger sample depending on the new cases from the cut-off.

We consider that our sample size is a strength of this study since it is very competitive compared to other similar studies. Some of its limitations are that a large amount of missing or non-obtained data is presented. Another aspect that we did not consider in this research, and that it would be important to incorporate in future studies, is the time of installation of the symptoms, as well as their duration.

There is no consensus on whether the oral manifestations of isolated cases or small series of recently published COVID-19 patients are incidental findings, or if they are associated in a secondary way with other symptoms such as fever, and the weakening suffered by these patients, or as a direct consequence of virus infection on the oral mucosa (Dos Santos et al.; Chaux-Bodard et al.; Sinadinos & Shelswell; Carreras-Presas et al., 2021). We agree with various researchers such as Martín Carreras-Presas et al. who affirm regarding the possibility that intraoral injuries could be going unnoticed due to the lack of detailed intraoral examinations, because when patients are hospitalized by COVID-19, care is focused to the serious aspects of the disease (Carreras-Presas et al.).

CONCLUSIONS

Arthralgia, dysgeusia, anosmia, myalgia, conjunctivitis and age older than 40 years are clinical
signs and symptoms associated with COVID-19. These signs could appear in the early stages of the disease so they could be important data for obtaining an early diagnosis.

In the final multivariate model only age older than 40 years and dysgeusia kept statistical significance. Most likely, if the sample had been larger, all the signs and symptoms of the bivariate analysis would have remained associated.

ETHICS APPROVAL

This research was approved by the hospital committee for bioethics and biosafety (constitutive act number 02/20-extraordinary sesi—on of June 23th, 2020) of the study hospital. The present study did not put the integrity and life of the patients at risk, since the procedures had diagnostic purposes for admission to the hospital (survey), the doctors in charge of the survey put on the protective equipment used by the study hospital for patients at risk of COVID-19.

PALABRAS CLAVE: COVID-19, disgeusia, odinofagia, anosmia, artralgia, mialgia, conjuntivitis.

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Pissurno, N. S. C. A.; de Castro Lichs, G. G.; Dos Santos, E. J. L.; Fernandes Druzan, A.; do Valle Leone de Oliveira, S. M. & Mi-
Corresponding autor:
Salvador Reyes Fernández
Av. Ruiz Cortines s-n
Col. Infonavit Alta Progreso
Acapulco
Guerrero
MÉXICO

E-mail: 10640@uaro.mx

Norma Samanta Romero Castro
Israel Colin Hernández
María Estela Godoy Reyes
Alicia García Verónica
Sergio Paredes-Solis
Salvador Reyes Fernández

orcid.org/0000-0003-3468-6437
orcid.org/0000-0001-5020-7841
orcid.org/0000-0003-3895-3176
orcid.org/0000-0002-5318-5155
orcid.org/0000-0002-3015-3038
orcid.org/0000-0002-4144-4113

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