Salivary IL-8 and TNF-α as potential diagnostic biomarkers for dental caries

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Abstract. Dental caries constitutes the major burden on oral health worldwide, with untreated dental caries being among the most prevalent health conditions. Cytokines play a critical role in the immunopathogenesis of dental caries. It is worth mentioning that the salivary levels of interleukin (IL)-8) and tumor necrosis factor-α (TNF-α) have been reported to differ between patients with caries and those without caries. The aim of the present study was to determine the diagnostic accuracy of salivary levels of cytokines (IL-8 and TNF-α) for differentiating between subjects with caries and those without caries. For the present case-control study, whole unstimulated salivary samples were collected from 44 adult individuals who were divided into two groups as follows: 22 subjects with dental caries and 22 without caries. Clinical parameters were recorded, including caries experience (decayed, missing, filled surfaces), plaque index and gingival index. Enzyme-linked immunosorbent assay was used to determine the salivary levels of cytokines. The results revealed that the mean levels of salivary cytokines (IL-8 and TNF-α) were elevated in the group with caries as compared to those without caries (the control group; $P<0.05$). IL-8 was able to discriminate between patients with dental caries from healthy controls (area under the curve value, 0.735). Moreover, the levels of salivary cytokines exhibited positive correlations ($P<0.05$). On the whole, the present study found higher amounts of cytokines in the saliva of patients with caries; thus, these cytokines perhaps contribute to the development of caries. IL-8 demonstrated moderate clinical accuracy in discriminating patients with caries from the controls.

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Introduction

Dental caries is a disease resulting from multiple factors, beginning with changes in the microbiological composition of the intricate biofilm and influenced by sugar intake, fluoride exposure, saliva flow and composition, as well as dental hygiene practices. Dental caries results from the transformation of fermentable sugars by bacteria in dental plaque into acids on the surface of teeth. Therefore, it is crucial to emphasize the reduction of sugar intake and the management of plaque (1). Dental caries is widely recognized to develop when the biofilm microbiota that typically exists in a state of balance in the oral cavity shifts to an acid-producing, acid-tolerant, and cavity-causing community as a result of regular sugar intake. The outcome of this change may be undetectable in clinical settings or cause a net loss of minerals in the hard tissues of the tooth, leading to the appearance of a cavity (2,3). Caries is recognized as the most common oral health issue globally, affecting children, teenagers and adults, and it is the leading cause of tooth loss in the population. In addition to caries, there are various other diseases of the mouth that can be identified and tracked using cytokines, which play a critical role in regulating the immune and inflammatory responses (4). Cytokines play a pivotal role in the immunopathogenesis of dental caries. Among the different cytokines under examination for their potential inclusion in caries conclusion are interleukin (IL)-4, IL-6, IL-8 and tumor necrosis factor-α (TNF-α) (5).

Cytokines play a major role in modulating the immune response, and are either pro-inflammatory or anti-inflammatory. They are critical for regulating immune responses. Any cell nuclei can release cytokines, but helper T cells and macrophages are the primary producer (6). The chemokine class prototype molecule is IL-8, a cytokine that provokes inflammatory reactions. Additionally, IL-8 is a key player in the acute inflammatory reaction and remains at the site of inflammation for a considerable amount of time (7). The protein TNF-α plays a role in alert responses and host defense. White blood cell molecules stick to endothelial cells and trigger phagocytic killing processes, which encourages cell proliferation. In addition to cytotoxic and cytostatic effects on cancerous cells. IL-8 and TNF-α products of immune cells also play an critical role in diseases of the oral

mucosa. However, patients with dental caries higher levels of IL-8 and TNF-α, leading to a lower number of osteoblasts and fibroblasts, and they support the demineralization of teeth and development of the dental caries process. These cytokines, which are produced locally by osteoclasts, have been shown to be a critical factor in regulating the differentiation of these cells and participating in resorption processes (6). The inflammatory aspect of caries disease, a known source for molecular diagnosis, remains unknown, and the diagnosis for the condition contuse to depend on clinical, visual and radiographic techniques (8). The aim of the present study was to assess the diagnostic precision of cytokines (IL-8 and TNF-α) in distinguishing between subjects with caries and those without.

Subjects and methods

Study design and ethics approval. The present study was a case-control study. The subjects included in the study were provided with a comprehensive explanation of the purpose and methods of the study. Their permission was gained via a document vetted via the Ethic Committee of the College of Dentistry, University of Baghdad (Reference no. 1000 on 7-1-2025).

Study subjects. A total of 44 subjects were enrolled in the present study (22 adults subjects with dental caries and 22 of the same age and sex without caries were randomly selected as the control group). There was a specific case sheet used to obtain information about the name, age, sex and general health of the adult and whether the subject was a smoker or alcoholic or not. A questionnaire about the general and oral health habits of the selected patients was prepared to ensure that they were free from any systematic diseases and did not take any medications for at least the past 1 month.

Inclusion and exclusion criteria. All participants recruited in the study as the test subjects had dental caries, >20 years, had no systemic disease with no antibiotic consumption for the past 3 months. The control group were subjects with healthy gingiva, exhibiting good oral hygiene without any history of dental caries or related symptoms. The present study excluded children and patients who had the following conditions: Smoking or alcohol consumption, unapproved consent, pregnant or lactating women, or those taking medications (antibiotics or any medications).

Oral examination. The assessment of clinical caries was performed by an examination of teeth and evaluation of decayed, missing and filled surfaces (DMFS) and plaque index (the amount of dental plaque at four surfaces of each tooth was assessed). The assessment of dental plaque was performed according to the plaque index system (9). The scores and criteria for this system were followed as proposed by authors, as follows: Score 0, no plaque in the gingival area; score 1, a film of plaque adhering to the free gingival margin and adjacent area of the tooth surface; score 2, moderate accumulation of soft deposits within the gingival pocket on the gingival margin and/or adjacent tooth surface which can be seen by naked eye; score 3, abundance of soft matter within the gingival pocket and/or on the gingival margin and the adjacent tooth surface.

Gingival index. The occurrence of gingival inflammation at four surfaces of each tooth was assessed using the criteria of gingival index system (9), as follows: Score 0, normal gingiva; score 1, mild inflammation, slight change in color, slight edema, no bleeding on probing; score 2, moderate inflammation, redness, edema and glazing, bleeding on probing; score 3, severe inflammation, marked redness and edema, ulceration, tendency for spontaneous bleeding.

Saliva sample collection. At least 1 h prior to saliva collection, all participants were requested to not consume anything other than water. The subjects then repeatedly rinsed their mouths with sterile water and waited 1 to 2 min for the water to drain; up to 2 ml whole unstimulated saliva was collected into tubes. The collected saliva was then centrifuged at 804.96 x g for 10 min at room temperature (~20˚C) and the resulting supernatant was stored at -20˚C in Eppendorf tubes until further processing (10,11).

Detection of IL-8 and TNF-α levels. The ELISA procedure for the present study was the sandwich-ELISA technique. According to the manufacturer of the kit (Shanghai YL Biotech Co., Ltd.), a capture antibody that is highly specific for the biomarker (IL-8 and TNF-α) was attached to the wells of the strip plate. During the incubation time (60 min at 37˚C), each biomarker sample and known standards were bound to capture antibodies, followed by binding the biotinylated anti-IL-8 (Human IL-8 ELISA KIT, cat no. YLA1210HU, Shanghai YL Biotech Co., Ltd.) and anti-TNF-α (Human receptor superfamily member 13B ELISA KIT, cat no. YLA0576HU, Shanghai YL Biotech Co., Ltd.) secondary antibody (to the analyte to create the captured complex. The secondary antibody and any extra unbound analyte were rinsed away. The HRP conjugation solution (provided with the aforementioned kits) was added to each well, even the zero wells, to attach to the complex. The excess conjugate was then carefully washed away following incubation (60 min at 37˚C). Adding a chromogen substrate solution (provided with the aforementioned kits) to the wells gradually caused the conjugate and chromogen to produce a blue-colored compound. The addition of acid then halted color development. After the sulfuric acid reaction was terminated, the yellow hue was produced. The concentration of each biomarker in the samples and standards directly relates to the intensity of the colorful formed complex. The absorbances were assessed spectrophotometrically at 450 nm using an ELISA plate reader (Glomax; Promega Corporation).

The data were analyzed using G power 3.1.9.7 software from Franz-Faul (Kiel University, Germany). Given these conditions, the sample size was determined to be 40 participants in total, 20 in each of the two groups, assuming a medium effect size of 0.6 between them. This gave the statistical test an overall power of 85% and an α error of probability of 0.05. Accordingly, 44 subjects were included in the study.

Statistical analysis. All statistical analyses of the data were performed and processed with the computerized analysis statistical package for the social sciences (SPSS) software program (version 25, IBM Corp.) and GraphPad Prism software (version 9.0, Dotmatics). A value of $P<0.05$ was considered to indicate a statistically significant difference. The distribution

Table I. Demographic characteristics and clinical parameters in study groups.

Demographic characteristics	Study group n=22	Control group n=22	P-value
Age			0.258 (NS)[a]
Range (years)	20-35	20-33	
Mean ± SD	29.90±5.42	28.68±5.16	
Sex			0.762 (NS)[b]
Female	12 (54.54%)	11 (50.0%)	
Male	10 (45.45%)	11 (50.0%)	
Clinical parameters			
PLI (mean ± SD)	1.56±0.52	0.45±0.05	<0.001[c]
GI (mean ± SD)	1.57±0.57	0.90±0.29	<0.001[c]
DMFS	32.12±19.05	-	-

Data were analyzed using the [a]t-test or [b]Chi-squared test. [c]Indicates a statistically significant difference (P<0.05). PLI, plaque index; GI, gingival index; DMFS, decayed, missing and filled surfaces; SD, standard deviation.

Table II. Mean salivary levels of IL-8 and TNF-α in the study groups.

Salivary cytokines	Study group n=22	Control group n=22	t-test (P-value)
IL-8 (pg\ml)			0.002[a]
Range	22.24-69.54	20.55-65.28	
Mean ± SD	52.79±11.69	42.63±11.08	
TNF-α (pg\ml)			0.011[a]
Range	4.83-41.35	7.57-33.77	
Mean ± SD	21.78±9.22	16.39±6.55	

[a]Indicates a statistically significant difference (P<0.05). SD, standard deviation; IL-8, interleukin 8; TNF-α: tumor necrosis factor-α.

of clinical and immunological data was determined using the Shapiro-Wilk test. Since the variables in the dataset were normally distributed, parametric tests were preferred. The data are presented as descriptive statistics involving the mean and standard deviation. The Chi-squared test was preferred to analyze sex distributions. When comparing two groups, the (Student's t-test) was utilized. Pearson' rank correlation analysis was used to analyze the correlations between clinical and immunological parameters. In addition, to determine the diagnostic potential of the cytokines, a receiver operating characteristic (ROC) curve was established.

Results

Patient demographics and clinical parameters. The mean and standard deviation values were calculated for the demographic variables and clinical parameters of the two study groups (Table I). The demographic data distributions for patients were determined for sex (12 females, 10 males and age (range, 20-35 years). The DMFS ranged from 9 to 70 with a mean value of 32.12±19.05, and the sample site analysis of the clinical parameters plaque index (PLI) and gingival index (GI) were revealed to be all significantly higher for dental caries (study) group compared to the healthy group (P<0.05) (Table I).

Salivary cytokine levels. The present study revealed that the mean values of IL-8 and TNF-α were significantly higher (P<0.05) in the dental caries group in comparison to the group without caries (Table II). Moreover, as demonstrated in Table III and Figs. 1-3, the results revealed that there was a significant positive correlation between IL-8 and TNF-α in the patient group (r=0.624, P=0.001), whereas there are no significant correlations between clinical parameters and cytokines in caries group.

Diagnostic accuracy of salivary cytokines. ROC analysis was performed to determine the sensitivity and specificity of salivary IL-8 and TNF-α to discriminate caries patients from healthy controls. IL-8 in saliva exhibited acceptable potentials in differentiating patients from healthy controls (Fig. 4). Furthermore, the area under the curve (AUC) values for salivary IL-8 and TNF between the study and control groups were 0.735 and 0.683, respectively, as shown in Table IV.

Discussion

In dental pulp, dental caries promote a host inflammatory reaction that is evidenced by the buildup of inflammatory leucocytes and the subsequent produce of pro-inflammatory

Table III. Pearson's correlation analysis of the correlation between cytokines and clinical parameters in the caries group.

	Parameter				
Parameter	PLI	GI	DMFS	IL-8	TNF-α
PLI	-	r=0.217 P=0. 330	r=0.089 P=0. 723	r=0.257 P=0.247	r=0.114 P=0. 612
GI	r=0.217 P=0. 330	-	r=0.070 P=0.726	r=0.183 P=0. 413	r=-0.018 P=0.936
DMFS	r=0.089 P=0. 723	r=0.070 P=0. 726	-	r=0.157 P=0. 484	r=0.217 P=0. 332
IL-8	r=0.257 P=0.247	r=0.183 P=0. 413	r=0.157 P=0.484	-	r=0.624 P=0. 001[a]
TNF-α	r=0.114 P=0.612	r=-0.018 P=0.936	r=0.217 P=0.332	r=0.624 P=0. 001[a]	-

[a]Indicates a statistically significant difference (P<0.05). PLI, plaque index; GI, gingival index; DMFS, decayed, missing and filled surfaces; IL-8, interleukin 8; TNF-α: tumor necrosis factor-α.

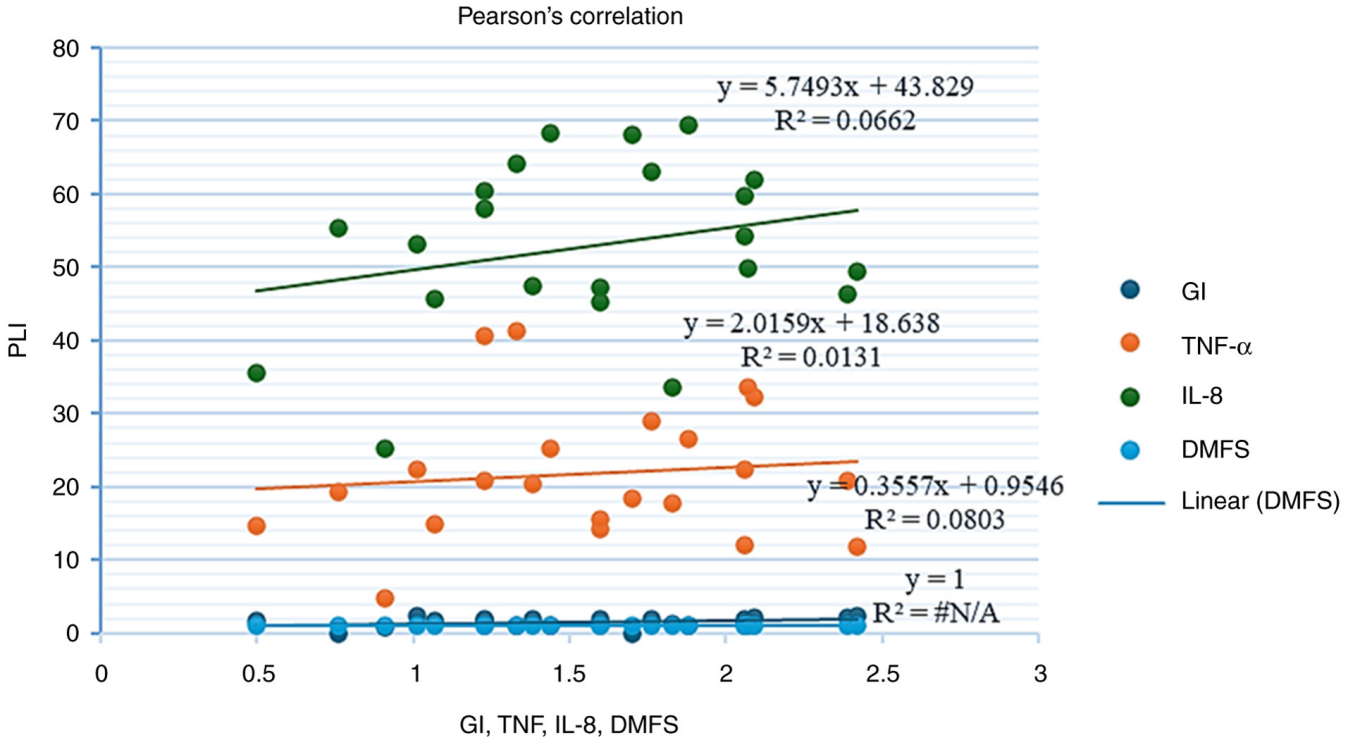

Figure 1. Scatter plot depicting the correlation between the PLI and GI, TNF-α, IL-8 and DMFS levels in the patient group. Each dot (•) represents a data point for an individual subject in this group. The line represents the linear regression line fitted to the data. The coefficient of determination (R^2) indicates the proportion of the variance in PLI that is predictable from other parameters. PLI, plaque index; GI, gingival index; DMFS, decayed, missing and filled surfaces.

cytokines (12). Cytokines were essential for inflammatory process and immune response. Saliva could be utilized as a non-invasive diagnostic liquid to evaluate biomarkers in the early and developed phases of the disease, and cytokines and other factors are helpful diagnostic and monitoring tools for the oral cavity (13). The present study assessed IL-8 levels in the participants and found that the dental caries group had higher levels than the control group. The IL-8 is a less commonly investigated interleukin among inflammatory biomarkers associated with dental caries. The present study demonstrated that the salivary levels of IL-8 exhibited a discriminative ability between healthy controls and patients with dental caries, with a sensitivity value of 0.95 and specificity value of 0.95. The diagnostic potential AUC value, as measured in the present study, was 0.735 with a cut-off point of 45.16 pg/ml. This finding is consistent with the findings of previous studies (14-16), which found increased levels of this cytokine among conditions with active dental caries compared to their control groups. According to Gornowicz *et al* (17), adolescents with dental caries had elevated amounts of this pro-inflammatory cytokine than those without dental decay, verifying the function of IL-8 as a pivotal chemokine in granulocytes chemotaxis. Likewise, Zhao *et al* (18) reported that patients with active carious lesions had a noticeably higher IL-8 concentration. Cariogenic pathogens are primarily Gram-positive, and their products, such as lipoteichoic acid, which is ubiquitous in cariogenic streptococci, promote Toll-like receptor 2

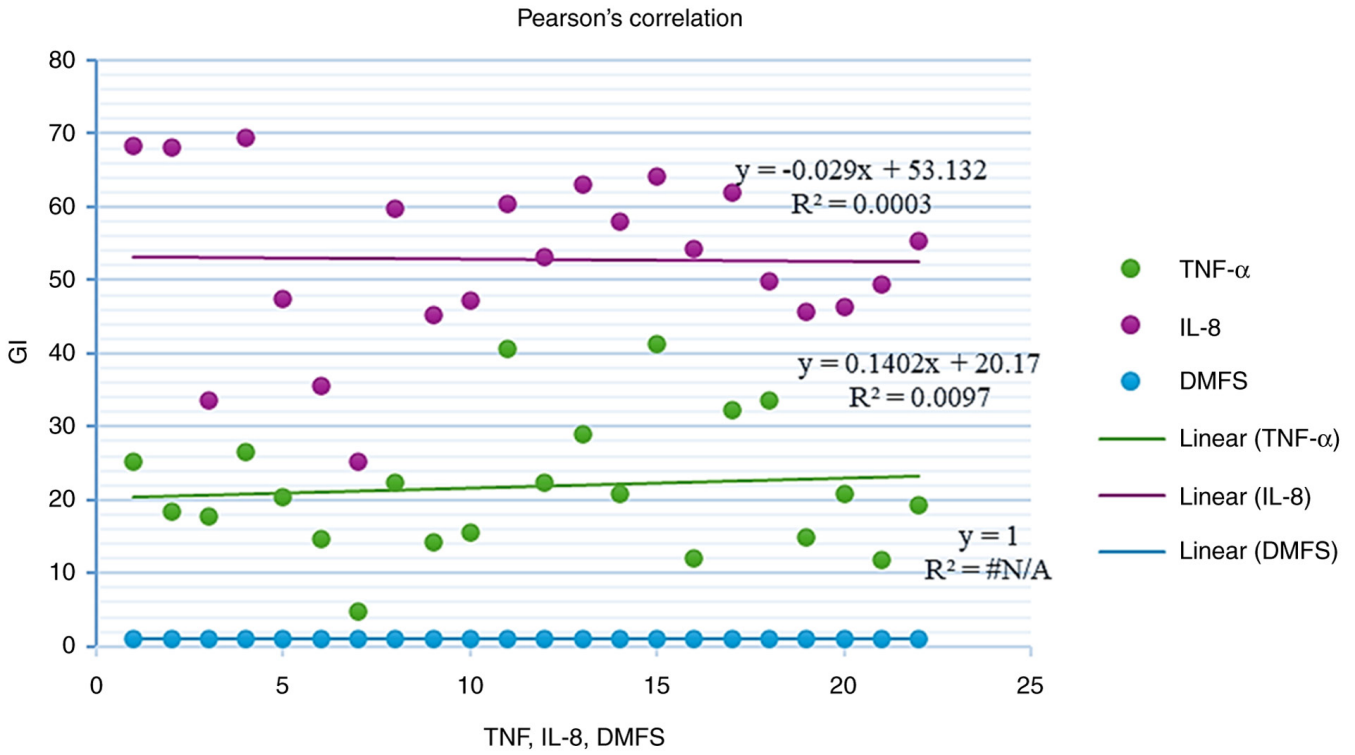

Figure 2. Scatter plot depicting the correlation between the GI and TNF-α, IL-8 and DMFS levels in the patient group. Each dot (•) represents a data point for an individual subject in this group. The line represents the linear regression line fitted to the data. The coefficient of determination (R^2) indicates the proportion of the variance in GI that is predictable from other parameters. PLI, plaque index; GI, gingival index; DMFS, decayed, missing and filled surfaces.

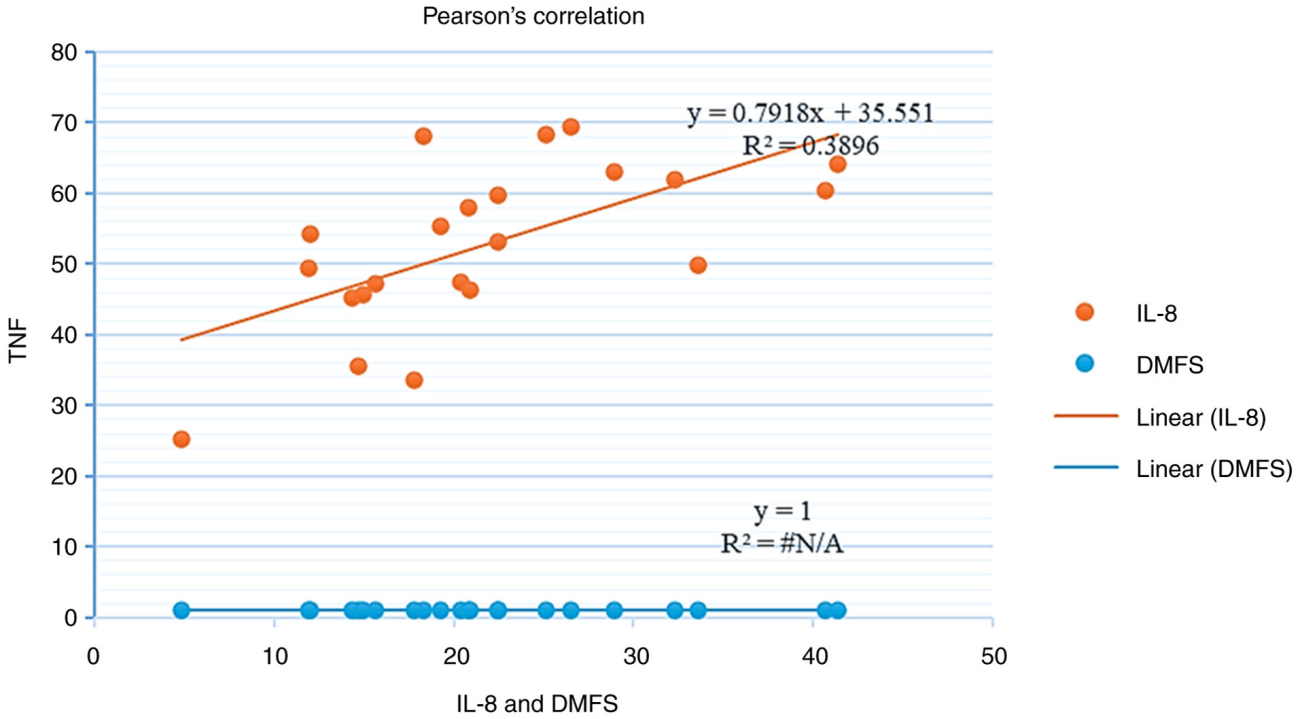

Figure 3. Scatter plot depicting the correlation between the TNF-α and (IL-8 and DMFS) levels in the patient group. Each dot (•) represents a data point for an individual subject in this group. The line represents the linear regression line fitted to the data. The coefficient of determination (R^2) indicates the proportion of the variance in TNF-α that is predictable from other parameters. PLI, plaque index; GI, gingival index; DMFS, decayed, missing and filled surfaces.

and inflammasomes peptides, which results in the marked production of this chemokine. This could explain the increase in the level of this mediator (19,20). However, two other studies (12,21) did not find any key variations between the caries and caries-free groups in terms of the salivary levels of IL-8.

Table IV. Comparison of the diagnostic properties of cytokines among the study groups.

Comparison	Test result variables (s)	AUC	P-value	Optimal cut of point	Sensitivity	Specificity
Dental caries vs. controls	IL-8	0.735	0.01[a]	45.16	0.95	0.95
	TNF-α	0.683	0.01[a]	22.43	0.95	0.95

[a]Indicates a statistically significant difference (P<0.05). IL-8, interleukin 8; TNF-α, tumor necrosis factor-α; AUC, area under the curve.

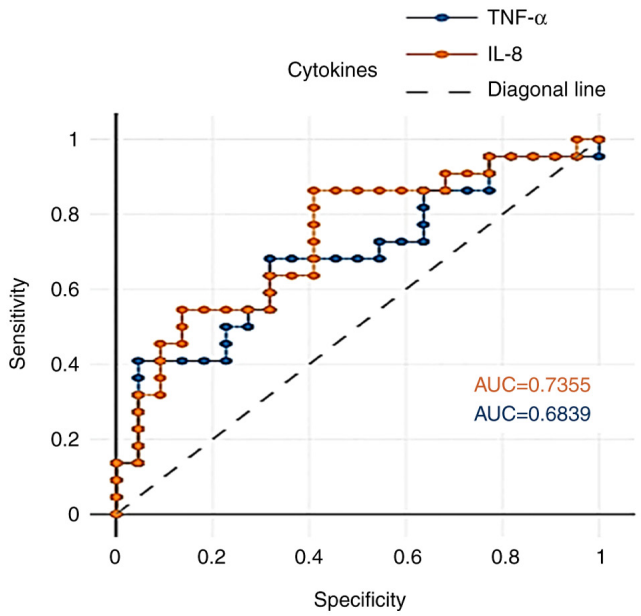

Figure 4. Receiver operating curves (ROC) for salivary cytokine levels in the patients vs. the controls. AUC, area under the curve.

Apart from IL-8, TNF-α levels was also analyzed in the present study, which were shown to be higher in the patients with caries. The salivary levels of TNF-α exhibited a discriminative ability between healthy controls and dental caries patients with a sensitivity value of 0.95 and specificity value of 0.95. The diagnostic potential AUC value, as measured herein, was 0.683 with a cut-off point of 22.43 pg/ml. Likewise, as regards the TNF-α level, previous studies (22-25) have demonstrated that the levels of this cytokine in the saliva of children and adults with dental caries are increased, and are associated with disease progression and severity. Higher levels of this cytokine may indicate an inflammatory response in the defenses of the body, leading to a production of TNF-α through damaging mechanisms. TNF-α is involved in various disease processes, including caries development (26,27). TNF-α is an empirical indicator that quantifies the amount of inflammation, perhaps beneficial for diagnosing caries (28). Kurtiş *et al* (29) found that increased levels of TNF-α in patients with dental caries reduced the total amount of osteoblasts and fibroblasts, promoting tooth demineralization and the occurrence of dental disease. However, only one study (16) reported higher levels of this cytokine in normal subjects than in individuals with the disease. The discrepancy between prior results and the current results may be attributable to variations in age or the use of non-parametric approaches for the analysis of data rather than the less conservative parametric approaches used in the present study. Furthermore, salivary TNF-α levels were found to be positively related to IL-8. This finding is not surprising, as TNFα and IL-8 are released by the same cell types, interact frequently and share numerous mechanisms, including inflammatory bone resorption. Moreover, These cytokines contribute to oral cavity immunity (17). TNF-α is an operational molecule that causes dental illnesses and increases IL-8 levels (6). In addition, the present study revealed that there was no significant association between cytokines levels and clinical parameters; however, according to Giudice *et al* (30), cytokine levels in children may increase as a result of poor plaque control, plaque buildup and periodontal inflammation.

The present study had a main limitation which should be mentioned. The present study did not include the severity of disease and anti-inflammatory cytokines were also not examined.

In conclusion, according to the findings of the present study, the salivary levels of the IL-8 and TNF-α cytokines were higher in patients with dental caries, suggesting a possible involvement of these cytokines in the etiology of dental caries. Moreover, IL-8 exhibited a moderate clinical accuracy in differentiating the patients from the controls. Thus, IL-8 and TNF-α may prove to be useful as diagnostic biomarkers for dental caries. The identification of IL-8 and TNF-α as potential biomarkers for dental caries opens new avenues for early detection, risk assessment and personalized treatments. These findings underscore the importance of inflammatory pathways in the pathogenesis of dental caries and highlight the need for further research to validate these biomarkers and their association with caries progression, in order to enhance diagnostic and therapeutic strategies. Moreover, the findings of the present study may pave the way for innovative, biomarker-driven approaches in preventive dentistry, ultimately reducing the global burden of dental caries.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BHAG and AAHA were involved in the conception and design of the study, in the literature search, in the clinical analysis, data analysis, statistical analysis, and in the preparation and reviewing of the manuscript. HKM, SSJ and FAMAK were involved in the conception and design of the study, as well as in data analysis, and in the preparation and reviewing of the manuscript. BHAG and HKM confirm the authenticity of all the raw data. The final manuscript has been read and approved by all authors.

Ethics approval and consent to participate

The Institutional Review Board's Ethics Committee of the Ethics Committee of the Dentistry School at the University of Baghdad, Baghdad, Iraq, gave its approval to this study (Reference no. 1000 on 7-1-2025). A written informed consent to participate in the study, as specified in the Declaration of Helsinki, was sought from each patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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