

Oral and Oropharyngeal Cancers and Possible Risk Factors Across Gulf Cooperation Council Countries: A Systematic Review

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Abstract

Background: In recent years, there is an emerging increase in the prevalence of oral and oropharyngeal cancers (O-OPCs) across the Arabian Gulf Cooperation Council (GCC) countries. Consequently, this review aimed to explore the epidemiology and possible risk factors of O-OPCs in GCC countries.

Methods: Data published after 2008 related to O-OPCs in GCC countries were obtained through electronic searches in Medline/PubMed, Scopus, Web of Science, EMBASE and Google Scholar. Keywords related to the association between O-OPCs metrics (epidemiology and risk factors) and GCC countries were used for electronic searches.

Results: The overall prevalence of OPCs increased significantly over time (40-51%) in some countries (Saudi Arabia and Arab Emigrated) of the Gulf regions. The pooled risk factor was 3.4 (2.5 - 4.7).

Among the risk factors, human papillomavirus and the use of smoke and smokeless tobacco revealed odds ratio (OR) 3.31 (3.13 - 4.5) and 0.60 (0.45 - 0.80) at 95% confidence interval (CI).

Conclusion: A positive correlation between factors like age, diet, hygiene, genetics, viral and bacterial infection, consumption of alcohol and tobacco products with OPC-MFC is suggested.

Keywords: Oral cancer; GCC countries; Oropharyngeal cancer; HPV; Tobacco

Introduction

Oral and oropharyngeal cancers (O-OPCs) group represents the sixth most common cancer with around 500,000 cases worldwide [1]. There is an alarming increasing incidence of O-OPCs in younger patients particularly in the Middle East (14.5%) and Africa (17.2%) [2]. A major variation in the epidemiology of O-OPCs was observed based on geographical distribution, sex and age worldwide [3]. Numerous risk factors have been implicated in the etiology of O-OPCs including tobacco use, alcohol consumption, human papillomavirus (HPV) infection, poor oral hygiene, low socioeconomic status and genetic factors [4, 5], and factors such as ethnic groups, lifestyle, occupational exposure, immune deficits, familial risk and lack of fruits/vegetable regular eating [6, 7].

There is a relatively complete paucity of published data on O-OPCs from Arabian Gulf Cooperation Council (GCC) states. The available published literature is either from Middle East Region or on separate cancer entities (anatomical sites) from the O-OPCs group. According to GLOBOCAN report 2012, O-OPCs ranked among the top 20 cancers and accounted for 1.5% of all human cancers with a male to female ratio of 1.38:1.00 in the Middle East and North Africa [8-10]. However, the estimated age-standardized rates (ASRs) for O-OPCs in GCC countries were described in Figure 1 [8, 9]. The most frequently discussed cancer entity in GCC countries is oral cancer. In Arab countries, the prevalence rates of oral cancer were counted in a range of 1.8 to 2.13 per 100,000 in-

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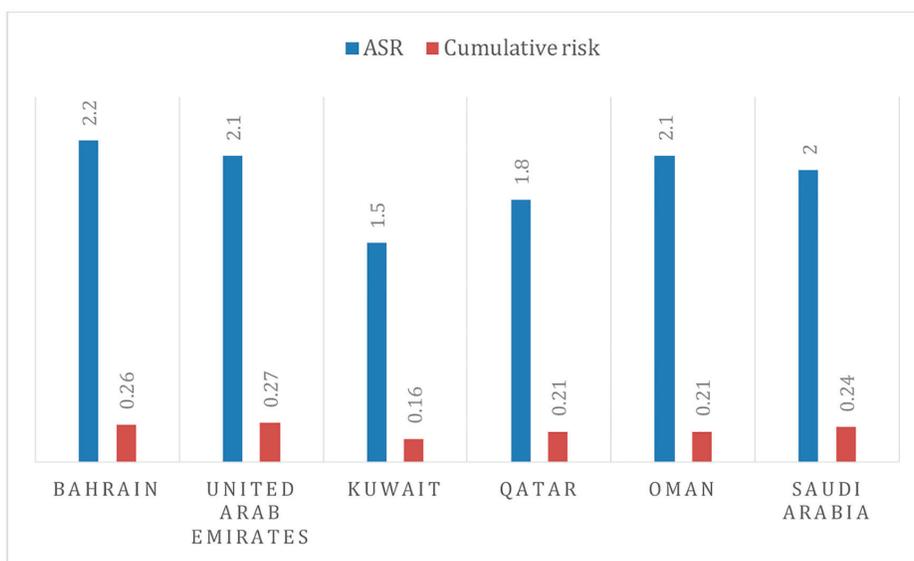


Figure 1. The age-standardized rates and cumulative risk of O-OPCs in GCC member states [8, 9].

dividuals, with tobacco use, alcohol consumption, solar radiation and HPV being the possible risk factors [9, 11]. Detailed available information regarding epidemiology and possible risk factors of O-OPCs in GCC countries will be explored in this review.

Methodology

Search strategy

Data published after 2008 related to O-OPCs in GCC countries were obtained through electronic searches in Medline/PubMed, Scopus, Web of Science, Excerpta Medica Database (EMBASE) and Google Scholar. Keywords related to the association between O-OPCs metrics (epidemiology and risk factors) and GCC countries were used for electronic searches. Relevant keywords (oral cancer, oral cavity cancer, oropharyngeal cancer, epidemiology, risk factor, incidence, etc.) were used during the electronic search pertaining to the GCC countries (Bahrain, United Arab Emirates, Kuwait, Qatar, Oman and Saudi Arabia). No filters were used during the electronic searches.

Selection of required publications

In-depth selection was made through the search engine following effective inclusion and exclusion criteria to establish the possible facts in this review.

Inclusion criteria

Electronically available literature published after 2008 and re-

lated to epidemiology and risk factors of O-OPCs from GCC states members were included. Only English written literature was included.

Exclusion criteria

Literature reported from other Gulf countries (other than GCC states) was excluded. Literature pertaining to non-cancerous oropharyngeal disorders, laboratory research including animal trials, was excluded.

Quality appraisal

After scanning the titles of all relevant publications and reading the abstracts of the selected publications, full-text papers were appraised by the assigned reviewers using PRISMA guidelines [12].

Assessment of heterogeneity

Valid statistical package (Comprehensive Meta-analyses ver. 3) was used to calculate the summary effect estimate and 95% confidence intervals (CIs) to test for heterogeneity [13, 14].

Results and Discussion

Epidemiology

In the GCC countries, the incidence rates of O-OPCs were estimated to be 1,268 (896 males and 372 females) with ASR

incidence rates of 0.1 - 3.2 in males and 0.1 - 1.3 in females [15]. The ASR mortality rates in the GCC countries ranged 0.1 - 1.8 in males and 0.1 - 0.7 in females with a male to female ratio of 2.41:1.00 and 2.59:1.00 for incidence and mortality rates, respectively [9, 10, 15]. The trends in the variations of O-OPCs among the GCC countries are shown in Table 1 [10, 13, 16-23]. The highest incidence rates and mortality rates of O-OPCs per 100,000 males were perceived in Saudi Arabia, representing 574 and 222 persons, followed by the United Arab Emirates (154 and 49), in this order. Similarly, among females, the highest incidence rates and mortality rates were encountered in Saudi Arabia (292 and 106) followed by the United Arab Emirates (39 and 10). According to recent estimates [24], the highest age-standardized incidence rates for O-OPCs were seen in Bahrain (3.2) followed by the United Arab Emirates (2.4) (Fig. 2). The highest oral cancer associated age-standardized death rates with respect to all cancers types are noticed in Saudi Arabia (1.74) followed by United Arab Emirates (1.24) then Qatar (1.21), Oman (0.89), Bahrain (0.80) and Kuwait (0.63). The epidemiological parameters including incidence, prevalence, mean age at diagnosis, histological types of cancer and risk factors are represented in Table 1.

Meta-analyses

The overall prevalence of O-OPCs indicated a pooled odds ratio (OR) of 0.43 (95% CI: 43.2 - 51.4) in a series of seven studies performed after the year 2008. Studies in 2013 - 2017 revealed a pooled OR of 0.613 (95% CI: 5.78 - 7.03); moreover, studies after the year 2017 indicated a pooled OR (95% CI) of 0.75 (5.02 - 7.6), indicating a significant increase in the prevalence ($P < 0.001$) (Table 1, Fig. 3). The prevalence significantly increased over time in Saudi Arabia ($P < 0.003$) and United Arab Emirates ($P < 0.002$). Data were insufficient for Bahrain, Kuwait, Qatar and Oman, and as a result, trend analyses over time could not be performed for these regions. However, in Figure 3, the pooled four studies showed the overall P-value is 0.187, suggesting no a significant difference, which might be due to the small number of studies or insufficiency of data in this context. The prevalence of O-OPCs differed by the country of recruitment demonstrating an overall pooled OR (95% CI) of 0.399 (2.83 - 4.82) in Saudi Arabia and 0.505 (5.00 - 7.21) in the United Arab Emirates. These differences in the prevalence rates were found to be statistically significant ($P < 0.001$).

Etiology

In the GCC region, the etiology of O-OPC has been attributed to multifarious factors. Frequently investigated risk factors are the growing usage of various tobacco forms, alcohol consumption [10], HPV infection [25], genetic factors [26] and dietary factors [27]. Besides, gender and age, physical activity [28] and environmental factors [29] also play a crucial role in the progression of the disease. Though alcohol is strictly prohibited in these countries, the role of alcohol in O-OPCs cannot

be ruled out.

Genetic factors and molecular pathogenesis

The molecular mechanism of oral squamous cell carcinoma (OSCC) is still unclear. However, few studies on the mechanism for cell proliferation resulting in carcinogenesis have revealed the role of differentially expressed genes (DEGs) in regulating the initiation and development of OSCC [30]. Recently polymorphism in the *EPHX1* gene encoding microsomal epoxide hydrolase has been attributed to causing many cancers including OPC [31]. The role of miRNAs [32], over-expression of RNA *TUG1* [33] has also been attributed to the progression of OSCC.

Biological factors

Viruses infection

One of the most comprehensively studied viruses to be involved in the carcinogenesis of oropharyngeal squamous cell carcinoma depending on molecular and epidemiological data is HPV [34-36]. It was found that the combined effect of HPV-16 and tobacco boost up oral cancer risk. Analysis of OR (95% CI) was only available for one related study [18] with an estimated OR (95% CI) of 3.13 (3.13 - 4.5). The risk difference in the study was 0.28 with PLN 0.639. Although it was reported that OPC Saudi cases harbored around 21% of HPV (the global 36-46%) [37], some recent studies from Saudi Arabia reported an absence of HPV particularly in oral cancerous and precancerous lesions [38, 11]. However, the HPV-associated O-OPCs literature from GCC is insufficient to compute statistically signified-values.

Bacterial infection

The oral mucosa-harboring microorganisms greatly vary in their features, from beneficial effects to carcinogenic effects [39]. Oral microflora may proliferate in oral mucosa, tongue and even the pharyngeal regions altering the oral epithelium making them vulnerable to local and systemic infection leading to carcinogenesis [40]. Several studies reported the responsibility of the oral pathogenic microbes in the development of atheromatous plaques, periodontitis and other systemic diseases leading to carcinogenesis [39, 41].

Chemical factors

Tobacco use

Tobacco use is a leading cause of mortality through diverse complex diseases including cancer. In a study that included 1.2 million participants, 566 genetic variants in 406 loci were

Table 1. Incidence, Prevalence and Possible Risk Factors of O-OPCs in GCC Countries

Study parameters	Country	Source of data	Period	No. of cases/ biopsies) under study (n)	Age group	Common malignant lesions type	The highest site of lesion	Risk factor distribution among patients	Reference
Retrospective study	Saudi Arabia	Cancer registry	1994 - 2007	5,862	29 - 71	OC, PC = 245 (4.2%)	Tongue (> 42%)	NS	[16]
A multicenter, retrospective study of oral biopsies	UAE	Hospital records	2008 - 2010	992	28 - 89	OSCC	Tongue (51.9%)	NS	[13]
Cross-sectional	Extended the Middle East* and North Africa	Cancer registry	2008	252	NS	OC, pharynx	OC	HPV	[18]
Case-control	Saudi Arabia	Hospital-based	2011 - 2013	599	≥ 18	NS	Smokeless keratosis (6.3%)	Tobacco chewers	[19]
Case-control	Saudi Arabia	Hospital-based	2014	48	About 65.3	OC	NS	Khat 2 (1/28%) Shannah 39 (27.08%) Cigarette 10 (6.94%) Pipe 9 (6.24%)	[20]
Prospective study	Saudi Arabia	Hospital records	2002 - 2009	2,232	36 - 54	Head and neck/ORN	Nasopharyngeal 35 (39.2%) Mandible 27 (30.4%)	Smoking 42 (47.3%) Smokeless 6 (6.7%)	[21]
Cross-sectional	Middle East# and North Africa	Public database	2012	8,928	NS	OCC-OPC, NS	NS	NS	[10]
Retrospective study	Saudi Arabia	Hospital records	NS	2,850	≤ 10 - 70	SCC, VC, S	Tongue (47%)	NS	[22]
Retrospective study	Saudi Arabia	Hospital records	2009 - 2014	714	< 1 - 100	OML-OSCC	Tongue	Shammah user OSCC 45.5% Male: 87 (31.6%) Female: 40 (68.4%)	[17]
Retrospective study	UAE	Hospital records/cancer registry	1998 - 2014	314	NS	ADC, SCC, MEC, ACC	Salivary gland tumor (74%)	NS	[23]

*Included in this study: Bahrain, Kuwait Oman; #Included in this study: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and UAE; NS: not specified; OSCC: oral squamous cell carcinoma; SCC: squamous cell carcinoma; OML: oral and maxillofacial; VC: verrucous sarcoma; S: sarcoma; ADC: adenocarcinoma; MEC: mucoepidermoid carcinoma; ACC: acinar cell carcinoma; O-OPCs: oral and oropharyngeal cancers; GCC: Arabian Gulf Cooperation Council; HPV: human papillomavirus.

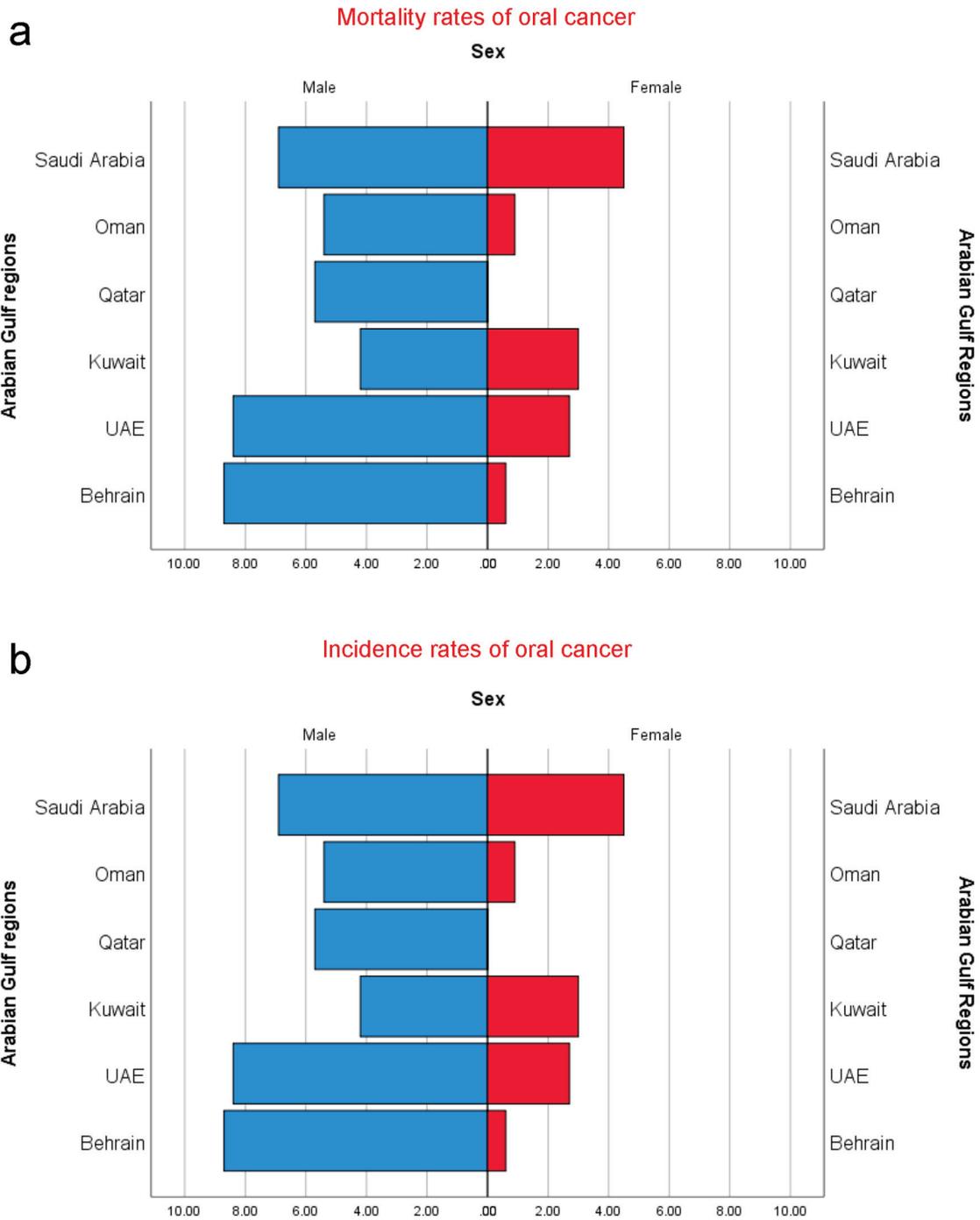


Figure 2. (a) Estimated age-standardized mortality rates of oral cancer individuals (CID-10: C00-C08) in GCC countries per 100,000 persons. (b) Estimated age-standardized incidence rates of oral cancer individuals (CID-10: C00-C08) in GCC countries per 100,000 persons.

identified associated with different tobacco use phases (initiation, cessation and heaviness) [42]. Both smoked and smokeless tobacco was found to cause O-OPCs, with elevated potentiality in the oral cavity [43, 44]. The most tobacco-associated oral cancer is being OSCC, particularly among smokeless to-

bacco users [45-47].

Increasing trends in smoking among GCC countries' populations were reported in several publications [48-50]. Available evidence suggests that alternative tobacco products such as hookah, shisha and narghile have been widely used by the

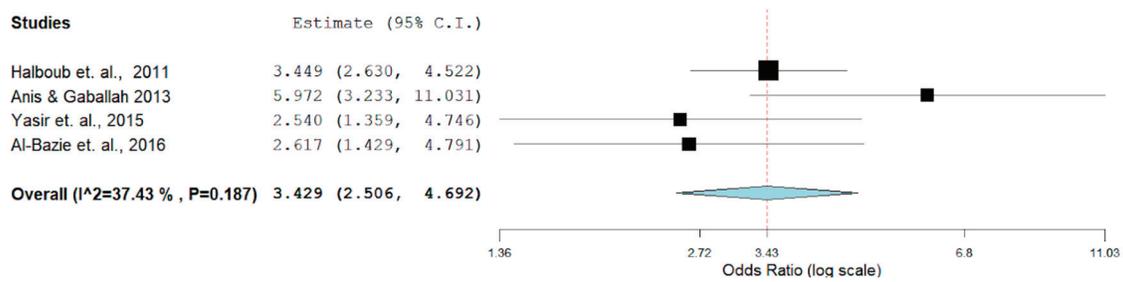


Figure 3. Meta-analyses (forest plot) of prevalence rates with respect to the report's country.

young generation in the GCC countries and might be one of the common risk factors for oral cancer [51]. A report from the United Arab Emirates showed cigarette smoking prevalence rates of 24.3% for males and 0.8% for females [52]. The prevalence rates of *shisha* (water pipe) smoking ranged 20-50% among men and 5-12% among women [53]. Though there is a scarcity of concrete evidence on the use of waterpipe smoking with cancer, few studies claimed its association with several types of cancerous conditions including nasopharyngeal cancer and oral dysplasia [54]. Midwakh use was the most common tobacco product used after cigarettes, and the users were predominantly men [55]. Shammah is another smokeless tobacco product comprised of tobacco, lime and black pepper mixture. Shammah is very popular in Yemen and Southern Saudi Arabia [16, 17, 56]. A total of four publications included in the review contained data from which OR was calculated on the risk of smoking (smoke/smokeless) and oral cancer. The overall prevalence of O-OPCs due to the use of tobacco or tobacco product (Table 1, Fig. 4) was 91.9%, the OR for both adjusted and non-adjusted varied from 0.19 (0.11 - 0.34) to 0.89 (0.78 - 1.0).

Alcohol consumption

Even though several studies established the carcinogenic effect of alcohol, it is not considered a direct carcinogen. However, some compounds of alcoholic beverages such as acetaldehyde, benzene, ethanol and formaldehyde are known to cause cancer in humans and its potentiality increases when used in combination with tobacco products [57]. Though there are strong leg-

islation and ban on the alcoholic beverage in GCC countries, globalization has led to its importation in some countries. The consumption of alcoholic beverages is more prevalent among young people [58].

Catha edulis, khat plant consumption

The chewing of leaves and twigs of Khat (*Catha edulis*) is commonly practiced among inhabitants of Yemen and East Africa [59, 60]. Although there is no direct correlation between the use of khat and the prevalence of oral cancer, studies from the region claimed its association with oral cancer [52, 57, 61].

However, there are ongoing efforts toward O-OPCs prevention and early detection in GCC member states. Changing lifestyles, lack of timely detection and awareness, poor treatment and access to palliative care are among the multitude of factors challenging the cancer patients. Poor database on incidence and mortality is another hurdle to mitigate the problem. Awareness among the public, implementation of effective health policies and timely action of healthcare practitioners (HCPs) may minimize the risk of O-OPCs [62, 63].

Conclusion

There is a tremendous paucity of epidemiological data relating to O-OPCs as a group from GCC countries. The available epidemiologic data show relatively higher O-OPCs prevalence

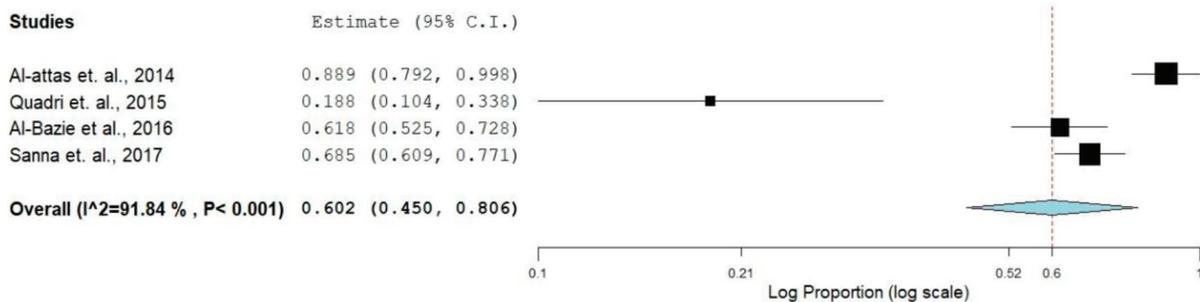


Figure 4. Forest plot of smoking and risk of oral cancer.

rates in GCC countries with some sorts of diversity among these countries. Besides the general O-OPCs risk factors, there are some risk factors pertained to the region, such as Shammah and Khat. This review represents a major source of O-OPCs-related data about GCC countries, which may orient further search in this context.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Informed Consent

Not applicable.

Author Contributions

Wedad Saeed Alqahtani and Nawaf Abdulrahman Almufareh: conceptual, data search, drafting and approval of final version. Halah A. Al-Johani and Bassam Ahmed Almutlaq: conceptual, data search and approval of final version. Rasil Khaled Alo-taibi, Consul Iworikumo Juliana, Nada Hamad Aljarba and Bandary Almarshedy: conceptual, data search, analysis and approval of final version. Abdulqader Saeed Alqahtani, Abdel-baset Mohamed Elsbali: data search, revision and approval of final version. Hussain Gadelkarim Ahmed: conceptual, data search, drafting, revision and approval of final version.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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