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RESEARCH ARTICLE

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Evaluation of human coronavirus OC43 and SARS-COV-2 in children with respiratory tract infection during the COVID-19 pandemic

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic is an overwhelming crisis across the world. Human Coronavirus OC43 (HCoV-OC43) is a Betacoronavirus responsible mostly for mild respiratory symptoms. Since the presentations of HCoV-OC43 and severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) are believed to resemble a lot, the aim of this study was to evaluate the frequency and characteristics of HCoV-OC43 in the current pandemic and the rate of coinfection for the two viruses. One hundred and seventeen patients referred to Children's Medical Center, Tehran, Iran with respiratory symptoms were included. Real-time reverse transcription-polymerase chain reaction (RT-PCR) methods were performed for the detection of HCoV-OC43 and SARS-COV-2. Totally, 23 (20%) had a positive RT-PCR for HCoV-OC43 and 25 (21%) were positive for SARS-COV-2. Two patients (2%) had a positive PCR for both HCoV-OC43 and SARS-COV-2. The two groups showed significant differences in having contact with family members with suspected or confirmed COVID-19 ($p = 0.017$), fever ($p = 0.02$), edema ($p = 0.036$), vomiting ($p < 0.001$), abdominal complaints ($p = 0.005$), and myalgia ($p = 0.02$). The median level of lymphocyte count in patients with HCoV-OC43 was significantly lower than patients with SARS-COV-2 infection ($p = 0.039$). The same frequency of SARS-COV-2 and HCoV-OC43 was found in children with respiratory symptoms during the COVID-19 pandemic. The rate of coinfection of SARS-COV-2 with HCoV-OC43 in our study was 0.08. Further research into the cocirculation of endemic coronaviruses, such as HCoV-OC43 and SARS-CoV2, in different regions, is highly recommended. Attempts to determine the geographic distribution and recruit more flexible test panel designs are also highly recommended.

KEYWORDS

children, HCoV-OC43, human coronavirus, SARS-COV-2

1 | BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic is a crushing outbreak raging across the world. As of May 2021, more than 152 million confirmed cases of COVID-19 and more than 3.2 million deaths have been reported by World Health Organization (WHO) globally. Many scientists have dedicated their work to Coronavirus, trying to comprehend the pathogenesis, routes of spread, ways to control, treatment, and any aspect whose better understanding might lead to better control of the disease.

The Betacoronavirus (β-CoVs or Beta-CoVs) is one of the four genera of coronaviruses (Alpha, Beta, Gamma, and Delta). This genus is described as enveloped, positive-strand RNA viruses that infect mammals.[1] Their natural reservoirs are bats and rodents.[2,3] Betacoronavirus genus contains four lineages: A, B, C, and D. The most common betacoronaviruses that can infect humans are HCoV-OC43 and HKU1 (which are believed to cause common cold symptoms) of lineage A, SARS-CoV, and SARS-CoV-2 (which has been found responsible for the current pandemic) of lineage B, and middle east respiratory syndrome coronavirus (MERS-CoV) of lineage C. HCoV-229E and HCoV-NL63 are the other coronaviruses associated with disease in humans, belonging to the Alpha genus, and are mostly known to cause mild respiratory symptoms.[4,5] The suspected animal-to-human spread of four betacoronaviruses, including the HCoV-OC43 (1890), SARS-CoV-1 (2003), MERS-CoV (2012), and SARS-CoV-2(2019), proposes their high potential to cause pandemics.[6,7]

Limited papers have been published to date studying the coinfection of COVID-19 with other respiratory viruses. The most common reported coinfections are rhinovirus, enterovirus, influenza, respiratory syncytial virus, and non-SARS-CoV-2 Coronaviruses, including Coronavirus NL63, HKU1, 229E, and HCoV-OC43.[8–10]

Strain HCoV-OC43 was found in 1967 in the nasopharynx of a patient with symptoms of a common cold.[1] Clinical manifestation reported in patients with HCoV-OC43 includes fever, rhinitis, pharyngitis, abdominal complaints, pneumonia, and less commonly, bronchitis, otitis, and laryngitis.[11] Lower tract respiratory manifestations can also be associated with HCoV-OC43 infection. Studies show that HCoV-OC43 infects the immunocompromised less than HKU1, 229E, and NL63 Coronaviruses.[12]

Since the presentations of HCoV-OC43 and SARS-COV-2 resemble each other to a large extent, it is valuable to know the prevalence of HCoV-OC43 in the current pandemic and the rate of coinfection with SARS-CoV-2. Studying the morbidity and mortality of HCoV-OC43 infection can enlighten the burden of the disease and highlight the necessity of diagnostic investigations in approach to a patient with symptoms of COVID-19.

Mastering the knowledge of the pandemic's viral pathology helps address the correct approach to the disease and its treatment. Since the presentations of HCoV-OC43 and SARS-COV-2 are believed to resemble a lot, the aim of this study was to evaluate the frequency and characteristics of HCoV-OC43 in the current pandemic and the rate of coinfection for the two viruses.

2 | METHODS

This study received ethical approval (IR. TUMS. CHMC. REC.1399.097) from the Tehran University of Medical Sciences in Tehran, Iran. All participants gave written informed consent, and the study was carried out following the guidelines of the Declaration of Helsinki.

One hundred and seventeen children with suspected COVID-19 and respiratory symptoms were referred to Children's Medical Center, Tehran, Iran, between April 1 and July 30 of 2020. The specimens were collected via nasopharyngeal swabs and were kept in the freezer with a temperature of −20°C until tested.

The demographic data, including age and gender, and also clinical manifestations were gathered in a questionnaire. Fever, cough, sore throat, conjunctivitis, edema, tachypnea, chest pain, rhinorrhea, vomiting, headache, abdominal complaints, diarrhea, myalgia, and rash were among the clinical manifestations investigated. Laboratory evaluation included complete blood cell counts and their differentiation, inflammatory markers, including procalcitonin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), electrolytes, and kidney and liver function tests.

Abnormal chest CT scan findings were considered as the most common and specific features found in COVID-19 patients, that is, peripheral, bilateral, ground-glass opacification (GGO) with or without consolidation or visible intralobular lines, multifocal ground-glass opacification or rounded morphology, or reverse halo sign or other findings of organizing pneumonia.[13,14]

The RNA of the collected samples was extracted using CinnaPure RNA Extraction Kit (SinaClone), following the manufacturer's guidelines, and complementary DNA (cDNAs) were then fabricated by First Strand cDNA Synthesis Kit (SinaClone).[15] Reverse transcription-polymerase chain reaction (RT-PCR) was performed for the detection of HCoV-OC43 and SARS-COV-2 using RNAse P as the housekeeping gene.[16,17] Briefly, each reaction was performed in a 20 µl volume, which consisted of 12.5 µl of buffer, 1 µl of the enzyme, 2 pmol of primers, 2 pmol of the probe, 5 µl of extracted nucleic acid and made to a final volume of 20 µl with nuclease-free water. The thermal cycling profile for the RT-PCR was 50°C for 30 min (1 cycle), 95°C for 10 min (1 cycle) followed by 90°C for 15 s, and 55°C for 30 s (45 cycles).

Antibody levels against SARS-CoV-2 were detected using anti-N SARS-CoV-2 antibodies by using SARS-CoV-2 immunoglobulin M (IgM) ELISA kits (Pishtaz Teb, http://pishtazteb.com) and SARS-CoV-2 IgG ELISA kits (Pishtaz Teb, http://pishtazteb.com) according to the manufacturer's protocol.[18,19]

2.1 | Statistical analysis

Patients were divided into three groups of HCoV-OC43, SARS-COV-2, and RT-PCR negatives. The characteristics, clinical, and laboratory findings of HCoV-OC43 patients were compared with those of two other groups using Statistical Package for the Social Sciences (SPSS version 18.0, SPSS Inc.). Fisher exact tests or χ^2 tests were used to compare categorical variables between different groups. Categorical data were described using percentages and continuous data as median with interquartile range (IQR). Comparison of the laboratory tests between the two groups was performed using Mann–Whitney *U* tests. A p value of ≤0.05 was considered as the level of significance.

3 | RESULTS

Totally, 117 patients were referred to Children's Medical Centre hospital, the most experienced and subspecialized hospital considered as a referral center for pediatric COVID-19 cases in Iran, with symptoms suggestive of Coronaviruses' infection. Among them, 23 (20%) had a positive RT-PCR for HCoV-OC43 and 25 (21%) were positive for SARS-COV-2. Two patients (2%) had a positive PCR for both HCoV-OC43 and SARS-COV-2. Out of the total number of patients, 56% were boys and 44% were girls. Gender distribution was not found to be significantly different in patients with positive HCoV-OC43 in comparison with the SARS-COV-2 group or the patients with negative RT-PCR. The ages of HCoV-OC43-positive patients ranged from 1 month to 14 years. There was no significant difference between the age of the patients with HCoV-OC43 (6.7 ± 4.0) and SARS-COV-2 infection (4.9 ± 4.3) ($p = 0.17$).

Among patients with HCoV-OC43 infection, 31% had abnormal chest CT scan findings in favor of COVID-19. Although 24% of HCoV-OC43-positive patients experienced severe symptoms, that is, dyspnea, hypoxia, or more than 50% lung involvement on CT scan within 24–48 h[20]; only one patient was admitted to the ICU, none of the patients was intubated, and fortunately, no mortality was reported. There was one death case in our study. He had a cardiovascular underlying disease and only SARS-CoV-2 RT-PCR was positive. Characteristics of patients with HCoV-OC43 infection are summarized in Table 1 and compared with SARS-COV-2 and RT-PCR-negative groups.

In spite of the fact that fever, cough, conjunctivitis, edema, vomiting, abdominal complaints, diarrhea, headache, and myalgia were all more frequently observed in the patients with HCoV-OC43 infection rather than the PCR-negative group, the only significantly higher encountered symptoms in HCoV-OC43 patients were abdominal complaints (p=0.028). Symptoms found in HCoV-OC43-positive patients are summarized in Table 2, alongside those of only SARS-COV-2 RT-PCR positive and RT-PCR-negative groups.

HCoV-OC43 and SARS-COV-2-positive patients were compared using χ^2 analysis regarding possible associations. The two groups showed significant differences in the history of contact with suspected or confirmed family members to COVID-19 ($p = 0.017$), fever ($p = 0.02$), edema ($p = 0.036$), vomiting ($p < 0.001$), abdominal complaints ($p = 0.005$), and myalgia ($p = 0.02$). Except for positive history of contact with suspected or confirmed family members to COVID-19, the frequency of all of these associations was higher in the HCoV-OC43 group. A comprehensive evaluation was performed for laboratory values in both groups are shown in Table 3. The median level of lymphocyte count in patients with HCoV-OC43 was significantly lower than patients with SARS-COV-2 infection ($p = 0.039$). CRP values showed general elevation in both groups ($p = 0.593$). The median CRP level in the HCoV-OC43 group was 8 mg/L (interquartile range [IQR]: 4–428 mg/L), while in the SARS-CoV2, the median was 16 mg/L (4.75–4.5 mg/L).

Although 39% and 24% of SARS-CoV-2 and HCoV-OC43-positive patients experienced severe symptoms, respectively, in two copositive SARS-CoV-2 and HCoV-OC43 patients no severe symptoms were found.

Serological findings showed that two and one patients with HCoV-OC43 infection had elevated levels of SARS-CoV2 IgG and IgM, respectively. In the SARS-CoV-2 RT-PCR positive group, three patients had elevated IgG and one patient had increased IgM levels for SARS-CoV-2. Anti-N SARS-CoV-2 antibodies in HCoV-OC43-positive groups did not show a significant difference with HCoV-OC43 RT-PCR negative groups. The same results were obtained in groups with SARS-CoV-2 infection.

4 | DISCUSSION

Since SARS-COV-2 shares clinical presentations with other respiratory viruses, and with special concern toward the critical circumstances of the COVID-19 pandemic, it is very important to describe the symptoms as much as possible and to perform highly accurate tests to distinguish the viruses, which necessitate urgent public health interventions and treatment.

HCoV-OC43 is a human infecting Coronavirus that is mostly known to cause mild respiratory symptoms. However, severe symptoms have also been reported in the literature.[11,12] HCoV-OC43 cases in our study, also, showed low rates of severity, and no mortality was reported. It is noteworthy that before the current pandemic, SARS-COV-2 was indeed known to be mostly responsible for trivial respiratory symptoms, and no one expected such a tragedy on its behalf.

Although it is generally believed that SARS-COV-2, responsible for the current pandemic of COVID-19, resembles a lot in manifestations to HCoV-43, our study revealed that significant differences could be observed in manifestations of the two viruses, while the incidence of most of the symptoms of HCoV-OC43 was not significantly different with those of PCR-negative. Although it is widely assumed that SARS-COV-2, which is responsible for the current COVID-19 pandemic, closely resembles HCoV-43 in manifestations, our study found that significant differences in manifestations of the two viruses could be observed, while the frequency of most HCoV-OC43 symptoms was not significantly different from that of PCR-negatives. The symptoms of COVID-19 resemble a lot in children and adults, but the frequency differs.[21] In a report of 5188 confirmed cases of COVID-19 in the United States, the following symptoms were introduced as the most common: fever, cough, headache, sore throat, myalgia, dyspnea, diarrhea, nausea/vomiting, abdominal pain, rhinorrhea, and loss of smell or taste.[22] The frequency of symptoms in HCOV-OC43 is not thoroughly discussed in the literature. Vabret et al. described an outbreak of HCoV-OC43 in 2001 in Normandie, France.[11] The following frequencies were reported for HCOV-OC43 symptoms: fever in 60%, general symptoms (i.e., headache, anorexia, and myalgia) in 30%, digestive problems (i.e., emesis, diarrhea, and abdominal pain) in 56.7%, rhinitis in 36.7%, pharyngitis in 30%, laryngitis in 3.3%, otitis in 13.3%, and lower respiratory tract infection in nearly one-third of the patients.

In our study, the frequency of fever, headache, edema, vomiting, abdominal complaints, and myalgia was significantly higher in the

TABLE 1 Characteristics of HCoV-OC43, SARS-COV-2, and RT-PCR-negative groups

Group		Age (Year)	Sex (Male)	Abnormal chest CT scan findings	Presence of underlying diseases	Severe symptoms	Intubation	ICU admission	Mortality	Contact with family members with COVID-19
HCoV-OC43 positive	Number	6.7 ± 4.0	13	5	8	5	0	1	0	6
N = 23	Percent		57	31	38	24	0	5	0	29
	Total surveyed number		23	16	21	21	21	21	21	21
SARS-COV-2 positive	Number	4.9 ± 4.3	14	8	13	9	0	2	1	14
N = 25	Percent		56	61.5	56.5	39	0	9	4	61
	Total surveyed number		25	13	23	23	23	23	23	23
Negative RT-PCR	Number	6.3 ± 4.1	39	23	26	9	0	4	1	31
N = 71	Percent		55	48	37	13	0	6	1	44
	Total surveyed number		71	48	71	71	71	71	71	71

Abbreviations: COVID-19, coronavirus disease 2019; HCoV-OC43, Human Coronavirus OC43; ICU, intensive care unit; RT-PCR, reverse transcription-polymerase chain reaction; SARS-COV-2, severe acute respiratory syndrome coronavirus 2.

TABLE 2 Clinical findings of children with HCoV-OC43 and SARS-COV-2

Symptom	Patients with HCoV-OC43 infection			Patients with SARS-CoV-2 infection			RT-PCR negative group		
	Number	Percent	*P* value	Number	Percent	*P* value	Number	Percent	*P* value
Fever	20	95	0.68	16	70	0.005	64	90	0.27
Cough	13	62	0.43	9	39	0.16	37	52	1.0
Sore throat	4	19	0.74	1	4	0.19	11	15.5	0.48
Conjunctivitis	4	19	0.74	2	9	0.52	11	15.5	0.71
Edema	4	19	0.27	0	0	0.12	7	10	1.0
Tachypnea	6	29	0.43	5	22	0.19	27	38	0.18
Chest Pain	1	5	1.0	4	17	0.047	3	4	0.26
Rhinorrhea	0	0	1.0	1	4	0.36	1	1	1.0
Vomiting	14	67	0.08	3	13	0.002	32	45	0.53
Headache	6	29	0.57	3	13	0.4	16	22.5	0.7
Abdominal complaints	11	52	0.028	3	13	0.074	19	27	0.5
Diarrhea	9	43	0.52	4	17	0.086	25	35	0.59
Myalgia	7	33	0.74	1	4	0.013	21	30	0.14
Rash	4	19	1.0	1	4	0.07	16	22.5	0.1

Abbreviations: HCoV-OC43, Human Coronavirus OC43; RT-PCR, reverse transcription-polymerase chain reaction; SARS-COV-2, severe acute respiratory syndrome coronavirus 2.

HCoV-OC43 group compared with the SARS-COV-2 group. Nevertheless, abdominal complaints were the only symptoms in the HCoV-OC43 group reported to occur significantly different from the PCR-negative group, and the higher incidence belonged to PCR-negatives.

In a systematic review performed by Liguoro et al., laboratory evaluations of children affected by COVID-19 were summarized. According to this study, 17.1% of the patients showed low WBC and lymphopenia or neutropenia (13.3%). Increased inflammatory markers, such as procalcitonin or CRP, were reported in 31.1% of the patients.[21] Since the disease attack rate in children appears to have been changing since the start of the outbreak, updated studies should be conducted addressing the laboratory findings in children with COVID-19.[23]

The importance of SARS-COV-2 and HCoV-OC43 cocirculation has been drawn into attention, especially during the COVID-19 pandemic. Since there might be cross-reactivity between SARS-CoV-2 and endemic Coronaviruses, such as HCoV-OC43, diagnostic challenges are proposed and should be well addressed in laboratory approaches. Interestingly enough, Li guo et al. demonstrated that elevated levels of HCoV-OC43 S-IgG can be found in SARS-COV-2 patients and the titer is associated with the severity of the disease. It is notable that none of the 257 SARS-COV-2 patients in this study presented a coinfection with HCoV-OC43.[24] In a recent study conducted by Dugas et al., 296 patients infected with SARS-COV-2 were examined for IgG antibodies against the nucleocapsid protein of HCoV 229E, NL63, OC43, and HKU1. They concluded that anti-OC43 antibodies can protect patients from severe courses of COVID-19 disease.[25] These findings highlight the cross-reactivity between the two viruses. Another study in favor of this hypothesis is the one conducted by Lineburg et al. in April 2021. The authors screened SARS-CoV-2 peptide pools and performed in-vitro peptide stimulation and crystal structure analyses, which demonstrated T-cell-mediated cross-reactivity with circulating HCoV-OC43 and HKU-1 but not 229E or NL63 coronaviruses because of different peptide conformations.[26] In our study, however, only one patient in each group had positive IgM levels, two patients in the HCoV-OC43 group and three patients in the SARS-CoV-2 group had elevated IgG levels for SARS-CoV-2. The low number of immunoglobulin positives could explain why no correlation was found between serology and PCR results. In a recently published study conducted in Canada, Marshal et al. examined respiratory specimens of 298,415 COVID-19 symptomatic patients for 18 possible cocirculating pathogens, including four endemic coronaviruses. This study found very low rates of SARS-COV-2 coinfection and significantly lower rates of coinfection for SARS-COV-2 virus in comparison with SARS-COV-2-negative specimens.[27] In the study conducted by Hazra et al., 2535 specimens were simultaneously tested for SARS-CoV-2 and other pathogens, including HCoV-OC43, on symptomatic patients. Of the total number of patients, 18.1% were positive for SARS-COV-2, of which 3.3% were also positive for at least one other pathogen. No coinfection could be found between SARS-COV-2 and HCoV-OC43.[28] In the study of Akagi et al. in Japan, among 2034 adult patients with respiratory symptoms, HCoVs were detected in 121 cases (6%) and HCoV-OC43 was identified in 21 patients (17%).[29] In the study of Kong et al. in China, the prevalence of HCoVs during 2015–2020 in adults was 3.59%, and HCoV-OC43 was the most commonly detected type of HCoVs.[30]

According to recent studies, precautions against SARS-CoV-2 during the pandemic were effective against other HCoVs, including HCoV-OC43, and the positivity rates of other HCoVs declined.[31,32]

TABLE 3 Laboratory results of patients with HCoV-OC43 and SARS-CoV-2 infection

	Patients with HCoV-OC43 infection Median (IQR)	Patients with SARS-CoV-2 infection Median (IQR)	*P* value
WBC (× 10^9 cells per L)	7.6 (5.2–9.8)	6.9 (5.8–12.8)	1.0
Hemoglobin (g/dl)	12.3 (11.1–13)	11.7 (10–12.8)	0.376
Platelet count (× 10^9 cells per L)	279 (219–371)	254 (184–411)	0.555
Neutrophil count (× 10^9 cells per L)	5.3 (4.12–6.89)	6 (2.35–10.14)	0.768
Lymphocyte count (× 10^9 cells per L)	1.26 (1.07–1.64)	2.7 (1.4–3.4)	0.039
Blood urea nitrogen (mg/dl)	12 (9–16)	14 (11–17)	0.87
Creatinine (μmol/L)	0.6 (0.5–0.7)	0.6 (0.5–0.6)	0.343
Creatine phosphokinase (U/L)	61 (36–168)	58 (28–79)	0.628
Lactate dehydrogenase (U/L)	520 (432–643)	533 (398–833)	0.751
Calcium (mg/dl)	9 (8.1–9.6)	8.8 (8.5–9.7)	1.0
Phosphorus (mg/dl)	3.7 (3.2–4.3)	4.3 (3.8–5.1)	0.139
Sodium (meq/L)	134 (132–138)	136 (132–137)	0.654
Potassium (meq/L)	4 (3.7–4.2)	4.1 (3.9–4.3)	0.463
Alanine aminotransferase (U/L)	28 (26–39)	32 (24–39)	0.898
Aspartate aminotransferase (U/L)	21(12.5–27.5)	15 (11–17)	0.083
Procalcitonin (ng/ml)	0.03 (0.01–2)	0.02 (0.01–0.05)	0.724
Prothrombin time (s)	13 (12–14)	13 (13–14)	0.76
Partial thromboplastin time (s)	34 (32–39)	33 (30–36)	0.269
International normalized ratio	1.1 (1–1.3)	1.1 (1–1.1)	0.509
C-reactive protein (mg/L)	8 (4–42)	16 (5–65)	0.593
Erythrocyte sedimentation rate (mm/h)	25 (12–3)	30 (10–50)	0.757

Abbreviations: HCoV-OC43, human coronavirus OC43; SARS-COV-2, severe acute respiratory syndrome coronavirus 2.

Interestingly, Agca et al. did not report any other HCoVs than SARS-CoV-2 during the first year of pandemic in Turkey.[31]

This study had some limitations. We only included highly suggestive patients for COVID-19. Performing bigger multicentric studies including both outpatient and inpatient children is highly recommended. We only measured anti-N SARS-CoV-2 antibodies and evaluation of HCoV OC43-specific antibodies was not performed.

In conclusion, the same frequency of SARS-COV-2 and HCoV-OC43 was found in children with respiratory symptoms during the COVID-19 pandemic. The rate of coinfection of SARS-COV-2 with HCoV-OC43 in our study was 0.08. Performing broad virology tests when COVID-19 is suspected can be impractical, especially in resource-limited areas. That is why thorough comprehension of coinfection rates can be beneficial so that targeted tests for the specific pathogen can be implemented. This might also trigger a need for further investigations into HCoV-OC43, its correlations and possible treatments. Gathering knowledge in this area can also enlighten our way in a possible future crisis to the pandemic. Further research in different regions focusing on the cocirculation of endemic coronaviruses, such as HCoV-OC43, with SARS-CoV2 is highly recommended.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

All participants gave written informed consent, and the study was carried out following the guidelines of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

Shima Mahmoudi had the idea for and designed the study and had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Reihaneh Hosseinpour Sadeghi performed molecular diagnostic tests. Kosar Asna Ashari wrote the first draft of manuscript. Nasrin Keshavarz

Valian and Babak Pourakbari contributed to data acquisition and data interpretation. Shima Mahmoudi contributed to the statistical analysis and revising of the manuscript. All authors reviewed and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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