Cleft lip and palate severity and COVID-19 related risk factors in five Arab Countries

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Abstract

Background: Little is known about factors associated with the severity of cleft lip with or without cleft palate (CL/P) especially during COVID-19 pandemic with its dramatic changes.

Objectives: The aim of this multi-national study is to measure the association between CL/P severity, COVID-19 infection, and fear of COVID-19 in Five-Arab countries.

Methods: This cross-sectional study took place in major governmental hospitals in Five-Arab countries from November-2020 to April-2023. Participants were infants born with CL/P and their mothers who were in their 1sttrimester during the COVID-19 pandemic. Clinical examination was carried out and CL/P cases were grouped according to phenotype (cleft lip and palate (CLP) versus cleft lip (CL)), cleft extension (incomplete versus complete) and site (unilateral versus bilateral) to assess severity. Information on maternal COVID-19 infection and fear of COVID-19 were gathered.

Results: The study recruited 274 CL/P infants. Maternal COVID-19 infection during pregestation and 1st trimester was significantly associated with higher odds of CL/P severity (AOR=2.707; P=0.002) than mothers without COVID-19 infection. Using supplements during pregnancy showed protective effect (AOR=0.573; P=0.065).

Conclusion: Mothers infected with COVID-19 before and during pregnancy had more than two folds' higher odds of having infant with a more severe CL/P phenotype.

Introduction

Non-syndromic orofacial clefts (NSOFCs) are the most common orofacial congenital anomalies [1]. They are grouped into two categories: cleft lip with or without cleft palate (CL/P) and cleft palate alone (CP). CL/P is further sub-grouped into cleft lip (CL) and cleft lip and palate (CLP). CL/P may be unilateral or bilateral according to the site of lip clefting, and complete or incomplete according to the extension of lip and palate clefting. This yields a range of phenotypes with various levels of cleft severity that range from a notch in the lip to complete bilateral cleft lip and palate.

NSOFCs have detrimental consequences for infants and their parents, affecting their quality of life [2], and increasing with the increase of their severity. The severity of clefts is presented with wider space between the cleft sides, more significant extension, and/or bilateral occurrence of the cleft. This results in insufficiency of available tissue, deficiency of development, congenitally missing more teeth and changes in the craniofacial anatomy [3]. Consequently, the child suffers difficulties in feeding, sucking, swallowing, and speech. In addition, the operator encounters challenges in cleft corrections [4] and the dentist in fixing dental problems. Furthermore, the severity of clefts is associated with an increase in the complexity of social and psychological stress on both children and parents [5]. This emphasize the need for studies aiming to control cleft severity through understanding its etiology and related risk factors.

The different phenotypic presentations of NSOFCs reflect their heterogeneous and complex etiologies [6]. There are many risk factors that were reported to be associated with NSOFCs occurrence. However, there are limited studies that evaluated their relationship with its severity. These factors include genetic, environmental, and gene-environmental interactions. Environmental factors such as viral infections, poor nutrition, exposure to tobacco smoke, alcohol, medications, stress in early pregnancy and consanguinity are important factors in NSOFCs etiology [7]. A recent meta-analysis showed a significant relation between maternal stress during pregnancy and having a child with NSOFC [8]. In addition, COVID-19 infection was suggested to have teratogenic effect by invading human cells' Angiotensin-converting enzyme receptor 2 (ACE2) that could result in neurodevelopmental malformations [9]. However, previous studies did not find a direct relationship between COVID-19 infection and NSOFC [10]. Besides, COVID-19 pandemic was reported to increase the stress in mothers and pregnant woman [11]. In addition, studies have shown an association between COVID-19 infection and stresses [12] and some oral conditions that can potentially heal or reverse over time; but, there is less focus on the impact of COVID-19 infection and stresses on irreversible or congenital oral conditions

Although the etiology of NSOFC was previously heavily investigated, little is known about the risk factors associated with greater CL/P severity, aside from older parental age and family history of CL/P s [13]. In addition, no study has assessed NSOFCs severity during the COVID-19 pandemic [14].

Therefore, the aim of this multi-country study is to measure the association between CL/P severity, COVID-19 infection and fear in five Arab countries.

Materials and Methods

Design, setting and ethical considerations

This cross-sectional study is nested within a case-control study that took place in major governmental hospitals in five Arab countries: Saudi Arabia, Egypt, Oman, Kuwait, and Jordan from November 2020 to April 2023. The first study published was a case-control study that focused on environmental risk factors related to COVID-19 that could trigger the development of NSOFC [15]. However, it did not investigate the CL/P different sub-phenotypes or their range of severity. In this study, we hypothesize that there are environmental risk factors related to COVID-19 infection which could increase CL/P severity rather than initiating its development. Thus, this study is novel. The study was approved by the Research Ethics Committee of King Abdulaziz University Faculty of Dentistry (KAUFD) (257-07-21), the Research Ethics Committee of King Fahd Armed Forces Hospital(KFAFH) (REC-391), the Institutional Review Board of the Ministry of National Guard at King Abdullah International Medical Research Center (KAIMRC) (H-01-R-005), the Institutional Review Board of the Ministry of Health in Riyadh (H-01-R012), the Institutional Review Board of the Ministry of Health in Jeddah (H-02-J-002), the Jordan University of Science and Technology (104/147/2022) in Jordan, Scientific Ethics Committee of Fayoum University (R446-session 105) and institutional review board–approved protocol (IRB# 2017 – 562) in Kuwait.

Prior to participation, parents were provided with an informed consent form to sign that explained the study purpose, confidentiality, and methodology.

Participants

In the present cross-sectional study, participants were infants born with CL/P and their mothers who were in their first trimester during the COVID-19 pandemic. Syndromic cases were excluded based on the geneticist and pediatrician diagnosis.

Sample size calculation of the original case-control study was based on a study assessing the relation between stress and CL/P development [16] because we could not find studies assessing the relation between CL/P severity and maternal stress. Based on the differences in maternal exposure to stress between children with CL/P (39.58%) and healthy children (21.13%), a power of 80% and a confidence interval of 95%, 78 children with CL/P (cases) and 156 children without CL/P (controls) were needed with a ratio of 1:2 between cases and controls and a total of 234 children.

Once an infant was born with CL/P in the hospitals included in the study, a member of the study team was contacted and the infant with his parents were scheduled for an appointment in the same week. Thus, all children born with CL/P in these hospitals during the study period was included in this cross-sectional study.

Data collection

Dependent variable

Clinical examination was carried out using mirror and illumination light in the neonatal intensive care unit (NICU) where infants with CL/Ps were admitted after their birth. The LASHAL; i.e. Lip, Alveolus, Soft Palate, Hard Palate, Alveolus, and Lip; classification system [17] was used for NSOFCs diagnosis. Severity of CL/P was scored according to phenotype (cleft lip and palate versus cleft lip), extension of cleft (incomplete versus. complete) and site (unilateral versus. bilateral) as follow: score 6: complete bilateral CLP; Score 5: incomplete bilateral CLP or complete unilateral CLP; score 4: incomplete unilateral CLP; score 3: complete bilateral CL; score 2: incomplete bilateral CL or complete unilateral CL; score 1 incomplete unilateral CL. Thus score 6 indicated the greatest severity and score 1 indicated the least severity.

Questionnaire

Parents were interviewed using a validated tool based on the World Health Organization questionnaire for congenital anomalies. It was tested, modified, and validated in a previous study on the Saudi population [18]. Face validity was ensured in the present study by feedback from 20 parents and content validity was assessed by six experts. The content validity index was 0.9.

The questionnaire collected information on the independent variables (maternal COVID-19 infection status before or during pregnancy and fear of COVID-19) and confounders. The questionnaire consisted

of the following sections:

1. COVID-19 factors: These represented the independent variables. Maternal COVID-19 infection status was assessed by a yes/ no question about whether she had tested positive for COVID-19 before or during the pregnancy. A series of questions assessed maternal fear of COVID-19 using the fear of COVID-19 scale, which had been previously validated in English and Arabic [19, 20]. The scale consists of 7 no/ yes questions scored 1 and 2 respectively. The internal consistency for the items was good (Cronbach alpha = 0.85). The total score of the scale is the sum of points of the 7 items ranging from 7 (low fear) to 14 (high fear).
2. Confounders were others stresses the mother may have been exposed to before or during pregnancy including life events stressors measured using the Prenatal Life Events Scale which was previously validated in English and Arabic [21, 22]. The scale consists of 6 life events with yes/no answers. If the mother was exposed to any of the 6 stressors, she was considered to have been exposed to stress. Another yes/ no question asked if the pregnancy was planned based on the assumption that maternal stress would be higher if parents were not prepared for the pregnancy [23].
3. Confounders also included other maternal exposures before and during pregnancy periods that were previously reported in the literature to have associations with CL/P [15, 24]. This included intake of supplements such as vitamins and folic acid, medications, illnesses such as fever and chronic diseases, and use of nicotine use; assessed using yes/ no questions. There were also questions assessing consanguinity and family history of birth defects using yes/no questions.
4. Confounders also included the socio-economic profile of the family. There were questions assessing residence, infant sex, place of birth, parental education (More than high school versus high school or less), family income (Low: if family was in debt; Moderate: if family income barely met routine expenses and High: if family income met routine expenses and covered emergencies), parental age at time of infant's delivery.

Statistical analysis

Data was entered into SPSS Statistics version 20 (IBM Corp. Inc., Armonk, NY). Frequencies, percentages, means and standard deviations were used for descriptive statistics. Mann-Whitney U test, and Kruskal Wallis followed by post hoc tests for multiple comparisons were used to compare mean severity scores among subgroups and Spearman's rank correlation coefficient was used to assess the correlation of the severity score with the quantitative variables (age and COVID-19 fear score).

We used adjusted ordinal logistic regression to assess the relation between the dependent variable, CL/P severity and the independent variables, history of maternal COVID-19 infection before or during pregnancy and COVID-19 fear. The model was adjusted for confounders including socioeconomic factors, stresses and exposure to known NSOFCs determinate. We calculated the adjusted odds ratios (AOR), 95% confidence interval (95%CI) and p values. The statistical significance level was set at $P < 0.05$.

Results

The study recruited 274 CL/P infants from five Arab countries: 137 (50.0%) form Saudi Arabia, 70 (25.5%) from Egypt, 22 (8.0%) from Oman, 35 (12.8%) from Jordan and 10 (3.6%) from Kuwait. The most common severity phenotype was unilateral incomplete CL (84, 21.8%) whereas there were 38 children with bilateral complete CLP, the most severe phenotype (9.8%) (Table 1). The mean ± SD age of fathers was 34.1 ± 7.7 and of mothers was 34.6 ± 7.0 and the mean ± SD of the fear of COVID-19 scale was 9.16 ± 2.39.

Table 1
Distribution of the sample according to CL/P severity phenotypes (n = 273).

CL/P Severity	**n (%)**
Level 1: Unilateral Incomplete CL	84 (21.8)
Level 2: Bilateral Incomplete CL **or** Unilateral Complete CL	7 (1.8)
Level 3: Bilateral Complete CL	1 (0.3)
Level 4: Unilateral Incomplete CLP	72 (18.7)
Level 5: Bilateral Incomplete CLP **or** Unilateral Complete CLP	72 (18.7)
Level 6: Bilateral Complete CLP	38 (9.8)
Total	274 (100.0)
Note. CL: Cleft lip. **CLP**: Cleft Lip and Palate	

Table 2 shows the bivariate association between CL/P severity and the independent variables and confounders. Infants whose mothers tested positive for COVID-19 had greater severity score than infants without COVID-19 infected mothers (mean ± SD = 4.30 ± 1.53 and 3.45 ± 1.90, P = 0.025). The correlation between the CL/P severity score and the COVID-19 fear score was weak, positive and non-statistically significant (Spearman rho = 0.069, P = 0.258). Exposure to life stress event, stress because of unwanted pregnancy and other exposures reported in the literature to be associated with CL/P had no significant relation with the severity of CL/P (P > 0.05). Country of residence (P < 0.001) and family income (P = 0.013) had significant association with the severity score. Infants from Saudi Arabia and Egypt (mean ± SD = 3.91 ± 1.74 and 3.79 ± 1.86) had significantly higher mean severity of CL/P than infants from Jordan (mean ± SD = 2.029 ± 1.445). Greater severity of CL/P was observed among infants from high income families (mean ± SD = 4.44 ± 2.10) than other families.

Table 2
The association between CL/P severity score and COVID-19 infection, fear of COVID-19 and confounders in bivariate analysis (n = 273).

Variables		n (%)	CL/P severity Score Mean ± SD	*P* value
COVID-19 factors				
Mother tested + ve with COVID-19	Yes	37 (13.6)	4.297 ± 1.525	**0.025**
	No	236 (86.4)	3.451 ± 1.899	
Maternal stresses before and during pregnancy				
Exposure to any of the life stress event?	Yes	105 (38.5)	3.781 ± 1.936	0.070
	No	168 (61.5)	3.432 ± 1.825	
Was the pregnancy planned?	Yes	87 (31.8)	3.609 ± 1.748	0.910
	No	187 (68.2)	3.545 ± 1.932	
Maternal exposures before and during pregnancy				
Medication	Yes	86 (31.5)	3.805 ± 1.829	0.195
	No	187 (68.5)	3.455 ± 1.887	
Supplementation	Yes	224 (82.1)	3.484 ± 1.895	0.141
	No	49 (17.9)	3.939 ± 1.737	
Illness	Yes	85 (31.1)	3.835 ± 1.876	0.092
	No	188 (68.9)	3.444 ± 1.863	
Father nicotine use	Yes	136 (49.8)	3.482 ± 1.941	0.667
	No	137 (50.2)	3.650 ± 1.805	

CL/P severity score ranges from 1 = mild severity to 6 = high severity.

Correlation between the severity score and mother's age (rho = 0.016, P = 0.792),

father's age (rho = 0.023, P = 0.711) and fear of COVID-19 score (rho = 0.069, P = 0.258).

Variables		n (%)	CL/P severity Score Mean ± SD	*P* value
Mother nicotine use	Yes	8 (2.9)	3.50 ± 2.204	0.985
	No	265 (97.1)	3.57 ± 1.867	
Family history of relatives with birth defects	Yes	89 (32.6)	3.678 ± 1.930	0.396
	No	184 (67.4)	3.511 ± 1.847	
Family history of consanguinity	Yes	116 (42.5)	3.632 ± 1.832	0.795
	No	157 (57.5)	3.516 ± 1.907	
Socio-economic profile				
Country	Saudi Arabia	137 (50.0)	3.905 ± 1.744	**< 0.001**
	Oman	22 (8.0)	3.091 ± 2.068	
	Egypt	70 (25.5)	3.786 ± 1.856	
	Jordan	35 (12.8)	2.029 ± 1.445	
Family income	Low	159 (58.0)	3.55 ± 1.905	**0.013**
	Moderate	99 (36.1)	3.45 ± 1.763	
	High	16 (5.8)	4.44 ± 2.097	
Infant's sex	Male	156 (57.1)	3.561 ± 1.823	0.958
	Female	117 (42.9)	3.573 ± 1.945	
Father's education	≤High school	193 (70.7)	3.451 ± 1.859	0.053
	>High school	80 (29.3)	3.840 ± 1.886	

CL/P severity score ranges from 1 = mild severity to 6 = high severity.

Correlation between the severity score and mother's age (rho = 0.016, P = 0.792),

father's age (rho = 0.023, P = 0.711) and fear of COVID-19 score (rho = 0.069, P = 0.258).

Variables		n (%)	CL/P severity Score Mean ± SD	*P* value
Mother's education	≤High school	182 (66.7)	3.486 ± 1.886	0.321
	>High school	91 (33.3)	3.725 ± 1.844	
CL/P severity score ranges from 1 = mild severity to 6 = high severity.				
Correlation between the severity score and mother's age (rho = 0.016, P = 0.792),				
father's age (rho = 0.023, P = 0.711) and fear of COVID-19 score (rho = 0.069, P = 0.258).				

Table 3 shows the adjusted ordinal regression estimates for the severity of CL/P as dependent variable, and COVID-19 infection and fear as independent variables controlling for confounders. If two factors showed a strong association with each other (collinearity), the less important factors or those that showed a higher P value were excluded. Therefore, father age, father nicotine use, maternal medication and parental consanguinity were excluded from the regression analysis to avoid collinearity, decreasing the number of variables and improving the quality of the outcome. In addition, we excluded the country which included only 10 subjects from the regression analysis. A history of maternal infection with COVID-19 before or during pregnancy was significantly associated with higher odds of more severe CL/P (AOR = 2.197, 95% CI: 1.153 to 4.185 and P = 0.017) than mothers with no history of COVID-19 infection. Exposure to life stress events and maternal nicotine use were associated with greater odds of more severe CL/P (AOR = 1.625, 95%CI: 0.991 to 2.665 and P = 0.055) for Exposure to life stress events and AOR = 1.38, 95% CI: 0.315 to 6.052 and P = 0.67) for maternal nicotine use although the association was not statistically significant. On the other hand, supplementations use during pregestation and 1st trimester was associated with non-significant lower odds of more severe CL/P (AOR = 0.654, 95% CI: 0.37 to 1.231 and P = 0.188). Regression analysis for the total factors is available in the supplementary table 1 showing a similar outcome.

Table 3
Adjusted ordinal logistic regression for the association between CL/P severity and COVID-19 infection and fear controlling for confounders.

Variables		AOR (95% CI)	*P* value
COVID-19 factors			
Mother tested + ve with COVID-19	Yes	2.197 (1.153–4.185)	0.017
	No	1.000	
Maternal stresses before and during pregnancy			
Exposure to any of the life stress event?	Yes	1.625 (0.991–2.665)	0.055
	No	1.000	
Maternal exposures before and during pregnancy			
Supplementation	Yes	0.654 (0.374–1.231)	0.188
	No	1.000	
Illness	Yes	0.987 (0.586–1.661)	0.959
	No	1.000	
Mother nicotine use	Yes	1.380 (0.315–6.052)	0.670
	No	1.000	
Family history of relatives with birth defects	Yes	1.472 (0.895–2.422)	0.128
	No	1.000	
Socio-economic profile			
Country	Saudi Arabia	5.767 (2.569–12.945)	< 0.001
	Oman	3.295 (1.084–10.014)	0.036
	Egypt	6.491 (2.664–15.815)	< 0.001
	Jordan	1.000	
Infant's sex	Male	0.777 (0.491–1.232)	0.284
	Female	1.000	
Father's education	≤High school	0.726 (0.429–1.228)	0.232
	>high school	1.000	
Mother age		1.006 (0.984–1.028)	0.607

AOR: Adjusted Odds Ratio. **CI**: Confidence Interval. **COVID-19**: Coronavirus disease − 19

Variables	AOR (95% CI)	*P* value
Total score of fear of COVID-19	1.071 (0.974–1.177)	0.156

AOR: Adjusted Odds Ratio. **CI**: Confidence Interval. **COVID-19**: Coronavirus disease – 19

Discussion

In five Arab countries, mothers who were infected with COVID-19 before or during pregnancy had more than two-fold higher odds of having a child with more severe CL/P. Fear of COVID-19 and other maternal stressors during the pandemic were not significantly associated with the severity of CL/P. To our knowledge, this is the first study to assess the impact of COVID-19 on the severity of CL/P controlling for the effects of other known risk factors associated with CL/P. Our study provides evidence suggesting that the effect of COVID-19 may occur at a much earlier stage of human development by impacting the normal growth and development of infants independently from known cleft determinants. The findings shed light on an effect of COVID-19 that has not been explored till now, thus filling a knowledge gap. The high odds and relatively narrow confidence interval suggest a strong association between COVID-19 infection and CL/P severity that is precisely estimated. The observed association seems to indicate a pathophysiological pathway rather than a psychosomatic route since the association with fear of COVID-19 infection was not significant. The study findings and the questions they raise call for future studies conducted in other countries where contextual factors may modify the observed association and for investigation of the pathways through which the observed effect occurs.

Only fewer studies assessed the determinants of CL/P severity. Two studies found a positive association between the severity of CL/P presentation and older parental age [25] as well as family history of NSOFC [26]. The etiology of NSOFC could be genetic, environmental, or as a result of genetic-environmental interactions [27]. Most previous studies focused on the occurrence of NSOFCs [28], with a case-control study reporting no association between maternal COVID-19 infection and CL/P occurrence in infants [29]. The field of epigenetics shows how the environment affect the way genes work with evidence showing effects on tooth development [30], oral cancer, craniofacial syndromes as well as caries and periodontal disease [31]. Infections may switch on and off specific genes responsible for different processes [31] thereby modify their action. For example, infection with Mycobacterium tuberculosis affects the IL-12B gene which weakens the immunity [32] and may favor the occurrence or progress of different diseases. Epigenetic modulation may be one mechanism through which COVID-19 infection before or in early pregnancy moderates the action of genes responsible for NSOFCs, increasing cleft severity. CL/P development has been previously associated with other infections during early pregnancy such as influenza [33], HIV and human papillomavirus infection yet results remain inconclusive [33, 34]. Infections that cross the placental barrier can lead to subsequent fetal infections [35]. COVID-19 infected placentas showed common features like maternal and fetal vascular malperfusion and cellular inflammation [36] which may restrict fetal growth, delay development, and possibly lead to stillbirth [37]. Further studies are needed to elucidate the mechanism by which COVID-19 increases the severity of NSOFCs.

In addition, we found higher odds of greater CL/P severity with exposure to life stressful events and fear of COVID-19 although the associations showed weaker effect sizes and were not significant. Previous studies showed that maternal exposure to stress during early pregnancy was associated with CL/P in infants [15] and before pregnancy stress exposure was associated with two-fold higher risk of NSOFC development [38]. Only one of these studies, however, considered the impact of COVID-19 which might have overshadowed the impact of these factors in the present study. Stress may increase the risk of NSOFC through activating the sympathetic nervous system to increase blood profusion leading to placental hypoperfusion which negatively impacts fetal development [39] and through higher level of cortisol, a primary stress hormone, which has a teratogenic effect on the developing fetus, resulting in craniofacial abnormalities [40].

Furthermore, although not significant, we found that the use of supplements before and in early pregnancy was associated with lower odds of more severe CL/P. This follow previous studies showing that an association between NSOFC and maternal nutritional deficiencies during early pregnancy [41] Vitamin B and folic acid supplementation were previously reported to be associated with lower risk of NSOFC in infants [42]. Also, an animal study on mice with CP mutation *(Tgf-B3-/-)* found that folic acid supplementation significantly minimized CP severity by improving palatal shelf adhesion and disposition of collagen IV, cytokeratin-17, laminin, and fibronectin [43].

Finally, we found higher odds of CL/P severity with maternal nicotine use. However, this association was not statistically significant due to the small number of mothers reporting smoking. This could have resulted from the social stigma against women using nicotine [44]. Furthermore, the lifestyle behavior changes during COVID-19 lockdown might have affected smoking prevalence and in some way affected the previously known association between smoking and CL/P [45].

There are a few limitations in this study. First, the history of COVID-19 infection might have been prone to some recall bias although this would be minimal considering the emphasis on COVID-19 infection status during the pandemic and that data collection occurred in the same week of delivery. Second, misclassification bias may be another limitation in the study since not all infected cases were tested, with chances for over or under estimation of the observed relation. Third, the generalizability scope of the findings is limited to the 5 countries included in the study and extrapolation to other countries needs to be carefully considered in view of the variation in the distribution of the exposures and determinants by country. Furthermore, the sample size, although exceeding the suggested sample size calculation, is recommended to be enlarged. However, in this study, the availability of cases was limited because it was conducted on a congenital anomaly; which is a rare condition (with 1.17/1000 prevalence) and was limited to the COVID-19 period [46]. Nevertheless, the study has several important findings.

Conclusion

This study is the first to assess the association between CL/P severity and COVID-19 factors including infection and fear controlling for known CL/Ps determinants during the COVID-19 pandemic in Arab

countries. Mothers who were infected with COVID-19 before and during pregnancy had more than two folds higher odds of having an infant with a more severe CL/P phenotype. Understanding the impact of COVID-19 on CL/P severity and the causal pathways and mechanism of action allow the design of evidence-based surveillance, monitoring and prevention programs.

Declarations

Author Contributions

HJS: Conceptualization, Methodology, Study Design, Data Collection, Data Analysis, Writing – original draft and Writing & editing of Final draft; MZ, OBA, TA, MAA, MK, LA, BA, SMR, MQ, FFT, BA, FDA, NSA, PSV, TA, OAB: Methodology and Data Collection; SMA: Methodology, Data Collection and Data Analysis; DB: Writing – Original draft and Writing & Editing of Final Draft; ME: Data Analysis and Writing & Editing of Final Draft; RAA: Methodology, Study Design and Writing & Editing of Final Draft.

Data availability

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

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Conflict of interest disclosure

All authors have no conflicts of interest to disclose

Ethics approval statement

The study was approved by the Research Ethics Committee of King Abdulaziz University Faculty of Dentistry (KAUFD) (257-07-21), the Research Ethics Committee of King Fahd Armed Forces Hospital(KFAFH) (REC 391), the Institutional Review Board of the Ministry of National Guard at King Abdullah International Medical Research Center (KAIMRC) (H-01-R-005), the Institutional Review Board of the Ministry of Health in Riyadh (H-01-R012), the Institutional Review Board of the Ministry of Health in Jeddah (H-02-J-002), the Jordan University of Science and Technology (104/147/2022) in Jordan, Scientific Ethics Committee of Fayoum University (R446-session 105)) and institutional review board–approved protocol (IRB# 2017-562) in Kuwait.

Patient consent statement

Prior to participation, parents were provided with an informed consent form to sign that explained the study purpose, confidentiality, and methodology.

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