

Temporomandibular disorder subtypes, emotional distress, impaired sleep, and oral health-related quality of life in Asian patients

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Abstract

Objectives: This study determined the differences in emotional states, sleep and oral health-related quality of life (OHRQoL) between patients with pain-related and intra-articular Temporomandibular disorders (TMDs), and associated emotional symptoms with sleep and OHRQoL.

Methods: Participants were recruited from a tertiary TMDs referral centre. The Depression, Anxiety, Stress Scales-21 (DASS-21), Pittsburgh Sleep Quality Index (PSQI) and Oral Health Impact Profile-TMDs (OHIP-TMDs) were used to assess emotional states, sleep and Oral health-related quality of life (OHRQoL), respectively. TMD-related and sociodemographic data were also gathered. Patients were divided into pain-related (PT), intra-articular (IT) and combined TMDs (CT) groups based on the Diagnostic Criteria for TMDs. Data were analysed using one-way ANOVA, Chi-square test, Pearson's correlation and logistic regression analysis with the significance level set at $P < .05$.

Results: Data from 1079 participants with a mean age of 29.6 ± 14.2 years were appraised (93.3% response rate). The severity/prevalence of emotional distress, impaired sleep and OHRQoL of the PT/CT groups were higher than the IT group. Moderate-to-strong inter-relationships between emotional, sleep and OHRQoL variables were more explicit for participants with painful TMDs. Logistic regression analysis demonstrated that painful TMDs were associated with higher stress and poorer OHRQoL with odds ratios (ORs) of 1.482 (95% CI 1.039-2.114) and 6.502 (95% CI 3.201-13.210), respectively.

Conclusions: Painful TMDs are associated with higher levels of emotional distress, sleep and OHRQoL impairments. Routine evaluation of the biopsychosocial distress, especially stress and life quality, is necessary for patients with painful TMDs.

KEYWORDS

emotions, oral health, quality of life, sleep disturbance, temporomandibular disorders

1 | INTRODUCTION

Temporomandibular disorders (TMDs) is a collective term encompassing a heterogeneous group of problems affecting the masticatory musculature, temporomandibular joints (TMJs), and/or associated structures. TMDs manifest as jaw joint noises, jaw pain and dysfunction. They are the most common cause of debilitating chronic pain in orofacial region.¹⁻³ The aetiology of TMDs is multi-faceted,⁴ and psychological factors, particularly depression and somatic awareness, were significant predictors of first-onset TMDs.⁵ Recently, studies have reported poorer sleep quality in TMD patients, especially those with chronic pain. Furthermore, sleep-related disturbance interacts with emotional distress to predispose, initiate, and/or perpetuate TMDs.⁶⁻⁸ Oral health-related quality of life (OHRQoL), is a multi-dimensional concept compatible with the biopsychosocial model of illness, entailing an individual's comprehensive appraisal of the functional, physical (pain/discomfort), psychological and social factors relating to his/her health.⁹ Studies have shown that TMDs negatively affect life quality and their impact might vary with different TMD symptoms.¹⁰⁻¹²

Earlier research had focused mainly on the inter-relationships between depression/somatization and TMDs, with limited emphasis on other emotional states such as stress and anxiety.⁴⁻⁶ However, chronic stress and anxiety may lead to depression as well as sleep disturbance.^{13,14} Although the impact of TMDs on OHRQoL had been investigated, most studies involved Caucasian samples and few had endeavoured to differentiate the influence of pain-related and intra-articular TMDs. The limited Asian studies also involved relatively small sample sizes.¹⁰⁻¹² Moreover, previous studies had employed generic QoL measures like the Short Form-36 Health Survey (SF-36) and Oral Health Impact Profile (OHIP). These generic measures may not contain items relevant to or prevalent in TMDs ensuing in 'floor effects' and 'insignificant associations'.¹⁵ The OHIP-TMDs, a condition-specific OHRQoL measure, was specifically developed to address this lack.^{12,16}

The Research Diagnostic Criteria for TMDs (RDC/TMD)¹⁷ has been superseded by the evidence-based Diagnostic Criteria for TMD (DC/TMD), which presents improved validity for pain-related TMDs.¹⁸ Based on DC/TMD, common TMDs are classified into pain-related and intra-articular TMDs. Given the paucity of investigations based on the DC/TMD and TMD-specific OHRQoL measures, more studies, especially large-scale ones, are merited. Accordingly, the objectives of this study were as follows: (a) to determine the differences in emotional states, sleep disturbance and OHRQoL between patients with different TMD subtypes, and (b) to ascertain the relationships between emotional states, sleep and OHRQoL in TMD patients.

2 | METHODS

The study was approved by the Biomedical Institution Review Committee of Peking University School of Stomatology

(PKUSSIRB-201732009). A minimum sample size of 432 for three TMD diagnostic groups was established a priori with the G*Power software Version 3.1.9.3 based on an ANOVA-model with a small effect size of 0.10, an alpha error probability of 0.05 and power of 95%. The minimal sample size was doubled to compensate for possible nonparticipation and incomplete surveys. In the present study, a total of 1,156 patients in the TMD and Orofacial Pain Center, Peking University School and Hospital of Stomatology from May 2018 to December 2019 were invited to participate. The exclusion criteria were as follows: (a) history of major trauma or operations; (b) history of drug abuse or major psychiatric disorders; (c) presence of uncontrolled systemic or metabolic diseases; (d) consumption of medications with central nervous system effects in the past two weeks; (e) non-TMD joint or muscle diseases; and (f) inability to understand the questionnaires independently or illiteracy.⁶ Written informed consent was obtained from all participants or their guardians if younger than 18 years old before administering a questionnaire containing information on sociodemographic parameters, medical history and the various measures of interest. DC/TMD history taking and clinical examination were performed by a trained TMD specialist. Diagnostic imaging including cone beam computerized tomography and magnetic resonance imaging were performed to confirm intra-articular disorders where appropriate. TMD diagnoses were established using the DC/TMD.¹⁸

Negative emotional states were evaluated with the Chinese version of the Depression Anxiety and Stress Scale-21 (DASS-21).^{19,20} It consists of 21-items and three domains, namely depression, anxiety and stress. Higher domain scores indicate greater emotional distress and cut-off points for different severity classifications (ie normal to extremely severe) are presented in the DASS manual.^{19,21} Sleep quality was assessed with the Chinese version of the Pittsburgh Sleep Quality Index (PSQI),²² which consists of 19-items and seven domains including subjective sleep quality, sleep latency/duration/efficiency/disturbances, use of sleeping medication and daytime dysfunction. A total PSQI score (t-PSQI) greater than 6 was used as the cut-off for poor sleep quality. Larger t-PSQI scores suggest worse sleep quality. OHRQoL was examined with the Chinese version of the OHIP-TMDs, which comprised 22-items and seven domains including functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap.²³ Larger total OHIP-TMDs scores (t-OHIP-TMDs) indicate poorer OHRQoL.²⁴ For this study, cut-off scores for moderate-to-extremely severe emotional symptoms (ie depression scores ≥ 14 , anxiety scores ≥ 10 , stress scores ≥ 19) along with t-PSQI scores ≥ 10 and t-OHIP-TMDs scores ≥ 66 were considered positive for emotional distress, impaired sleep and OHRQoL respectively as advocated in prior studies.^{6,12,25}

According to the DC/TMDs, pain-related TMDs include myalgia, arthralgia and headaches attributed to TMDs while intra-articular TMDs encompass disc displacements with reduction with/without intermittent locking, disc displacements without reduction with/without limited opening, degenerative joint disease and subluxation.¹⁸ The participants were subsequently allocated into the

following three subgroups: pain-related TMDs (PT), intra-articular TMDs (IT) and combined TMDs (CT) (ie both pain-related and intra-articular TMDs).

P-P (probability-probability) plots were used to explore data normality. As DASS-21, PSQI and OHIP-TMDs data were all normally distributed, one-way ANOVA with the Tukey post hoc test was used to compare age, emotional states, sleep and OHRQoL scores among the three TMD subgroups. Chi-square test was used to compare gender distribution and frequency of emotional distress, impaired sleep and OHRQoL. Pearson's correlation was used to ascertain the inter-relationships between DASS-21, t-PSQI and t-OHIP-TMDs scores. Stepwise logistic regression analysis was used to explore the independent associations between emotional states, sleep quality as well as OHRQoL and pain/joint-related TMDs. All data were analysed using SPSS software 24.0 (IBM Corporation) with significance level at $P < .05$.

3 | RESULTS

About 93.3% (1079/1156) of the patients qualified for and consented to participation. The mean age of the participants was 29.6 ± 14.2 years (range 11 to 86 years) and 79.3% were females. Distribution of the TMD subgroups were as follows: pain-related TMDs (PT) group 10.8% (116/1079); intra-articular TMDs (IT) group 51.9% (560/1079); and combined TMDs (CT) group 37.3% (403/1079). Mean age was the greatest for the PT group (40.0 ± 16.6 years) and smallest for the IT group (25.9 ± 11.3 years) with the CT group in between (31.8 ± 15.2 years) ($P < .001$). A female preponderance was observed for all three subgroups ($P < .05$).

Mean DASS-21 scores for the three TMD subgroups are shown in Table 1. Both the PT and CT groups had greater depression, anxiety and stress scores than the IT group ($P < .05$). No significant difference in symptom scores was, however, noted between the PT and CT groups.

Table 2 shows the mean t-PSQI and domain scores for the various TMD subgroups. Ranking of t-PSQI scores was as follows: PT group >CT group >IT group. Significant differences were observed between the three TMD subgroups. PSQI domain scores for the PT/CT groups were generally greater than the IT group.

Mean scores for total and domain OHIP-TMDs scores are displayed in Table 3. Both the PT and CT groups had higher t-OHIP-TMDs scores than the IT groups ($P < .001$). No significant difference

was, however, noted between the PT and CT groups. Similar significant differences were also observed for all domains except for functional limitations. For functional limitations, the ranking of the domain scores was as follows: CT group >PT group >IT group ($P < .001$).

As there were no significant differences between the PT and CT groups for the majority of variables evaluated, the two subgroups were pooled together and the participant cohort was afterwards dichotomized into those with painful (WP) and nonpainful (NP) TMDs. The occurrence of emotional distress, impaired sleep and OHRQoL was greater in the WP group (depression 22.0%, stress 22.9%, disturbed sleep 20.8% and impaired OHRQoL 13.9%) than the NP group (depression 12.7%, stress 13.9%, disturbed sleep 12.9% and impaired OHRQoL 1.8%), apart from anxiety ($P < .001$).

Associations between depression, anxiety, stress, sleep quality and OHRQoL for WP and NP groups are presented in Table 4. Based on the classification of correlation coefficients (r) by Dancey et al (weak 0.1-0.3; moderate 0.4-0.6; strong 0.7-0.9),²⁶ for both WP and NP groups, moderate to strong correlations were found between OHRQoL and emotional states, sleep quality and emotional states, as well as between the various emotional states ($P < .01$). However, a weak correlation was noted between OHRQoL and sleep quality. Generally, correlation coefficients were larger in the WP group.

Stepwise logistic regression analyses showed that moderate to severe stress and poor OHRQoL were associated with higher odds in WP group when compared to the NP group. The results were still significant even after controlling for the confounding effect of other variables including age, sex, disease duration, other emotional states, sleep and OHRQoL (Table 5). Participants with painful TMDs were often older and those in the WP group usually sought treatment earlier than the NP group.

4 | DISCUSSION

This study is probably the largest cross-sectional investigation on Asian TMD patients using the DC/TMD protocol. Patients experiencing painful TMDs (ie PT/CT groups) showed more severe emotional symptoms, poorer sleep and OHRQoL. Correlations between emotional states, sleep and OHRQoL were largely stronger for the painful TMD groups than the nonpainful ones. Furthermore, stress and impaired OHRQoL were independently and more closely associated with painful TMDs after controlling for other confounding factors.

TABLE 1 Comparison of emotional scores among different subtypes of TMDs

		Pain-related TMD (n = 116)	Intra-articular TMD (n = 560)	Combined TMD (n = 403)
Depression	Mean \pm SD	9.3 \pm 11.2 ^a	5.1 \pm 7.3 ^b	7.6 \pm 9.7 ^a
Anxiety	Mean \pm SD	10.1 \pm 9.7 ^a	7.9 \pm 7.6 ^b	9.2 \pm 8.4 ^a
Stress	Mean \pm SD	12.4 \pm 12.0 ^a	8.7 \pm 9.2 ^b	11.5 \pm 10.5 ^a

Note: a, b: one-way ANOVA with the Tukey post hoc test.

The same letter between the groups indicated no significant difference and different letters indicated significant differences.

		Pain-related TMD (n = 116)	Intra-articular TMD (n = 560)	Combined TMD (n = 403)
Subjective sleep quality	Mean ± SD	1.4 ± 0.1 ^a	1.1 ± 0.0 ^b	1.1 ± 0.0 ^b
Sleep latency	Mean ± SD	1.3 ± 0.1 ^a	1.0 ± 0.0 ^b	1.1 ± 0.1 ^{a,b}
Sleep duration	Mean ± SD	1.3 ± 0.1 ^a	0.9 ± 0.0 ^b	1.1 ± 0.0 ^a
Sleep efficiency	Mean ± SD	0.8 ± 0.1 ^a	0.3 ± 0.0 ^b	0.5 ± 0.0 ^c
Sleep disturbances	Mean ± SD	1.3 ± 0.1 ^a	1.0 ± 0.0 ^b	1.1 ± 0.0 ^c
Use of sleep medication	Mean ± SD	0.5 ± 0.1 ^a	0.2 ± 0.0 ^b	0.2 ± 0.0 ^b
Daytime dysfunction	Mean ± SD	1.7 ± 0.1 ^a	1.4 ± 0.0 ^a	1.5 ± 0.1 ^a
Global score	Mean ± SD	8.2 ± 0.3 ^a	5.9 ± 0.2 ^b	6.6 ± 0.2 ^c

Note: a, b, c: one-way ANOVA with the Tukey post hoc test.

The same letter between the groups indicated no significant difference and different letters indicated significant differences.

TABLE 2 Comparison of PSQI scores among different subtypes of TMDs

TABLE 3 Comparison of OHRQoL scores among different subtypes of TMDs

		Pain-related TMD (n = 116)	Intra-articular TMD (n = 560)	Combined TMD (n = 403)
Functional limitation	Mean ± SD	4.5 ± 2.4 ^a	3.2 ± 2.3 ^b	5.8 ± 1.9 ^c
Physical pain	Mean ± SD	9.2 ± 4.8 ^a	4.2 ± 3.6 ^b	9.1 ± 4.1 ^a
Psychological discomfort	Mean ± SD	9.7 ± 5.0 ^a	6.8 ± 4.5 ^b	9.7 ± 4.2 ^a
Physical disability	Mean ± SD	3.8 ± 2.2 ^a	2.4 ± 2.0 ^b	4.4 ± 2.0 ^a
Psychological disability	Mean ± SD	9.0 ± 6.1 ^a	5.3 ± 4.8 ^b	8.6 ± 5.2 ^a
Social disability	Mean ± SD	2.7 ± 2.7 ^a	1.2 ± 1.7 ^b	2.3 ± 2.1 ^a
Handicap	Mean ± SD	3.8 ± 2.7 ^a	2.0 ± 2.1 ^b	3.6 ± 2.4 ^a
Total OHIP	Mean ± SD	42.7 ± 21.8 ^a	25.2 ± 19.0 ^b	43.5 ± 19.6 ^a

Note: a, b, c: one-way ANOVA with the Tukey post hoc test.

The same letter between the groups indicated no significant difference and different letter indicated significant differences.

TABLE 4 Pearson correlations between emotional states, sleep and life quality

	t-OHIP-TMDs		Depression		Anxiety		Stress		t-PSQI	
	WP	NP	WP	NP	WP	NP	WP	NP	WP	NP
t-OHIP-TMDs	1	1								
Depression	0.554	0.470	1	1						
Anxiety	0.495	0.461	0.759	0.730	1	1				
Stress	0.597	0.526	0.816	0.782	0.807	0.782	1	1		
t-PSQI	0.357	0.337	0.464	0.448	0.485	0.436	0.492	0.429	1	1

Note: WP, With painful TMDs group; NP, With nonpainful TMDs group.

The DC/TMD protocol and diagnostic algorithms were adopted for this study considering its better validity compared with the RDC/TMD.¹⁸ The DASS-21 is the short-form version of the original DASS that consists of 42-items. It excludes common somatic and general distress contents from the depression measure but is still capable of differentiating anxiety from depression and stress. The reduced number of items translates to substantial time-saving and greater

subject acceptance.²⁷ The PSQI has been used to categorize sleep quality into good or poor in other TMD studies.²² The OHIP-TMDs was selected as it is a condition-specific OHRQoL measure designed to draw on the symptoms and impacts connected to TMDs.^{16,23}

The present study has addressed many inadequacies of previous studies by recruiting a large sample of Asian TMD patients, using the validated DC/TMD, and a TMD-specific OHRQoL measure.

TABLE 5 Logistic regression analysis for painful and nonpainful TMD patients

	With painful TMDs (n = 519)	With nonpainful TMDs (n = 560)	OR ^a (95% CI)	OR ^b (95% CI)
Age (y)	33.7 ± 15.9	25.9 ± 11.3	1.043 (1.033-1.053)**	1.042 (1.032-1.053)**
Disease duration (mo)	8.6 ± 16.8	15.2 ± 31.8	0.989 (0.983-0.994)**	0.988 (0.982-0.994)**
Stress	22.9% (119)	13.9% (78)	1.838 (1.342-2.519)**	1.482 (1.039-2.114)*
Impaired OHRQoL	13.9% (72)	1.8% (10)	8.859 (4.519-17.367)**	6.502 (3.201-13.210)**

Note: mo, month; OR, odds ratio; CI, confidence interval; a, unadjusted OR; b, adjusted OR.

* $P < .05$; ** $P < .01$.

Nonetheless, our study had several limitations. First, the cross-sectional design in the present study remains vulnerable to biases and definite causative relationships cannot be established between TMD subtypes and emotional states/sleep/OHRQoL. Second, the study only involved a convenience sample with participants recruited from a TMD centre in a tertiary hospital in northern China. The findings may be district- and selection-biased. Third, as not all participants received MRI examinations, some intra-articular disorders, particularly disc displacements without reduction without limited opening, might be inevitably missed out. Fourthly, we utilized only a sole TMD specialist for clinical examination and deriving the TMD diagnoses. While this may lead to more consistent TMD subtype diagnosis and categorization, a standardized error could be present. The diagnostic reliability of the single examiner could be confirmed via incorporating a second assessor.

Our findings showed that the type of TMDs significantly impacted the emotional states of participants. Participants with pain-related TMDs (PT/CT groups) had significantly higher depression, anxiety and stress scores than those with intra-articular TMDs (IT group). Findings were consistent with previous studies indicating that participants with pain showed the highest level of psychological distress among TMD samples.^{5,6,28} However, the prevalence of moderate-to-extremely severe anxiety was not significantly different between those with and without painful TMDs. This corroborated the work of Reiter et al, who suggested a less significant role of anxiety in TMDs.²⁹ Kindler et al also found that anxiety symptoms are specific for muscle pain while depression symptoms are specific for intra-articular pain.²⁸ However, after controlling for other confounding factors, only stress was independently associated with painful TMDs in this study. Participants with painful TMDs displayed high levels of stress, which could contribute to the other emotional states. Symptoms of anxiety and depression could be secondary to high levels of stress and therefore indirectly associated with TMDs.^{13,14} Previous studies have rarely emphasized the impact of stress on TMDs.⁴⁻⁶ Although the variance could also be explained in part by differences in TMD diagnostic criteria and sample populations, our findings highlighted the importance of stress in TMDs.

Sleep is essential for cognitive maintenance and normal physical as well as psychological functions. Our findings revealed that participants with painful TMDs had significantly poorer sleep quality, of which sleep efficiency and sleep disturbances were the most diminished sleep components. This corroborated previous work that

reported disturbed sleep to be a worrisome concern of TMD patients.^{6,7,10,30} Pain-related TMDs seems to have a greater impact on sleep quality^{6,7} and vice versa.³¹ A mutual vicious circle does exist between sleep and TMD pain. Therefore, it may be prudent to incorporate sleep assessment into routine TMD history taking and examination, especially as sleep improvement may improve TMD treatment outcomes.³²

The appraisal of TMD-specific OHRQoL presents a paradigm shift from the traditional biomedical model of medicine to the multi-dimensional biopsychosocial model of illness.⁹ Our findings showed that participants with painful TMDs had poorer life quality than those with only intra-articular problems. Findings were consistent with previous studies indicating that OHRQoL was related more with muscular and joint pain than with TMJ disc displacements in TMD patients.^{33,34} Chronic pain in TMD patients could adversely affect OHRQoL by negatively influencing physical and psychosocial domains, which has been considered the most important impact factors on OHRQoL.³⁵⁻³⁷ Furthermore, patients with both pain-related and intra-articular TMDs reported the lowest OHRQoL with functional limitations being the most compromised domain. Previous studies also reported similar outcomes, suggesting that the type and number of TMDs impacted OHRQoL differently.^{34,38} We speculated that most of the symptoms of intra-articular TMDs were painless and usually had no significant bearing on individuals' daily life. However, with the presence of comorbid pain-related TMDs, they would suffer from jaw pain and dysfunction simultaneously, which in turn strengthens their perception of pain, functional limitations and poorer OHRQoL.

Depression, anxiety, stress, sleep and OHRQoL showed moderate to strong correlations to each other, underpinning the complex and multi-directional relationships among these biopsychosocial factors in TMDs. Therefore, logistic regression analyses were performed to identify the independent associations between these factors and TMDs. The latter indicated that patients with painful TMDs suffered from higher stress and poorer OHRQoL than those with only intra-articular TMDs. Psychological well-being has been reported to be modulated by some recognized genetic factors such as catechol-O-methyltransferase (COMT) and adrenergic receptor $\beta 2$ (ADRB2). The imbalance of these genes can also contribute to enhanced analgesia in the central nervous system, and initiate TMD pain conditions thereafter.^{39,40} As the shared genes define both psychological profile as well as painful TMD conditions, patients

suffering from one disorder are also prone to the other. This may explain partially the high prevalence of psychological comorbidities associated with painful TMDs. OHRQoL is reported directly by patients without impositions by clinicians and is helpful towards the understanding of patients' subjective complaints and their potential impairments.⁴¹ Impaired OHRQoL still stands out as the most powerful factor associated with painful TMDs, underlying the magnitude of influence painful TMDs have on OHRQoL. This also draws attention to the importance of routine OHRQoL assessment in the management of painful TMDs.

The present study showed that intra-articular TMDs are the major TMD conditions, accounting for 51.9%, which was notably higher than that of a previous population-based TMD study.⁴² Besides racial/ethnic disparities and the wide age range of the participants, the variance may be explained partly by the recruitment of participants from a TMD and Orofacial pain centre where patients were referred for the management of complex intra-articular TMDs. The present study also showed a higher prevalence of nonpainful TMD in younger subjects. Previous systematic reviews suggest an increasing prevalence of disc displacements even in children and adolescents. The prevalence of intra-articular disorders in children/adolescents was as high as 16%.⁴³⁻⁴⁵ Moreover, TMJ degenerative joint disease (DJD) was also present in ~60% of joints with disc displacement without reduction, and the risk of developing DJD was ~5 times higher one month after the first onset of TMJ closed-lock.⁴⁶ A meta-analysis also indicated that older adults were more sensitive to mechanically associated pain than the younger ones.⁴⁷ The aforesaid were consistent with our findings on age-related differences among the various TMD subtypes and supported the higher frequency of nonpainful TMDs in younger persons.

In conclusion, participants with painful TMDs reported high levels of emotional distress, disturbed sleep and impaired OHRQoL. Stress and impaired OHRQoL were associated with painful TMDs, notwithstanding the complex and multi-directional relationships between emotional states, sleep and OHRQoL. The present study underscored the importance of stress management and OHRQoL assessment in the management of painful TMDs. Future work could include repeating this study in the general population and at multiple centres across the country. A longitudinal design should also be considered to clarify the time-ordering of the association between the aforementioned factors and TMDs.

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CONFLICT OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Jie Lei: Funding acquisition, Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Original draft preparation. Adrian U Jin. Yap: Conceptualization, Methodology, Data curation, Reviewing and Editing. Minjuan Zhang: Methodology, Investigation, Data curation, Formal analysis. Kai-Yuan Fu: Funding acquisition, Conceptualization, Methodology, Investigation, Data curation, Reviewing and Editing. All authors read and approved the manuscript.

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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