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The role of close contacts of COVID-19 patients in the SARS-CoV-2 transmission: an emphasis on the percentage of nonevaluated positivity in Mexico

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Objectives: To determine the percentage of positivity of close contacts of coronavirus disease 19 (COVID-19) patients to depict the importance of asymptomatic infections in the patient-to-patient transmission of COVID-19.

Methods: One hundred subjects were included. Nineteen index COVID-19 cases and 81 traced close contacts were screened for coronavirus 2 of severe acute respiratory syndrome (SARS-CoV-2) using real-time reverse transcription-polymerase chain reaction. Immunoglobulin M and G against SARS-CoV-2 were evaluated by rapid test.

Results: Thirty-four (42%) contacts in the study were positive for SARS-CoV-2. Twenty-three (67.6%) manifested less than 2 respiratory symptoms, and 5 (14.7%) remained asymptomatic. The average of positive contacts by index COVID-19 case (R0) was 4.3 and the mean of time of positive COVID-19 test at sampling time was 18.9 days. Positive antibody test against SARS-CoV-2 was observed in 16% of the participants.

Conclusion: The proportion of close contacts of COVID-19 patients infected with SARS-CoV-2 (42%) and with less than 2 or with no respiratory symptoms (82.4%) was high in the study population. A low proportion of COVID-19 patients had a positive test for antibodies against SARS-CoV-2. The screening for SARS-CoV-2 in close contacts of COVID-19 positive patients should be encouraged to avoid spreading the infection and the expansion of the disease.

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INTRODUCTION

The coronavirus disease 19 (COVID-19) epidemic represents a health problem with the characteristics of contagiousness, quick transmission and general susceptibility. According with Johns Hopkins Center for Systems Science and Engineering data, to date, worldwide more than 32 million of cases have been confirmed, of which 979,701 cases died. In Mexico up the end of 24 September 2020, the statistics showed 743,435 patients infected with coronavirus 2 of severe acute respiratory syndrome (SARS-CoV-2) and 76,647 deaths due to COVID-19.

The SARS-CoV-2 infection is directly linked with the recognition and binding of its spike protein to the human angiotensin-converting enzyme 2 receptor. This receptor is mainly located in the lung alveolar epithelial cells, which are potentially target of this virus. As a result of a pro-inflammatory response, the SARS-CoV-2 may cause acute respiratory distress syndrome and in severe cases may result in fatal outcomes. SARS-CoV-2 has a high homology with SARS-CoV and like SARS-CoV its transmission mode is human-to-human. The number of secondary cases produced by a single infected person with SARS-CoV-2 in a susceptible population (R0) has been estimated to be between 2 and 3, which is higher than that previously reported for SARS-CoV.

The fast capacity to spread of SARS-CoV-2 highlights the importance of having a sensitive and specific virus detection method. The gold standard for COVID-19 diagnosis is the molecular detection of the genome of SARS-CoV-2 in pharyngeal swab samples using a real-time reverse transcription-polymerase chain reaction (RT-PCR) assay. The enzyme-linked immunoassay for specific immunoglobulin M (IgM) and G (IgG) has been suggested as an acceptable choice to reduce the false negatives rate that could occur with the RT-PCR method. In addition to an accurate method of detection, a good screening strategy should allow to break the channels of viral transmission. At this point, the person-to-person contact in the spread of disease has an important role, especially when asymptomatic infected patients are involved, because the absence of symptoms may lead to them not being screened and, therefore, remain undetected. Asymptomatic individuals represent a substantial fraction of the SARS-CoV-2 infected population estimated at 17.9%.

In a recent study Hu et al. (2020), evaluated 24 asymptomatic COVID-19 infections from the screening of close contacts of COVID-19 patients in China. Nineteen patients remained asymptomatic during hospitalization and the median communicable period (defined as the interval from the first day of positive nucleic acid tests to the first day of continuous negative tests), was 9.5 days (up to 21 days among the 24 asymptomatic cases). These results suggest that infected asymptomatic close contacts, could become an important cause of virus transmission and, therefore, a strict monitoring of close contacts via multiple screening should be prioritized.

Mexico is in phase three of the COVID-19 pandemic and since the first reported case (February 28, 2020), the Mexican government increased measures to contain the spread of the virus. These measures have included social distancing, closing schools, the obligatory use of mouth masks, and canceling massive events, among others. However, the SARS-CoV-2 screening tests in Mexico (until August 24, 2020), have been focused on people who met the operational criteria established by the Mexican Health Authority’s consensus. These criteria included meeting 2 out of 3 of the following symptoms: fever ≥ 38°C, dry cough and/or headache, in addition to other COVID-19 related symptoms and the presence of a comorbidity. Considering the World Health Organization (WHO) recommendations regarding the need to increase the number of SARS-CoV-2 tests and the isolation and tracing of contacts, here, we conducted an investigation to evaluate the percentage of positive COVID-19 patients without diagnosis in Mexico because the total or partial absence of symptomatology in close contacts of COVID-19 patients. We sought to depict the importance of asymptomatic infections in the patient-to-patient transmission of COVID-19 and the relevance of tracing and testing close contacts to contain potential outbreaks.

METHODS

Patients and study definitions

The ethics committees of the Academic Unit of Human Medicine and Health Sciences from Universidad Autonoma de Zacatecas and the Alpha Medical Center approved this cross-sectional study carried out in Zacatecas, Mexico from June 2020 to July 2020 (Approval ID: AMCI-FSARSC2-006 and 007). We retrospectively reviewed documents on epidemiological investigations of nineteen patients with laboratory test confirmation for COVID-19.

Using patients’ epidemiological records, we traced 81 close contacts for medical evaluation and sampling. Indicated patients and their contacts (aged > 18 years old) were contacted by telephone and invited to participate in the study. The patient recruitment was carried out in the Centro de Salud “Francisco Villa” from Secretaría de Salud de Zacatecas and in the Molecular Medicine Laboratory from the Academic Unit of Human Medicine and Health Sciences from Universidad Autónoma de Zacatecas. A questionnaire consisting of demographic and clinical data and signs and symptoms related to COVID-19 was administered to the participants. There were no exclusion criteria for this study. A close contact was defined as an individual who has had closer than <6 feet for ≥15 min with people with a positive diagnosis for COVID-19, whether they were symptomatic or asymptomatic according to the Center for Disease Control and Prevention (CDC) definition.

Throughout the protocol, the operational definition of suspicious case of COVID-19 was defined according to the Mexican Health Guidelines (August 24, 2020) as follows: a patient who met 2 out of 3 of the following symptoms: a fever ≥ 38°C, dry cough and/or headache, and have at least 1 other COVID-19 related symptoms (asthenia, odynophagia, myalgia, arthralgia, rhinorrhea, conjunctivitis, anosmia, dysgeusia, nausea, abdominal pain, and diarrhea) and underlying risk conditions (pregnancy, immunosuppression, previous lung disease, diabetes mellitus, systemic arterial hypertension, adults > 65 years old, or obesity).

Biological samples and SARS-CoV-2 screening

Nasopharyngeal and oropharyngeal swab samples were obtained from each participant before being packed and transported in triple packaging at a low temperature (4°C) following the WHO and Pan American Health Organization guidelines of handling and transporting viral SARS-CoV-2 specimens. Specimens were sent to the Molecular Medicine Laboratory of the Academic Unit of Human Medicine and Health Sciences from Universidad Autónoma de Zacatecas. This Laboratory is an authorized COVID-19 diagnosis laboratory by the Instituto de Diagnóstico y Referencia Epidemiológicos “Dr. Manuel Martínez Báez,” which is the institution of Ministry of Health of Mexico, in charge of diagnosis, control, referral, research, and technological development for the surveillance of epidemiological diseases.

Exudate samples were screened for SARS-CoV-2 with a 1-step RT-PCR assay using the CDC real-time RT-PCR panel (Integrated DNA Technologies, Coralville, IA). SARS-CoV-2 detection was analyzed in a StepOnePlus Real-Time PCR system (Thermo Fisher Scientific, Waltham, MA) and interpreted according to the manufacturer’s instructions. IgM and IgG against SARS-CoV-2 were determined using a total blood sample through a 2019 nCoV IgG/IgM rapid test (Genrui Biological samples and SARS-CoV-2 screening

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Biotech, Shenzen, China). RT-PCR, antibody detection, and clinical findings were recorded in a predesigned database.

Data analysis

General characteristics of the study population were represented as the mean ± standard deviation (SD) and percentages. Comparisons of the risk factors and the clinical findings among the groups were performed using a χ2 or Fisher exact test for categorical variables and a t test or Mann-Whitney U test for continuous variables. The odds ratios (OR) with Yates continuity correction were calculated for significant comparisons. Statistical analysis was carried out with the SigmaPlot v12.0 (Systat Software Inc., San Jose, CA) software and a significance level of P < .05 was considered significant.

RESULTS

One hundred patients were included in the study. Nineteen of them were index COVID-19 cases and 81 were close contacts (Fig 1). The median age of the index cases was 41.7 years (range: 23–68 years) whereas the average age of the close contacts was 35.4 years old. Forty-seven were women. Among the close contacts, 20.9% were nurses, 18.5% teachers, and 18.5% were students (Table 1). The most frequent comorbidity among the index patients was type 2 diabetes mellitus (T2DM) with 2 cases (10.5%), while arterial hypertension, dyslipidemia, and thyroid disease were present in only 1 indicated patient, respectively (5.2% each). Otherwise, the most frequent comorbidities amid the close contacts group were arterial hypertension with 8 cases (9.8%), thyroid disease with 6 cases (7.4%), and T2DM with 4 cases (4.9%). Considering both index patients and close contacts, 4 (21%) index patients and 33 (40.7%) close contacts usually smoked and 5 (26.3%) index cases and 36 (44.4%) close contacts affirmed alcohol consumption (Table 2). There was no statistical significance between the general characteristics or risk factors for COVID-19 between the groups of index cases and close contacts (P > .05).

SARS-CoV-2 screening test

The mean time of the index COVID-19 patients’ diagnosis after onset of symptoms was 2.7 ± 1.9 days. Figures 1–2 and Table 3 show a summary of the results of index COVID-19 cases and their contacts.

**Table 1**

| Characteristics | Index COVID-19 Cases (n = 19) | Close Contacts (n = 81) | P-value |
|-----------------|-------------------------------|------------------------|---------|
| Sex n (%)       |                               |                        |         |
| Male            | 9 (47.4)                      | 34 (41.9)              | 0.865   |
| Female          | 10 (52.6)                     | 47 (58.0)              |         |
| Age (years)     | 41.7 ± 12.9                   | 35.4 ± 16.3            | 0.027ast|
| Occupation (%)  |                               |                        |         |
| Nurse           | 5 (26.3)                      | 17 (20.9)              | 0.353   |
| Doctor          | 3 (15.7)                      | 8 (9.8)                |         |
| Other health workers | 2 (10.5)         | 7 (8.6)                |         |
| Housewife       | 1 (5.2)                       | 8 (9.8)                |         |
| Administrative work | 2 (10.5)          | 10 (12.3)              |         |
| Teachers/student | -                            | 15 (18.5)              |         |
| Retired/ unemployed | 1 (5.2)             | 5 (6.1)                |         |
| Others          | 2 (10.5)                      | 11 (13.5)              |         |
| Comorbidities n (%) |                     |                        |         |
| Type 2 diabetes mellitus | 2 (10.5) | 4 (4.9)                | 0.302   |
| Arterial hypertension | 1 (5.2)           | 8 (9.8)                |         |
| Dyslipidemia    | 1 (5.2)                       | 2 (2.4)                |         |
| Rheumatic diseases | -                  | 2 (2.4)                |         |
| Hyper/hypothyroidism | 1 (5.2)           | 6 (7.4)                |         |
| Neurologic diseases | -                  | 5 (6.1)                |         |
| Addictions n (%) |                               |                        |         |
| Smoking         | 4 (21.0)                      | 33 (40.7)              | 0.182   |
| Alcoholism      | 5 (26.3)                      | 36 (44.4)              | 0.235   |

Data are represented as frequency and percentages. *P < 0.05.

![Fig 1](image-url) Summary of results of SARS-CoV-2 RT-PCR screening and antibodies by traced contacts and COVID-19 patients. The flowchart shows the traced close contacts related with index COVID-19 patients. Most of the symptomatic patients were RT-PCR positive for SARS-CoV-2 (29/81). Fourteen close contacts had positive antibodies against SARS-CoV-2 at the sampling time.
From the 19 index COVID-19 cases, 9 of them attended the second SARS-CoV-2 test (Fig 2). At the sampling time, 77.8% of the index COVID-19 patients remained positive for SARS-CoV-2 (Fig 2) with an average of positivity time of 18.9 ± 15.9 days. Thirty-four (42%) of the close contacts included in the study were RT-PCR positive. The average of positive contacts by index case was 4.3 ± 3.8 contacts. This value is the first approximation to the epidemiological parameter $R_0$, the reproductive number for SARS-CoV-2 in Mexican population. This parameter is defined as the average number of secondary infections caused by 1 infected individual during his/her entire infectious period. Further statistical analysis may prove if this sample is representative for the population, and confirm the validity of the reproductive number.

**SARS-CoV-2 IgM and IgG detection**

Only 67.1% of the study population had more than 2 weeks after their contact with a COVID-19 case. From the 100 participants, 87 of them had rapid test results available. Regarding the close contacts of COVID-19 cases, 13 (16%) showed positive results for IgM and/or IgG (23.1% for IgM, 7.7% for IgG, and 69.2% for IgG/IgM).

### Table 2
Comparison of the signs and symptoms between RT-PCR positive and negative close contacts

| Symptom (%) | Index COVID-19 cases (n = 19) | Close contacts (n = 81) | P-value | Odds ratio (95% CI) |
|-------------|-------------------------------|------------------------|---------|--------------------|
| Fever       | 6 (31.5)                      | 5 (14.7)               | 1 (2.1) | 0.078              | 7.9 (0.8–71.3) |
| Cough       | 5 (26.3)                      | 10 (29.4)              | 5 (10.6) | 0.063              | 3.5 (1.1–11.4) |
| Headache    | 6 (31.5)                      | 13 (38.2)              | 13 (27.6) | 0.444              | 1.6 (0.6–4.1) |
| Dyspnea     | 2 (10.5)                      | 6 (17.6)               | 1 (2.1) | 0.038*             | 9.8 (1.1–86.2) |
| Irritability| 3 (15.8)                      | 6 (17.6)               | 0 (0.0) | 0.004*             | –                |
| Diarrhea    | 4 (21.0)                      | 6 (17.6)               | 2 (4.2) | 0.063              | 4.8 (0.9–25.6) |
| Chest pain  | 3 (15.8)                      | 9 (26.4)               | 0 (0.0) | <0.001*            | –                |
| Chills      | 2 (10.5)                      | 4 (11.7)               | 2 (4.2) | 0.232              | 3.0 (0.6–17.4) |
| Odynophagia | 3 (15.7)                      | 12 (35.2)              | 7 (14.8) | 0.061              | 3.1 (1.1–9.1) |
| Myalgia     | 5 (26.3)                      | 13 (38.2)              | 5 (10.6) | 0.007*             | 5.2 (1.6–16.5) |
| Arthralgia  | 5 (26.3)                      | 9 (26.4)               | 4 (8.5) | 0.062              | 3.9 (1.1–13.9) |
| Asthenia    | 6 (31.5)                      | 7 (20.5)               | 3 (6.3) | 0.086              | 3.8 (0.9–15.9) |
| Rhinorrhea  | 5 (26.3)                      | 10 (29.4)              | 4 (8.5) | 0.031*             | 4.4 (1.3–15.8) |
| Polyneura   | 2 (10.5)                      | 3 (8.8)                | 1 (2.1) | 0.304              | 4.4 (0.4–44.8) |
| Vomit       | 1 (5.2)                       | 0 (0.0)                | 1 (2.1) | 1.000              | –                |
| Abdominal pain | 1 (5.2)              | 1 (2.9)                | 0 (0.0) | 0.420              | –                |
| Conjunctivitis | 2 (10.5)            | 5 (14.7)               | 0 (0.0) | 0.011*             | –                |
| Cyanosis    | 1 (5.2)                       | 0 (0.0)                | 0 (0.0) | 1.000              | –                |
| Anosmia     | 6 (31.5)                      | 5 (14.7)               | 0 (0.0) | 0.011*             | –                |
| Dysgeusia   | 6 (31.5)                      | 3 (8.8)                | 0 (0.0) | 0.070              | –                |
| Skin problems | 2 (10.5)           | 0 (0.0)                | 1 (2.1) | 1.000              | –                |

P-values were obtained from the comparison of symptoms between close contacts with SARS-CoV-2 RT-PCR (+) and RT-PCR (−).

Significant P-values are highlighted with an asterisk.

Odds ratio for the comparison between the proportions of close contacts with SARS-CoV-2 RT-PCR positive and negative. Data are represented as frequency and percentages.

From the 19 index COVID-19 cases, 9 of them attended the second SARS-CoV-2 test (Fig 2). At the sampling time, 77.8% of the index COVID-19 patients remained positive for SARS-CoV-2 (Fig 2) with an average of positivity time of 18.9 ± 15.9 days. Thirty-four (42%) of the close contacts included in the study were RT-PCR positive. The average of positive contacts by index case was 4.3 ± 3.8 contacts. This value is the first approximation to the epidemiological parameter $R_0$, the reproductive number for SARS-CoV-2 in Mexican population. This parameter is defined as the average number of secondary infections caused by 1 infected individual during his/her entire infectious period. Further statistical analysis may prove if this sample is representative for the population, and confirm the validity of the reproductive number.

**SARS-CoV-2 IgM and IgG detection**

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Symptomatology and SARS-CoV-2 screening

Table 2 displays a summary of the signs and symptoms of the study population. Regarding the presence of symptoms as a classifier variable, from the 34 trace positive contacts, 29 of them (85.3%) were symptomatic and the most common symptoms were headache (38.2%), odynophagia (35.2%), myalgia (38.2%), cough (29.4%), and rhinorrhea (29.4%). The most common combinations of symptoms were odynophagia/rhinorrhea (24.1%) and headache/myalgia (20.6%). The combinations of cough/odynophagia, headache/cough, and headache/odynophagia, were present in a frequency of 17.2%. From the symptomatic patients infected with SARS-CoV-2, only 6 (17.6%) met the operational criteria established by the Mexican Health Authority's consensus for a suspicious case of COVID-19. Twenty-three (67.6%) had only 1 of the 3 main symptoms established by the Mexican operational criteria (a fever ≥38°C, headache, or dry cough). Five COVID-19 positive contacts (14.7%) remained asymptomatic. There were significant differences in the proportions of contacts with dyspnea, irritability, chest pain, myalgia, rhinorrhea, conjunctivitis, or anosmia, between groups of SARS-CoV-2 RT-PCR positive and those with a negative test for SARS-CoV-2 (P < .05). The calculated OR for the presence of these symptoms and a COVID-19 positive test ranged between 4.4 (rhinorrhea) and 9.8 (dyspnea). In the studied population, anosmia, conjunctivitis, chest pain, and irritability were symptoms that appeared only in the COVID-19 positive patients (P < .05). Regarding only the close contacts, met the Mexican operational definition for a COVID-19 suspected case did not significantly affect the rate of having a positive test for SARS-CoV-2 among the studied population (OR: 3.1; 95% confidence interval [CI]: 0.73–13.6; P = .156).

There were 29 symptomatic patients identified in the study and 24.1% had antibodies against SARS-CoV-2 (10.3% showed IgM, 3.4% IgG, and 17.2% both IgG and IgM). From the 5 asymptomatic COVID-19 contacts, only 2 showed IgG/IgM antibodies (Fig 1).

DISCUSSION

In this study, we evaluated laboratory, clinical, and epidemiological information of 100 subjects, including 19 index COVID-19 patients and their 81 close contacts. After screening for SARS-CoV-2, 42% of the close contacts were positive. The average of the SARS-CoV-2 of secondary cases produced by a single index infected person was calculated in 4.3. This data could be the first attempt to the estimation of R0 for SARS-CoV-2 for Mexican population and it is higher than that estimated for SARS-CoV and SARS-CoV-2 by Zhang S. et al. (R0: 2–3). Similar results reported by Ying Liu et al.4 with a R0 of 3.28 for SARS-CoV-2 and R0 of 3 for SARS-CoV, surpassed the WHO estimates (range: 1.4–2.5). In our study, 14.7% of the positive close contacts were asymptomatic with this percentage being higher than that observed in other populations as reported in Gao M. et al., Graham LA et al., and Long QX et al.4,5,11 studies. An example of this observation is the study reported by Hong-Jun Zhang et al.9. In their study, the authors evaluated 284 close contacts from asymptomatic COVID-19 patients and identified only 2.7% of the close contacts as positive for SARS-CoV-2.20 Therefore, as the low percentage of asymptomatic close contacts were positive for COVID-19, the probability of infectivity from asymptomatic SARS-CoV-2 might be weak.15 However, even if the percentage of asymptomatic COVID-19 close contacts in our study was lower than the 17.9% reported on the “Diamond Princess” cruise, the nonevaluated SARS-CoV-2 asymptomatic patients may contribute to the rapid transmission and spread of the disease as the median duration of viral shedding is approximately 19 days, significantly longer than the 14 days in symptomatic patients.20

An important finding in our study was that the most common symptoms observed (headache, myalgia, odynophagia, cough, and rhinorrhea) in the contacts group were mostly presented without fever, contrary to other related studies in which fever is considered as a common symptom.5,7,20,21 Moreover, there was not a statistical difference in the presence of fever between the groups of contacts with or without SARS-CoV-2 infection (P = .078). It is important to note in our study that anosmia, conjunctivitis, chest pain, and irritability were symptoms exclusively presented by COVID-19 positive contacts (P < .05) but in the Mexican operational criteria they are grouped as the secondary symptoms group.13 Considering our results and because the importance of these symptoms has been widely recognized, they should be considered as an essential criterion for the indication of SARS-CoV-2 testing by molecular diagnosis.22

Health workers constituted an important proportion in our study as they formed 32% of the total sample and from these, 2 COVID-19 indicated patients had the most SARS-CoV-2 positive close contacts.
This proportion was in agreement with the results of another study in which 25.3% of their close contacts were healthcare contacts.\textsuperscript{23} Regarding only the close contacts with COVID-19, meet the Mexican operational definition for a COVID-19 suspected case did not significantly affect the rate of having a positive test for SARS-CoV-2 among the studied population, (OR: 3.1: 95% CI: 0.73–13.6; \( P = 156\)). As only 5 (14.7%) of our COVID-19 positive contacts met the operational criteria, the importance of close vigilance and screening of contacts of COVID-19 confirmed patients, even if they do not meet with that definition should be an essential measure to avoid the disease spreading.

Finally, of the thirty-four COVID-19 contacts with positive antibodies against SARS-CoV-2, only 8.8%, 2.9%, and 17.6% had an IgM, IgG, and IgG/IgM positive test, respectively. These results are dissimilar to that reported by Qung-Xin Long et al.\textsuperscript{20} in which they reported 82.4% of the COVID-19 positive samples had IgG, and 70.2% had IgM. Another example is a study carried out in Sweden in which in a sample of 29 COVID-19 confirmed patients, 27 of them had IgG antibodies in their rapid test result, reaffirming differences in the immune response against the virus between populations.\textsuperscript{24} However, it is important to emphasize that the sample size in this study was small and therefore variations in the proportions could be found if our results are compared with large-scale investigations. On the same sense, because the most of the participants had no severe COVID-19-related symptoms is important to identify the COVID-19 population in which the serology test will be useful and if the rapid test should be used to reduce the false negatives rate that could occur with the RT-PCR method and/or as an evolution follow-up factor of disease.

CONCLUSION

There was a high proportion (42%) of close contacts of COVID-19 patients infected with SARS-CoV-2 and with less than 2 respiratory symptoms (67.6%). There were notable differences in the presence of anosmia, conjunctivitis, chest pain, and irritability symptoms between close contacts of COVID-19 patients, with and without SARS-CoV-2 infection. The average of SARS-CoV-2 infected close contacts by index COVID-19 case was 4.3 among the studied population, with the mean of time of positive test for SARS-CoV-2 being calculated as 18.9 days. The screening for SARS-CoV-2 by RT-PCR in close contacts of positive COVID-19 patients should be encouraged to avoid a source of spreading the infection and expanding of the disease.

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ETHICS APPROVAL

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript is in line with the recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals and aim for the inclusion of representative human populations (sex, age, and ethnicity) as per those recommendations. Informed consent was obtained from all participants.

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