






Analysis of Tongue Color-Associated Features among Patients with PCR-Confirmed COVID-19 Infection in Ukraine

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ABSTRACT

Objective: To evaluate and systematize tongue color-related manifestations among patients with PCR-confirmed COVID-19 infection. **Material and Methods:** This retrospective study included analysis of tongue images obtained from patients with PCR-confirmed COVID-19 infection. Evaluation of coronavirus disease severity (mild, moderate, severe, critical) was provided, considering clinical symptomatology and results of laboratorial and instrumental diagnostic methods. Each picture was analyzed considering the parameters of color of the tongue and color of the tongue plaque by two dental specialists. Cochran-Armitage test for trend was used to evaluate associations between the tongue color and tongue plaque color, and coronavirus disease severity. **Results:** The most prevalent tongue colors were pale pink, red and dark red (burgundy color). A total of 64.29% of patients with mild disease demonstrated pale pink color of the tongue. Patients with moderate coronavirus disease were characterized with the adverse trend: 62.35% of them presented with red-colored tongue, while in 37.64% of cases, the tongue was pale pink. Severe COVID-19 patients, almost in 90% of the cases, had either red or burgundy color of the tongue. **Conclusion:** SARS-COV-2 infection is not manifested by tongue-targeted or tongue-specific signs and features; however, coronavirus disease itself provokes changes within the tongue color and tongue plaque color similar to those registered during other internal pathologies.

Keywords: Coronavirus Infections; Severe Acute Respiratory Syndrome; Tongue.

Introduction

State of health could be indirectly evaluated by the analysis of the tongue color and the color of plaque accumulated on it before and during the clinical course of different internal diseases [1-5]. A clean tongue without plaque is a sign of a healthy person, while some of the somatopathologies are characterized with adjacent tongue manifestations, which either could be pathognomonic or included within the set of general symptoms [6].

Tongue-related features could be used as valuable diagnostic signs for health evaluation purposes under the machine learning processing approach, which includes the implementation of multi-modal algorithms to relate tongue changes (as image biomarkers) with other symptoms and pathological conditions (including coronavirus disease) [7-10]. Nevertheless, tongue features seem to be mostly related to the syndrome rather than the disease itself [11]. Previously it was found that lung diseases, such as tuberculosis, amyotrophic lateral sclerosis, a chronic obstructive pulmonary disease characterized with corresponding tongue manifestations [12-15].

Globally at the date of 13th of January 2021, there have been more than 90 million confirmed cases of COVID-19 reported to WHO, including 1,954,336 deaths [16]. In Ukraine, more than 1 million confirmed cases of COVID-19 with 20,214 deaths have been reported to the above-mentioned date [16]. Considering the COVID-19 pandemic situation, ongoing study of the manifestations related to this pathology within the oral cavity, particularly on the tongue, remains as an important practical and scientific objective [17-20]. The most common oral symptoms among persons who have suffered from a coronavirus infection include punctate hemorrhages in the form of red bumps, candidiasis, ulcers and various other lesions of the tongue and mucous membranes [17-19].

Chemosensory dysfunctions regarding smell and taste are considered one of the most prevalent screening signs among patients with influenza-like symptomatology, who could potentially be diagnosed as COVID-positive [21-23]. The nature of the COVID-related taste disorder remains under further investigation since this sign could be conceivably associated with developing hyposalivation, changes in saliva composition and neurological alterations [21,22].

Several studies have already investigated tongue-related features as the symptoms of COVID-19 and found statistically significant differences between COVID-19 patients and healthy people [24,25]. But there are only a small number of publications that address the topic of COVID-associated changes of the tongue related to the coronavirus disease severity. Previously it was found that the level of greasy coating and tenderness of the tongue are the most diagnostically sensitive signs for COVID-19 severity differentiation [26]. Pang et al. [26] concluded that studies regarding the quantification of tongue manifestations during coronavirus disease should be provided with the purpose to improve diagnostics, differentiation, and treatment of COVID-19 during the present pandemic era.

This study aimed to evaluate and systematize tongue color-related manifestations among patients with PCR-confirmed COVID-19 infection considering disease severity.

Material and Methods

Study Design and Data Collection

The design of the study was retrospective and included analysis of tongue images obtained from patients with PCR-confirmed COVID-19 infection. Analyzed patients' cohort was formed out of persons hospitalized in the reorganized COVID-Department of Uzhhorod Regional Clinical Hospital with COVID-

associated symptomatology and further identified having SARS-COV₂ by PCR method using oropharyngeal and nasal swabs samples.

Tongue pictures were obtained by the infectious disease specialist, who was directly providing treatment for COVID-19 patients in the corresponding department using smartphone devices without considering some specific technical characteristics of photodocumentation due to the relevant sanitary restrictions limited possibilities to obtain high-quality photos. Each image was taken with no magnification effect and no filters used. As a result, tongue photos were received with respect to all implemented restrictions and sanitary requirements while not compromising any affiliated risk of infection for medical personal or patients.

Obtained tongue pictures were coded and anonymized with the additional description provided just for the severity of coronavirus disease associated with each photo at the day of its' reception, age, and gender of the patient. Evaluation of coronavirus disease severity (mild, moderate, severe, critical) was provided by professional infectionists due to the World Health Organization recommendations [27], considering clinical symptomatology of the patients and results of additional laboratorial and instrumental diagnostic methods.

Binary informational blocks in the amount of 167 pairs consisted of tongue photo in *.jpeg format and text info with a description of verified COVID-19 severity, patient's age and gender were sent to the Department of Therapeutic Dentistry (Uzhhorod National University) via restricted access to Google Drive folder. Each picture was analyzed considering the parameters of color of the tongue and color of the tongue plaque by two dental specialists (experts) independently. Experts were assigned from the personal of the Department of Therapeutic Dentistry and Department of Prosthetic Dentistry (Uzhhorod National University) (chosen experts were previously calibrated by taking participation in various epidemiological and clinical studies).

With the purpose to exclude the effect of the interpretation error, which could occur during expert evaluation and comparison of study object (tongue image) with some addressable classification' referent, dental specialists who provided analysis of the tongue pictures were asked to describe them considering the color of the tongue or the color of tongue plaque without referring to any classification or categorization system by one or two color-associated adjective words.

Out of 167 tongue images, 32 were excluded from the study sample due to the presence of blurring effect, critical contrasting, cropping of some tongue part on the picture and moving-associated artefacts.

Data Analysis

Statistical argumentation of obtained differences considering correspondences between the tongue color and tongue plaque color to COVID-19 severity within groups of patients with mild, moderate and severe stages of the coronavirus disease was based on inter-groups' prevalence parameters comparison [28-30]. Cochran-Armitage test for trend was used to evaluate associations between the tongue color and tongue plaque color and coronavirus disease severity [31,32]. Such an approach was modified from Pang et al. [26], at which authors used the Chi-square test for trend analysis. Registered outcome values were validated as statistically significant if $p < 0.05$. Reproducibility of two dental specialists who provided analysis of tongue images considering the evaluation of the tongue color and tongue plaque color was calculated by the Cohen's kappa, parameters of which reached 0.83 ± 0.06 and 0.80 ± 0.09 respectively, while inter-rater percentage agreement was 86.7% and 83.4% respectively [32,33]. Final categorization of obtained tongue images, received description and numerical values were provided due to the following targeted parameters: tongue color, tongue plaque color, patient's age group (due to the 10 years period distribution), patient's gender (male/female).

Statistical data processing was held within Microsoft Excel software (Microsoft Office 2019, Microsoft Corp., USA) with the additional use of add-ins, such as Analyse-it (Analyse-it Software Ltd., Leeds, UK) and XLSTAT (Addinsoft Inc., New York, N.Y, USA).

Ethical Aspects

This study was previously affirmed by the Ethical Committee of Faculty of Dentistry at Uzhhorod National University 2020 (Protocol No. 1/10092020). All the patients signed modified informed consent form included in their general medical documentation, which contained the section about the possibility of using their medical data with the research and investigation purposes for the improvement of medical care quality during COVID-19 era while providing full guarantee and security of personal issues (including obligatory anonymization) and in the correspondence of established ethical principles.

Results

Among 135 patients, who's tongue images were analyzed, 64 were males (47.41%) and 71 were females (52.59%). The average age was of the patients was 48.7 ± 13.2 years varying in the range from 18 to 82 years old. Distribution of patients regarding age criteria presented in Table 1.

Table 1. Distribution of patients with PCR-confirmed cases of COVID-19 due to the age criteria.

Age Group (Years)	N	%
<20	8	5.88
21-30	15	11.03
31-40	17	12.50
41-50	28	20.50
51-60	23	16.91
61-70	17	12.50
71-80	14	10.29
> 80	13	9.56

“The distribution of patients regarding coronavirus disease severity was as follows: 14 (10.37%) patients with mild coronavirus disease severity; 85 (62.96%) patients with moderate coronavirus disease severity; 36 (26.67%) patients with severe coronavirus disease; and no patients with critical severity of pathology were observed in this study.

The most prevalent tongue colors were pale pink, red and dark red (burgundy color). A percentual of 64.29% of patients (n=9) with mild disease demonstrated pale pink color of the tongue, while the rest, 35.71% (n=5), had a red-colored tongue. Patients with moderate coronavirus disease were characterized with adverse trend: 62.35% of them (n=53) presented with red-colored tongue, while in 37.64% cases (n=32), the tongue was pale pink. Severe COVID-19 patients almost in 90% of the cases (n=32) had either red or burgundy color of the tongue, while the rest of the patients (11.11%; n=4) in this group had pale pink tongue color (Figure 1).

A total of 91.11% of patients (n=123) were characterized by the presence of tongue plaque. Patients with no tongue plaque were distributed among those having mild (n=9) and moderate (n=3) coronavirus disease, while 100% of patients with severe pathology demonstrated the presence of tongue plaque.

The most common colors of the tongue plaque were white, gray, yellow. Among patients with mild disease, no plaque was found in 64.28% of patients (n=9), while the other 35.71% of patients (n=5) had a white plaque. Patients with moderate disease severity were mostly characterized with white (15.29%; n=13), yellow (25.88%; n=22) and gray (55.29%; n=47) plaque. A total of 3.52% of patients (n=3) with moderate disease

demonstrated no plaque present on the tongue. Patients presented with severe coronavirus disease had a white plaque in 27 cases (75.0%) and yellow plaque in 9 cases (25.0%). Visually amount of white plaque in severe patients' cases was thicker than in mild or moderate diseases cases (Table 2 and Figure 2).

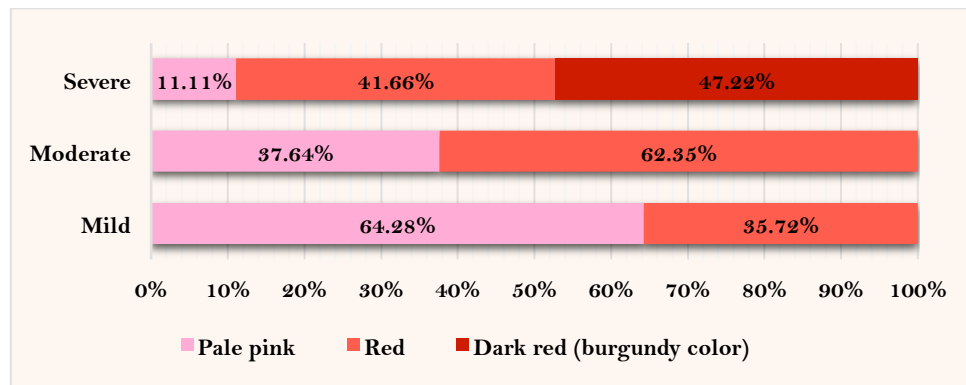


Figure 1. Distribution of tongue colors among COVID-19 patients with different disease severity.

Table 2. Tongue features related to coronavirus disease severity.

Tongue Features	Categories	Coronavirus Disease Severity		
		Mild N (%)	Moderate N (%)	Severe N (%)
Tongue Color	Pale Pink	9 (64.28)	32 (37.64)	4 (11.11)
	Red	5 (35.71)	52 (62.35)	15 (41.66)
	Dark Red (Burgundy Color)	-	-	17 (47.22)
Tongue Plaque Color	White	5 (35.71)	13 (15.29)	27 (75.0)
	Grey	-	47 (55.29)	-
	Yellow	-	22 (25.88)	9 (25.0)
	No Plaque Present	9 (64.28)	3 (3.52)	-



Figure 2. (A) Patient with mild severity of coronavirus disease: red tongue with no plaque; (B) Patient with mild severity of coronavirus disease: pale pink tongue with white plaque; (C) Patient with moderate severity of coronavirus disease: red tongue with no plaque; (D) Patient with moderate severity of coronavirus disease: pink tongue with grey plaque; (E) Patient with moderate severity of coronavirus disease: red tongue with yellow plaque; (F) Patient with severe coronavirus disease: pink tongue with white plaque; (G) Patient with severe coronavirus disease: pink tongue with white plaque; (H) Patient with severe coronavirus disease: red tongue with white plaque.

Statistically significant differences were observed regarding tongue color among groups of patients with different coronavirus disease severity ($p < 0.05$), while an analogical trend was also noted considering tongue plaque color between mild and severe forms ($p < 0.05$) and between moderate and mild forms ($p < 0.05$). Patients within age groups of 41-50 years, 51-60 years, 61-70 years, 71-80 years and more than 80 years always demonstrated the presence of tongue plaque and more prevalent red and dark red color of the tongue, supreme prevalence of which was statistically significant ($p < 0.05$). A similar trend was also noted regarding grey and yellow tongue plaque among the above-mentioned age groups ($p < 0.05$). No gender-associated differences were found regarding changes of tongue color and tongue plaque color within analyzed study sample ($p > 0.05$).

Discussion

All the signs, which potentially could be classified as COVID-distinctive, should be carefully verified regarding their specificity and sensitivity as diagnostic markers, with further in-depth analysis of such at different biological organizational levels.

Considering oral mucous changes during COVID-19, some clinical cases demonstrated the development of oral ulceration and blisters formation, even though such also could be identified during other virus diseases [17,19,21,22]. Moreover, it should be noted that the immunological status of patients with a pronounced viral infection commonly is compromised, which also could play a role in the secondary development of oral lesions associated with underlying pathology [22]. In the brief literature review, it was found that the most frequently affected zones of the oral cavity during coronavirus disease include areas of hard palate, dorsum of the tongue and labial mucosa [17], while specifically, ulcers were the most commonly noted at the dorsum of the tongue.

Several researches demonstrated tropism relation of SARS-COV2 to the tongue and salivary glands due to the expression of angiotensin-converting enzyme 2 by their epithelial cell [34,35]. In 8 described cases of COVID-19 infection, Brandão et al. [34] collected next tongue-related manifestations: clinical case 1 – painful ulcerations and necrotic ulceration of anterior dorsal tongue surface; clinical case 2 – shallow necrotic lesions of anterior dorsal tongue part; clinical case 3 – painful ulcer lesion projected at the right margin of the tongue; clinical case 4 – no specific tongue changes were described; clinical case 5 – multiple ulceration elements located at the apex and lateral border of tongue; clinical case 6 – no specific tongue changes were described; clinical case 7 – ulcer located at ventral part of tongue; clinical case 8 – aphthous-like ulceration with necrotic crust localized above it projected at lateral tongue surface. Provided research highlights the potential role of tongue and salivary glands as target organs regarding coronavirus invasion [34].

The biggest study related to the tongue's manifestations among COVID-patients was provided by Pang et al. [26] and included 1043 persons with different levels of coronavirus disease severity. Authors have found that tongue color changes from pale to purple were related to disease progression, analogically to tongue coating color from white to yellow and grayish-black [26]. Relations between such tongue features and coronavirus disease severity were statistically significant ($p < 0.001$) [26]. An analogical trend was also noted in our study since most patients with mild disease had pale pink tongue color, while patients with severe COVID-19 infection demonstrated red and burgundy tongue color. But considering tongue plaque color, we have found yellow and gray plaque mostly presented among patients with moderate disease, while yellow and white were mostly registered among severe pathology cases. In Pang et al. [26] study, 54.90% of patients with a moderate form of the disease were characterized with a white coating and 44.80% with yellow coating, while

44.90% with severe pathology were characterized with white coating, 53.74% with yellow coating and 1.36% with grayish-black coating. So main difference between our and Pang et al. study [26] was related due to the distribution of tongue plaque colors. Such discrepancies in results could be augmented by the fact that in our study, we have not used any classification system of tongue features for manifestations differentiation, but in Pang et al. study [26], researchers used previously developed table included in Diagnostics of Chinese Medicine and Color Atlas of Chinese Medical Tongue Diagnosis. Such an approach in Pang et al. study was highly reasoned since images of the tongue further could be analyzed in a specifically designed Tongue Features Objective Research System (TFORS) [26], while in our study, we wanted to exclude the effect of interpretation error and identify the condition of each analyzed tongue on the image by fact without referring it to any classification or categorization systems. Analogically to Pang et al. study [26], we have found that patients of older age (above 40 years) are characterized with more prevalent red and dark red tongue color, present tongue plaque and yellow coating of such. Also, the amount of identified tongue plaque among COVID-positive patients was found to demonstrate greater visual accumulation in patients older than 40 years and among those with severe pathology.

Dos Santos et al. [19] presented results of ongoing COVID patient's monitoring supported by the detailed analysis of tongue changes: 1) after four weeks of hospitalization patient developed white plaque on tongue dorsum (treated with the antifungal drug but with no regression effect) with multiple pinpoint yellowish ulcers (potentially herpetic lesion); 2) two weeks after that patient was observed with a developed geographic tongue of severe manifestation form, but with no pain symptoms (areas of atrophy with adjacent yellow-white lesions elevated above the surface level), white plaque covering was fully resolved; 3) geographic tongue of moderate form was noted 10 days after discharge (44 days after hospitalization).

Such an approach of ongoing in-detail analysis of intraoral COVID-related signs used by Dos Santos et al. [19] provides a variety of perspectives for further research since such methodology seems reasonable for categorization and comparative analysis of tongue changes during coronavirus disease onset, progression and resolution. In our study, we provided just analysis of correspondence between registered COVID-19 severity and tongue color-associated manifestations, but our complex research is ongoing and at the nearest publication, it will be possible to provide results for the above-mentioned comparative analysis of COVID-associated oral features at different stages of pathology progression.

Within the case series study structured as a Web-based questionnaire among 140 COVID-patients, just 9 persons demonstrated plaque-like changes of tongue and 4 reported swelling of the tongue [36]. Also, the authors reported a statistical correlation between plaque-like changes of the tongue and altered tongue sensation ($p < 0.001$) [36]. Based on the described design of the study, all patients included in the Biadsee et al. [36] research were characterized with mild symptoms of coronavirus diseases (categorized by WHO joint report), while in our study patients demonstrated mild, moderate and severe clinical symptoms of COVID-19, associated with corresponding facts of white or no plaque present on the tongue during mild severity of pathology.

In three clinical cases described by Díaz Rodríguez et al. [37], two patients demonstrated following tongue changes which potentially could be associated with COVID-19 infection, general state of immunosuppression or influence of adjacent factors (such as stress or self-related habits): bilateral tongue surface atrophy accompanied with lateral dorsum depapillation, and tongue surface atrophy associated with fungal patch-like lesions (pseudomembranous candidiasis) and fissures localized at tongue dorsum. In addition, several studies also demonstrated the following tongue manifestation during COVID-19: small painful

ulcerations with non-regular borders on the reddish background of anterior tongue, asymptomatic ulcers at the dorsum of the tongue, multiple macules of various size, aphthae on the ventral tongue side, tongue papilla inflammation [17,38], asymptomatic purple bulla [39].

Riad et al. [40] presented an analysis of 26 COVID-positive patients with no adjacent somatopathologies and mild or absent respiratory symptoms in which they noted the occurrence of ulcers on the dorsum, side and ventral parts of the tongue with different onset time. Tongue ulcers appeared mostly 5 days after PCR-testing (among 53.8% patients), with 1-7 lesions per patient varying by 1-5 mm in size [40]. Researches also noted an interesting finding, that the localization of ulcers on the tongue was the only one in the oral cavity with such lesions absent on other oral mucous regions [40]. Irregular tongue ulcer also was mentioned as being an inaugural sign among COVID-19 patients [18].

Asymptomatic COVID-19 case presented by Corchuelo and Ulloa [41] was characterized with white zones on the posterior tongue portion and bacterial plaque accumulation at the middle third of the tongue, suggesting candidiasis diagnosis, which resolved two weeks after supportive treatment by antifungal drugs and oral hygiene measures.

In da Silva Pedrosa et al. [22] review, the authors also mentioned that xerostomia associated with reduced salivary flow among COVID-patients was noted to become more prominent with the age. In our study, we could not relate potentially present age-associated lower salivary flow with greater deposition of tongue plaque because of sanitary restrictions regarding the possibility of providing structured clinical investigation among COVID-positive patients, but such dependencies could be logically prognosticated. Also, older patients could be characterized by the possible presence of adjacent internal comorbidities, which could impact the tongue condition independently of the presence or absence of coronavirus disease.

Nevertheless, the diagnostic role of tongue during COVID-19 infection remains under debate. Resected specimen of ulcerated squamous cell lesion of the tongue of a patient with coronavirus disease demonstrated the presence of SARS-CoV-2 strain's RNA [42]. On the other hand, tongue swabs were characterized with relatively lower sensitivity for detecting SARS-CoV-2 than swabs obtained from nose or mid-turbinate [43].

For safety reasons, many physicians refrain from examining the oral cavity of patients with confirmed COVID-19. Most patients do not remove the mask from the face at all while being in the hospital. Patients themselves may simply ignore the changes of the tongue on the background of many other manifestations of COVID-19 in the acute form. Photodocumentation of tongue condition represents argued approach for its further analysis regarding color of the tongue and color of the tongue plaque. Due to the quarantine restrictions, photoregistration of the tongue could be provided either by the patient himself or by the staff directly taking part in the treatment management of COVID-patients, with possible further transfer of such images to the dental specialist considering all the ethical aspects and issues related to personal data safety.

Ethical aspects of personal medical data use (including personal data safety issues) are reasoning the need for developing specific patient informed consent form under the condition of COVID-19 pandemic due to which doctors could investigate anonymized and blinded patients' information for the acceleration of diagnostics and treatment, provision of rapid response in life-threatening cases and relevant upgrowth of the evidence base.






Limitations of the present study related to the sanitary restrictions implemented to reduce COVID-19 spread within hospital conditions, which also influenced the possibility of more detailed analysis of other tongue-related changes, including the thickness of present plaque, tenderness of the tongue, and its' condition

during palpation. Nevertheless, we have found that even visually identified changes of the tongue color and tongue plaque color could support coronavirus disease severity differentiation when combined with other clinical symptoms. Another limitation of present research related to the study's design, since we have evaluated tongue-associated features only once for each patient at the specific severity of coronavirus disease relevant for some certain moment. But in future studies, we will provide results of ongoing monitoring of tongue manifestations during long period screening, which will help us to verify how the color of the tongue and color of the tongue plaque are changing during pathology onset, progression and further resolution. Also, we have obtained information about coronavirus disease severity of each patient included in the study sample from the infectious disease specialists via digital information transferring to reduce the risk of infection for dentists, but in the future, it would be beneficial to analyze medical documentation of such patients with possibility to find some potential relationships not only among tongue manifestations and severity of pathology, but also among tongue signs and some other COVID-related clinical and laboratorial parameters changes.

Conclusion

Considering limitations of provided study and restrictions related to the lack of dental screening methodology developed specifically for COVID-positive patients, it could be concluded that SARS-COV-2 infection is not manifested by tongue-targeted or tongue-specific signs and features; however, coronavirus disease itself provoke changes within the tongue color and tongue plaque color similar to those registered during other internal pathologies. Taste disturbances remain the most diagnostically-prominent tongue-related symptom during COVID-infection, nevertheless conclusion about the absence of other high-avid tongue signs during coronavirus disease should be made with caution, since the corresponding database continues to grow and some pathology-specific manifestations could be recognized at system-, organ- or tissue-levels among greater study cohort or during further epidemiological studies. Due to the received data, we may hypothesize that tongue color and color parameters of tongue plaque related to the COVID-infection severity with positive type of interrelation: red tongue color and prominent white-yellow tongue plaque were identified the most frequently among severe disease cases. However, further clinical investigations should be provided to distinguish tongue-related manifestations on such, caused specifically by COVID-infection, and such, associated with the effect of provided treatment.

Authors' Contributions

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MG		https://orcid.org/0000-0002-7482-3881	Conceptualization, Validation, Formal Analysis, Investigation, Data Curation, Writing - Original Draft, Visualization and Supervision.
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All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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None.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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