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Research Article

Changes and Roles of IL-6, hsCRP, and proCT in Patients with Chronic Periodontitis in Head and Neck Cancer Pre/Post Radiotherapy

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Abstract

Background: Head and neck cancer (HNC) patients frequently undergo radiotherapy as a standalone treatment or in combination with chemotherapy. Radiotherapy is associated with adverse effects, including detrimental impacts on periodontal health, which increase the risk of periodontitis. ***Objective***: To investigate the clinical significance of interleukin-6 (IL-6), high-sensitive C-reactive protein (hsCRP), and procalcitonin (proCT) as prognostic indicators. ***Methods***: 150 participants were divided into three groups: (n=50, HNC post-RT) patients with head and neck cancer who had radiation treatment six months ago (n=50, HNC pre-RT), and individuals with periodontal health as the control group (*n*=50). Probing pocket depth (PPD), clinical attachment loss (CAL), gingival bleeding index (GBI), plaque index (PI), and hyposalivation were meticulously recorded. To quantify serum concentrations of IL-6, hs-CRP, and proCT, an electrochemiluminescence immunoassay (eCLIA) was used. ***Results***: Serum levels of IL-6, hsCRP, and proCT were significantly elevated in two groups of patients with chronic periodontitis with head and neck cancer post-radiotherapy (CP+HNC post-RT) and patients with chronic periodontitis with HNC pre-radiotherapy (CP+HNC pre-RT) compared to a control group. ROC analysis demonstrated the diagnostic accuracy of IL-6, hsCRP, and proCT for both clinical cases. Furthermore, all clinical periodontal index scores (CAL, PPD, PI, and GBI) were significantly elevated compared to a control group. ***Conclusions***: HNC post-RT patients presented significantly higher serum IL-6, hs-CRP, proCT, and periodontal score levels than HNC pre-RT.

Keywords: Cytokines, Head and neck cancer, Periodontal disease, Radiotherapy.

التغييرات وأدوار IL-6 و hsCRP و proCT في المرضى الذين يعانون من التهاب دواعم السن المزمن في سرطان الرأس والرقبة قبل/ بعد العلاج الإشعاعي

الخلاصة

الخلفية: كثيرا ما يخضع مرضى سرطان الرأس والرقبة (HNC) للعلاج الإشعاعي كعلاج مستقل أو بالاشتراك مع العلاج الكيميائي. يرتبط العلاج الإشعاعي بالآثار الضارة، بما في ذلك صحة اللثة، مما يزيد من خطر الإصابة بالتهاب اللثة. **الهدف**: التحقيق في الأهمية السريرية للإنترلوكين -6 و hsCRPوالبروكالسيتونين كمؤشرات تنبؤية. **الطريقة**: تم تقسيم 150 مشاركا إلى ثلاث مجموعات، 50 مريضا في كل مجموعة (HNCبعد RT المرضى الذين يعانون من سرطان الرأس والرقبة الذين خضعوا للعلاج الإشعاعي قبل ستة أشهر) و (HNCقبل RT) والأفراد ذوي اللثة الصحية كمجموعة تحكم. تم تسجيل عمق الجيب (PPD) ، وفقدان التعلق السريري (CAL)، ومؤشر نزيف اللثة (GBI) ، ومؤشر البلاك (PI) ، ونقص اللعاب بدقة. لتحديد تركيزات مصل IL-6 و hsCRP و proCT ، تم استخدام المقايسة المناعية الكهربية (eCLIA). **النتائج**: كانت مستويات مصل IL-6 و hsCRP و proCT مرتفعة بشكل ملحوظ في مجموعتين من المرضى الذين يعانون من التهاب دواعم السن المزمن مع سرطان الرأس والرقبة بعد العلاج الإشعاعي (CP + HNC post-RT) والمرضى الذين يعانون من التهاب دواعم السن المزمن مع HNC قبل العلاج الإشعاعي (CP + HNC pre-RT) مقارنة بمجموعة التحكم. أظهر تحليل ROC الدقة التشخيصية ل IL-6 و hsCRP و proCT لكلتا الحالتين السريريتين. علاوة على ذلك ، كانت جميع درجات مؤشر اللثة السريري CAL و PPD و PI و GBI مرتفعة بشكل ملحوظ مقارنة بمجموعة التحكم. **الاستنتاجات**: ظهر لدى مرضى HNCبعد RT مستويات مصل IL-6 و hsCRP و proCT واللثة أعلى بكثير من مستويات HNC قبلRT .

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INTRODUCTION

Head and neck cancers (HNCs) are a wide range of malignant tumors that may develop in the larynx, pharynx, oropharynx, nasopharynx, and sinonasal canals, among other anatomical places. According to GLOBOCAN 2020, HNC is ranked as the seventh most common cancer globally, accounting for around 325,000 fatalities and 660,000 newly diagnosed cases annually [1,2]. Radiation therapy is one of the main treatments for most HNC patients. It may be used alone or with other therapies to control tumor cells. The progressive loss of periodontal tissues is a characteristic of periodontal disease, an inflammatory

condition of the tooth-supporting structures caused by a subgingival accumulation of anaerobic gram-negative bacteria [3]. Radiation therapy can exert a profound influence not only on the tumor-surrounding immunological microenvironment but also on the composition, quantity, and types of immune cells infiltrating the tumor. Furthermore, it simultaneously wields a direct and destructive impact on the tumor cells [4]. HNC radiation causes several negative implications, including a reduction in the immune system of the periodontium and a heightened risk of periodontitis and attachment loss [5-9]. Additionally, a patient's quality of life concerning psychological, social, functional, and visual aspects may be affected by the severity of their periodontitis [10]. Therefore, head and neck cancer patients who receive radiation treatment need to have their oral health monitored by medical and dental professionals [6]. The information above highlights the critical requirement for sensitive biomarkers to estimate the initial identification of radiation therapy-induced periodontal tissue loss. Several cells, including muscles, adipose tissue, fibroblasts, keratinocytes, and immune cells, produce proinflammatory cytokines, including interleukin-6 (IL-6) [11]. By its relationship to biological mediators of active periodontal degradation (APD) and the development of periodontitis, IL-6 contributes to the pathogenesis of periodontitis and plays a significant role in inflammation and infection responses. It also influences the host response to bacterial infections [11,12]. Furthermore, IL-6 can activate host responses and tissue-damaging cascades, including other pro-inflammatory cytokines [11,13]. Moreover, IL-6 suppresses bone formation, exerting pro-osteoclastic and anti-osteogenic effects on bone homeostasis [13]. However, a knowledge gap remains concerning using oral fluid indicators for real-time monitoring and prediction of HNC radiation side effects [14], releasing acute-phase reactants like C-reactive proteins (CRP) during the disease's destructive phase. High-sensitive CRP (hs-CRP) is an acute proinflammatory marker in both periodontal disease and many systemic infections [15]. This study aims to bridge this gap by investigating the association between serum IL-6, hs-CRP, and proCT levels and the prevalence of periodontitis in individuals who have obtained radiotherapy for head and neck cancer. By elucidating the potential link between these biomarkers and post-radiotherapy periodontal health, this research contributes to a deeper understanding of the systemic implications of cancer treatment on oral health. In the following sections, we will delve into the rationale behind selecting these biomarkers, the significance of periodontal health in the context of head and neck cancer treatment, and the broader implications of our findings for clinical practice. This investigation holds the promise of improving the management of periodontitis in cancer survivors and sheds light on the intricate interplay between systemic health and oral well-being.

METHODS

Participants

In this study, a total of 150 participants were enlisted. They include 50 cases of chronic periodontitis plus head and neck cancer receiving radiotherapy (CP+HNC post-RT) after six months; 50 cases of chronic periodontitis plus head and neck cancer pre-radiotherapy (CP+HNC pre-RT); and 50 health subjects saved as a control group. The investigation conformed with the principles outlined in the Declaration of Helsinki. It was approved by the Research Ethics Committee of Anbar Cancer Center, Ministry of Health, Iraq (Reference number 2022057, Date: 22 August 2022). All subjects gave informed written consent. The HNC patients included in the study were explicitly chosen from those pre/post radiotherapy treatments at the Anbar Cancer Center (ACC), Iraq, diagnosed with HNC by an oncologist according to NCCN guidelines [16]. To ensure that a comparable percentage of cases fit into the categories determined by the selection variable (age and sex), groups were chosen from an established age range (28-62 years), and sex, males made up about 80% of the cases and controls.

Exclusion criteria

We excluded individuals who satisfied any of the following criteria: a) had a history of salivary gland or oral diseases; b) had a confirmed diagnosis of systemic disease, multiple sclerosis, or xerostomia; and c) had refused to participate in the study.

Inclusion criteria

The following criteria were used to enroll patients: a) a pathologically identified malignant tumor of HNC (derived from epithelial cells); b) they have not received radiation treatment in the past; c) there is no history of previous salivary gland surgeries; d) there are no distant metastases; and e) a projected survival time of more than a year and an overall physical state with an ECOG performance score of (0–1) is considered satisfactory.

Sample collection

The serum of 150 participants was stored at -20 ºC. The blood was obtained from the participants via venipuncture and incubated in a water bath for 10 minutes until clotted, then centrifuged for 10 minutes at 2500 rpm. The serum was transferred into Eppendorf tubes after labeling each tube. Tubes were stored in a deep freezer until analysis. Samples were incubated at room temperature until thawing naturally during the experiment using eCLIA.

Chemicals and reagents

The reagent pack consists of MB, RA, RB, and calibrators (Nipigon Health Corp., Ontario, Canada, ProClinTM). Different lots cannot be used simultaneously or mixed up together. Unopened reagents should be stored at 2 °C and valid for 12 months. Opened reagents should be stored at 2 °C for

28 days, otherwise trashed. Materials and instruments required but not provided: Auffer, Buffer, Concentrated Washing Buffer, Robot_R1 Automated ECL Analyzer, and assay cup.

Automated ECL immunoassay analyzer

A recent fully automated analyzer based on electro-chemiluminescence immunology with more than 90 parameters, including IL-6, hs-CRP, and proCT as inflammation markers, was used in this study. The automated ECL immunoassay analyzer was set up for the following markers: IL-6, hs-CRP, proCT with calibrator, and control before testing time. Simply insert the (IL-6, hs-CRP, proCT) rack pack into the correct analyzer slot to automatically suspend magnetic beads at least 30 min before testing. The sample volumes required for each IL-6, hs-CRP, and proCT test are 30µl, 5µl, and 30µl, respectively. Afterward, the samples were thawed at room temperature and immediately run according to the manufacturer's protocol (Nipigon Health Corp., Ontario, Canada, ProClin^{TM}).

Clinical periodontal examination

Six months after irradiation concluded, a dentist (E.R.) checked periodontal parameters. Clinical parameters were evaluated, including probing pocket depth (PPD), clinical attachment loss (CAL), gingival bleeding index (GBI), and plaque index (PI) [14]. The clinical qualities of the current teeth, including the third molars, were evaluated. Clinical periodontal data were gathered at six sites, four for each tooth, respectively. A CAL index was performed from the bottom of the periodontal pocket to a junction of the cement and enamel. The GBI score was determined (0 or 1) based on bleeding present or absent for 10 seconds after probing [15]. PI determined a score (0–3) [17]. Williams Periodontal Probe (PW) was used for all hand probing measurements. The patients were diagnosed using the updated periodontitis classification method [18].

Data analysis

Categorical variables were characterized by frequency and percentage and were compared using the chi-square test. An independent-sample t-test was used to examine the continuous abnormally distributed data's mean and standard deviation (SD). The Mann-Whitney test between two groups or the Kruskal-Wallis test between several groups was used to investigate continuous variables having a skewed distribution. The mean and interquartile range for these variables were given. Pearson's coefficient correlation was used for correlation analysis. The receiver operating characteristic (ROC) curve analysis was used to evaluate the efficacy of serum indicators for (CP+HNC post-RT) and (CP+HNC pre-RT). When $p<0.01$, the data between differences were considered significant statistically. GraphPad Prism version 10.2.3 and IBM SPSS version 27 were used to process the analyses.

RESULTS

The characteristics and demographics of patients with head and neck cancer (HNC) and chronic periodontitis (CP) are shown in (Figure 1 and Table 1).

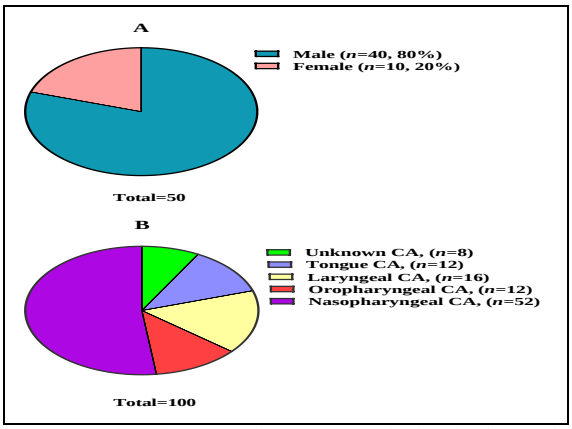

Figure 1: The Pie-Square for HNCs study involved **(A)** the Distribution of HNC patients by gender for each group and demographical data involved **(B)** Tumor sites.

Table 1: Demographic and medical characteristics of cases and controls

Variables	CP+HNC Post RT	CP+HNC Pre-RT	Control (Healthy)
Age (year)	41.34±8.41	40.06±6.41	40.12±6.40
Gender			
Male	40(80)	40(80)	40(80)
Female	10(20)	10(20)	10(20)
BMI (kg/m^2)	26.01±5.74	27.91± 4.61	25.45±4.91
Stage of Tumor n(%)			
1-2	9(18)	10(20)	N/A
3-4	41(82)	40(80)	
Smoking n(%)			
Yes	36 (72)	31 (62)	0 (0.0)
No	14 (28)	19 (38)	50 (100)
Drinking n(%)			
Yes	13 (26)	5 (10)	0 (0.0)
No	37 (74)	45 (90)	50 (100)
Stage of periodontitis n(%)			
Stage I	0 (0.0)	15 (30)	
Stage II	9 (18)	24 (48)	
Stage III	19 (38)	9 (18)	Absent
Stage IV	22 (44)	2 (4)	
Grade of periodontitis n(%)			
Grade A	0 (0.0)	19 (38)	
Grade B	0 (0.0)	31 (62)	Absent
Grade C	50(100)	0 (0.0)	
Type of treatment n(%)			
CT	22(44)	50(100)	N/A
CT+RT	28(56)	0 (0.0)	

Values are expressed as frequencies, percentages, and mean±SD. Abbreviations: CP: Chronic Periodontitis, HNC Post-RT: Head and Neck Cancer Post-radiotherapy, HNC Pre-RT: Head and Neck Cancer pre-radiotherapy, RT: Radiotherapy, CT+RT: Chemoradiotherapy, N/A: Not Applicable.

The mean age of patients was 41.34 years (28–62 years), and 40 (80%) of the patients had a history of smoking. The radiation dose was a mean of 6350 cGy and a range of 5700–7000 cGy. In addition to radiation, twenty-eight patients (56%) received concurrent systemic treatment (2–3 doses) with cetuximab or cisplatin. Also, the study included chronic periodontitis patients with HNCs pre-radiotherapy who received systemic drugs only. The age range of the patients was 28 to 60 years on average, with 40 (80%) of them being male. Thirty-

one (62%) and five (10%) of them had previously used alcohol, respectively, and more than half of them had smoked. Lastly, the research included a control group with a mean age of 40.12 years (29-60 years) to ensure periodontally healthy participants. The result showed a significant statistical difference (p=0.001) between the CP+HNC post-RT and CP+HNC pre-RT groups in terms of increased Clinical Attachment Level (CAL), Probing Pocket Depth (PPD), Plaque Index (PI), and Gingival Bleeding Index (GBI) compared to the healthy group. Additionally, the oral pH of the three groups (control, CP+HNC pre-RT, and CP+HNC post-RT) varied; at p= 0.001, the mean oral pH values were 7.12, 7.77, and 6.0, respectively. In addition, the average hyposalivation rates were 0.155, 0.30, and 0.35 milliliters per minute, respectively. As seen in Table 2, hyposalivation levels were considerably lower in the chronic periodontitis groups (p=0.001) in groups (CP+HNC post-RT) and (CP+HNC pre-RT), compared to the healthy group.

Table 2: Clinical features of head and neck cancer post/pre-RT on periodontal health

Variables	CP+HNC Post-RT	CP+HNC Pre-RT	Healthy (Control)
CAL (mm)	7.02±0.43[a]	6.34±0.78[b]	-
PPD (mm)	7.1±0.46[a]	6.12±0.61[b]	3.05±0.15[c]
PI (mm)	2.52±0.61[a]	1.94±1.03[b]	0.3±0.46[c]
GBI (%)	90.38±0.58[a]	63.12±0.60[b]	4.25±0.39[c]
Oral saliva pH	6.0±0.67[a]	7.77±0.28[b]	7.12±0.16[c]
Hyposalivation (ml/min)	0.15±0.04[a]	0.30±0.04[b]	0.35±0.05[c]

Values are expressed as mean±SD. Values with non-identical superscripts (a,b,c) are significantly different within the same parameter (p<0.05, Mann-Whitney test). Abbreviations; CAL: Clinical attachment level, PPD: periodontal pocket depth, PI: plaque index, GBI: gingival bleeding index.

The results appeared to increase serum IL-6 levels in cases CP+HNC post-RT (16.59 [7.94–24.81] pg/mL, p< 0.001) and CP+HNC pre-RT (11.12 [8.29–15.40] pg/mL, p< 0.001), compared to control (4.73 [0.22–10.07] pg/mL, p< 0.001) (Figure 2 and Table 3).

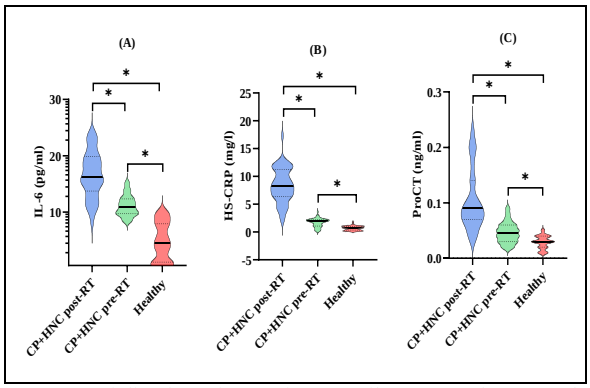

Figure 2: Violin plots of mean, interquartile range, and upper and lower levels for all groups involved: **(A)** serum IL-6 levels. **(B)** serum hs-CRP. **(C)** serum proCT levels. * Significant difference; Mann-Whitney or Kruskal-Wallis test.

It has been found that serum hsCRP levels were increased in cases CP+HNC post-RT (8.40 [2.04–17.32] pg/mL, p< 0.001) and CP+HNC pre-RT (1.68 [0.15–3.62] pg/mL, p< 0.001), compared to control (0.67 [0.15–1.76] pg/mL, p< 0.001) (Figure 2 and Table 3).

Table 3: The levels serum of IL-6, hs-CRP, and proCT in groups (CP+HNC Post-RT, CP+HNC Pre-RT, and healthy)

Variables	CP+ HNC Post-RT	CP+HNC Pre-RT	Healthy (Control)
IL-6 (pg/ml)	16.59±4.09[a]	11.12±1.84[b]	4.73±3.34[c]
hs-CRP (pg/ml)	8.40±3.12[a]	1.68±0.76[b]	0.67±0.38[c]
proCT (ng/ml)	0.104±0.09[a]	0.045±0.04[b]	0.028±0.03[c]

Values are expressed as mean±SD. Values with non-identical superscripts (a,b,c) are significantly different within the same parameter (p<0.05, Mann-Whitney test).

Furthermore, serum proCT levels were increased in patients CP+HNC post-RT (0.104 [0.03-0.23] pg/mL, p< 0.001) and CP+HNC pre-RT (0.045 [0.02–0.09] pg/mL, p< 0.001), compared to control (0.028 [0.01–0.05] pg/mL, p<0.001) (Figure 2 and Table 3). Receiver Operating Curve Characteristic (ROC) analyses indicated that serums IL-6, hs-CRP, and proCT might more accurately identify patients with CP+HNC post-RT (AUC= 0.993, 1.000, 0.962), respectively, than CP+HNC pre-RT (AUC= 0.961, 0.845, 0.737). In patients with CP+ HNC post-RT, increased cut-off values of IL-6, hs-CRP, and proCT (10.195, 2.471, 0.052) pg/mL, respectively, might more accurately predict clinical remission with a sensitivity of 96%, 98%, and specificity of 100%, 100%, 96%, respectively; p= 0.001. In patients with CP+HNC pre-RT, decreased cut-off values of IL-6, hsCRP, and proCT (8.162, 1.143, 0.036) pg/ml, respectively, might more accurately predict clinical remission with a sensitivity of 100%, 74%, 68%, and specificity of 82%, 94%, 76%, respectively; p= 0.001). Meanwhile, serum IL-6, hsCRP, and proCT displayed good ability to distinguish between moderate-to-severe patients with CP+HNC post-RT (AUC = 0.993, 1.000, 0.962, sensitivity = 96%, 98%, 88%, specificity = 100%, 100%, 96%, respectively) and CP+HNC pre-RT (AUC= 0.961, 0.845, 0.737, sensitivity = 100%, 74%, 68%, specificity = 82%, 94%, 76%, respectively) (Figure 3 and Table 4).

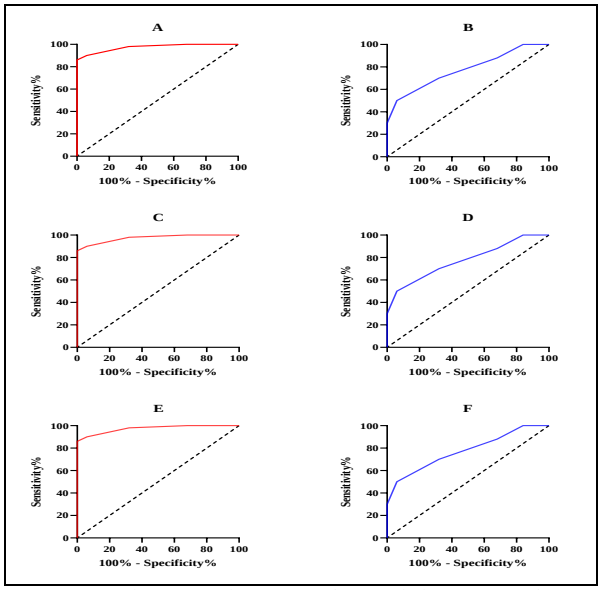

Figure 3: Receiver Operating Curve Characteristic (ROC) analyses involved: **(A)** IL-6 for (CP+HNC post-RT). **(B)** IL-6 for (CP+HNC pre-RT). **(C)** hs-CRP for (CP+HNC post-RT). **(D)** hs-CRP for (CP+HNC pre-RT). **(E)** proCT for (CP+HNC post-RT). **(F)** proCT for (CP+HNC pre-RT) patients.

Table 4: Receiver Operating Curve Characteristic (ROC) analyses serum IL-6, hs-CRP, and proCT to identify clinical remission

Variables	Groups	AUC	Cut-off	Sensitivity (%)	Specificity (%)	*p*
IL-6 (pg/ml)	CP+HNC Post-RT	0.993	10.195	96	100	0.001
	CP+HNC Pre-RT	0.961	8.162	100	82	0.001
hsCRP (pg/ml)	CP+HNC Post-RT	1.000	2.471	98	100	0.001
	CP+HNC Pre-RT	0.845	1.143	74	94	0.001
proCT (ng/ml)	CP+ HNC Post-RT	0.962	0.052	88	96	0.001
	CP+HNC Pre-RT	0.737	0.036	68	76	0.001

The results of the correlation appeared, and the periodontal parameter scores for measurements: Clinical Attachment Level (CAL), Probing Pocket Depth (PPD), Gingival Bleeding Index, and Plaque Index (PI) revealed a statistically significant positive correlation with serum IL-6, hsCRP, and proCT levels (p<0.01) and a significantly negative correlation with hyposalivation (p < 0.01), as shown in Table 5.

Table 5: Correlations among variables in CP+HNC post-RT patients involved IL-6, hs-CRP, proCT, hyposalivation, and Clinical periodontal parameters (CAL, PPD, PI, and GBI)

Variables	IL-6 (pg/ml)		hsCRP (pg/ml)		proCT (ng/ml)	
	r	*p*	*r*	*p*	*r*	*p*
CAL (mm)	0.764	0.001	0.583	0.001	0.500	0.001
PPD (mm)	0.951	0.001	0.794	0.001	0.853	0.001
PI (mm)	0.609	0.001	0.529	0.001	0.807	0.001
GBI (%)	0.822	0.001	0.857	0.001	0.859	0.001
Hyposalivation (ml/min)	- 0.710	0.001	- 0.782	0.001	- 0.565	0.001

DISCUSSION

The primary objective of the current study was to look into the association between clinical periodontal parameter levels in HNC pre/post-RT and blood levels of IL-6, hsCRP, and proCT. Serum IL-6, hsCRP, and proCT were also examined for their capacity to predict inflammatory condition. For the first time, the current findings validate the potential role of serum levels of IL-6, hsCRP, and proCT in monitoring periodontitis therapy and disease activity in HNC after RT. The eCLIA techniques used for analysis of IL-6, hsCRP, and proCT may be more suitable for identifying large-scale clinical samples because they can measure these markers quickly, provide reliable, quantitative data, and are entirely automated. Compared to classic ELISA techniques [20–23], eCLIA procedures provide rapid measurement, consistent, quantitative results, and total automation, making them possibly more suitable for identifying large-scale clinical samples. Our work provides a unique perspective by identifying the link between CP and the effects of radiation in patients with head and neck cancer (CP+HNC post-RT). We also compared this association in a group of patients with chronic periodontitis and head and neck cancer before exposure to radiation treatment (CP+HNC pre-RT), focusing on time-varying biomarkers to demonstrate the impact and harm produced by radiation. Previous clinical research has looked at serum concentrations of various inflammatory biomarkers as a first step toward understanding the link between periodontal disease and overall periodontal health in the older population. Furthermore, a study found that patients with periodontitis have higher levels of inflammatory markers than healthy people [24–26]. To date, there has been little research looking into the role of IL-6, hsCRP, and proCT in patients with CP and post-radiotherapy head and neck cancer. However, several studies have looked at pro-inflammatory biomarkers to better understand the impact of chronic periodontitis, which has been linked to various systemic conditions like cardiovascular disease [27], diabetes [28], and metabolic syndrome [29]. Our findings revealed that serum levels of IL-6 increased in both clinical conditions and were higher than in periodontally healthy individuals. Several investigations have shown that IL-6 pro-inflammatory activities play an important role in the development of lesions associated with apical periodontitis [30]. Previous studies found a considerable increase in IL-6 levels in symptomatic lesions compared to asymptomatic lesions and the control group [31–33]. The current investigation discovered that hsCRP and proCT levels were significantly higher in CP+HNC post-RT patients than in CP+HNC pre-RT and periodontally healthy people. Previous research has demonstrated that circulating proCT is a more discriminatory biomarker for periodontitis than serum hsCRP in patients with underlying arthritis [34]. Furthermore, previous research aimed to assess blood proCT levels in T2DM patients with CP versus periodontally healthy controls [20]. This study also shows that these three cytokines are closely linked to the development of CP by showing that serum IL-6, hsCRP, and proCT levels in the CP+HNC group were significantly higher at six-month post-radiotherapy than in cases of CP+HNC pre-RT compared to the control group. The pathologic mechanism of CP includes severe inflammation, which is thought to be a major contributor to oral issues in HNC patients after radiation. Nonetheless, it plays a crucial role in the progression of CP. According to previous research, polymorphonuclear leucocytes (PMNs) and monocytes, which are prominent in periodontal inflammation, interact with periodontitis endotoxins produced by gram-negative bacteria detected in subgingival plaque samples via Toll-like receptors (TLR). The complex formed when endotoxins and TLR interact activates both innate and adaptive immunity, resulting in the release of cytokines that coordinate the local and systemic inflammatory response [35]. Pro-inflammatory cytokines generated in the sick region cause liver cells to produce acute-phase proteins as a general response. Cytokines such as IL-1, IL-6, IL-8, and TNF are more important in controlling acute-phase protein synthesis than glucocorticoid hormones. These proteins attach to bacteria, activating complement proteins and eliminating pathogens [35]. The observed results

describe for the first time the importance of periodontal indices in HNC post-RT patients higher than CP with HNC pre-RT; as a result, the radiation dosage received by the submandibular and parotid glands in HNC patients is linked to alterations in the oral microenvironment [36,37]. The study also found that hyposalivation may develop periodontitis due to oral dryness in patients with CP+HNC post-RT. Furthermore, utilizing RT in the head and neck region alters oral microbes, resulting in bacteria associated with periodontal disease [38,39]. The study's single-variate analysis revealed an inverse relationship between hyposalivation and periodontal indicators with periodontitis. This is consistent with the results of our investigation. The higher periodontal loss observed in HNC post-RT patients may explain the decreased saliva (hyposalivation), demonstrating a clear link between periodontal features and hyposalivation. Furthermore, our findings indicate a significant negative association between IL-6, hsCRP, and proCT levels and hyposalivation. The current investigation revealed that the level of IL-6 was significantly and positively linked with the levels of hsCRP, proCT, and periodontal index. After six months of radiation, hsCRP showed a strong positive correlation with IL-6, proCT, and periodontal index scores. This is consistent with the results of our investigation. Periodontal impairment observed in HNC post-RT patients may explain the increases in IL-6, hsCRP, and proCT, revealing a clear association between periodontal parameters and blood levels of IL-6, hsCRP, and proCT. Future research should focus on prospective and randomized control studies with defined biological and clinical characteristics to discover the specific etiology of periodontal inflammation and HNC after RT. Furthermore, the importance of biomarkers in determining the link between these disorders requires further exploration.

Conclusion

The findings of this research are significant in terms of using IL-6, hsCRP, and proCT as markers to determine the severity of periodontitis, especially in patients pre/post-radiotherapy for head and neck cancer and chronic periodontitis.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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