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RESEARCH ARTICLE

Bascil et al: CARWL score and radiation periodontitis

CARWL score as a predictor of radiation-induced periodontitis in locally advanced head and neck cancer undergoing concurrent chemoradiotherapy

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ABSTRACT

Although concurrent chemoradiotherapy (CCRT) has improved outcomes in locally advanced head and neck cancer (LA-HNC), radiation-induced periodontitis (RIP) remains an under-recognized oral toxicity with significant consequences, including tooth loss and osteoradionecrosis. This study evaluates the utility of the novel CARWL score—a combined index of the C-reactive protein-to-albumin ratio (CAR) and significant weight loss (SWL)—for stratifying the risk of RIP in LA-HNC patients without baseline periodontitis undergoing CCRT. We conducted a retrospective analysis of 67 LA-HNC patients who underwent CCRT and received detailed oral examinations before and after treatment; none had periodontitis at the initiation of CCRT. Receiver operating characteristic (ROC) curve analysis identified an optimal pretreatment CAR cutoff of 3.07, with SWL defined as greater than 5% body weight loss in the preceding six months. Based on CAR (≥3.07 vs. <3.07) and SWL (present vs. absent), patients were categorized into three CARWL groups. The primary endpoint was the association between the baseline CARWL group and the rates of RIP following CCRT. RIP was diagnosed in 17 patients (25.4%) during follow-up, with incidences increasing progressively across CARWL-0, CARWL-1, and CARWL-2 groups (11.8% vs. 20.8% vs. 38.5%; $p = 0.007$). In multivariable Cox proportional-hazards analysis, a higher CARWL score emerged as an independent predictor of increased RIP risk (adjusted HR = 3.64; 95% CI 1.41–9.37; $p = 0.007$), and supplementary logistic regression sensitivity analysis corroborated these findings (adjusted OR = 3.58; 95% CI 1.35–9.45). These findings demonstrate that the pretreatment CARWL score serves as a straightforward and readily available biomarker that effectively stratifies the risk of radiation-induced periodontitis in LA-HNC patients treated with CCRT.

Keywords: C-reactive protein, serum albumin, significant weight loss, periodontitis, head and neck cancer, chemoradiotherapy.

INTRODUCTION

The mainstay of treatment options for locally advanced head and neck cancers (LA-HNCs) includes organ-sparing definitive concurrent chemoradiotherapy (CCRT) and neoadjuvant or adjuvant RT with or without chemotherapy, depending on the patients' performance and pathological risk factors (1,2). Advances in radiotherapy (RT) planning systems and delivery techniques have significantly improved the survival rates of these patients with tumor control (3). However, despite these advances in treatment, RT and CCRT are well-known to cause numerous acute and chronic complications, especially in the oral cavity (4-7). Tooth caries, tooth loss, osteoradionecrosis, radiation-induced trismus, and severe radiation-induced periodontitis (RIP) are some of the most serious problems associated with RT and CCRT, which significantly impact the quality of life in head and neck cancer (HNC) patients (8). Regrettably, RIP has received less attention in comparison to other radiation-induced toxicities despite its potential for severe consequences such as tooth loss and osteoradionecrosis.

Periodontitis is a prevalent issue in many populations, but it poses a particularly significant risk to the health of those who undergo RT in the head and neck region. These individuals are more susceptible to oral maladies, with RIP being a significant worry (8). After undergoing RT, about 70% of patients experience an increase in periodontal attachment loss (9, 10). Alterations in vascularity and cellularity in soft and hard tissues, impairment of salivary glands, and modification of collagen synthesis are attributed to the effects of RT and CCRT (8). These catastrophic changes result in hypovascular, hypocellular, hypoxic, hyperinflated, and hyperfibrotic oral tissues, impairing the ability of bone and soft tissues to heal appropriately and increasing the risk of infections and bone/soft tissue necrosis (8, 11, 12). Since RT alters both the blood vessels and the cellular composition of periodontal tissue, it impairs the synthesis of the periodontal ligament, misaligns existing Sharpey fibers, and increases the space within the periodontal ligament (13). These radiation-induced adverse tissue changes increase susceptibility to RIP and impair the capacity to regenerate and restore bone (14). RT or CCRT may alternatively cause severe RIP by inducing oral dysbiosis, replacing a healthy microbiome with pathogenic dominance. This dysbiotic oral niche may increase susceptibility to plaque accumulation and loss of periodontal attachment, key factors that pave the way for severe RIP (15). In this context, the radiation dose, particularly the mean oral-cavity

dose (MOCD), is a critical determinant of oral toxicity risk, reflecting cumulative exposure of soft and hard tissues to therapeutic irradiation. Higher MOCD values have been linked to increased rates of mucositis, xerostomia, and other oral complications, suggesting a potential role in the development of RIP as well.

So far, few investigations have assessed the progression of RIP in patients with HNC. The research conducted by Marques et al. (10) revealed a notable decrease in periodontal attachment in the irradiated areas 6-8 months after RT, compared with the non-irradiated regions. Similarly, the research conducted by Schuurhuis et al. observed an increase in periodontal pocket depth (pockets deepened by 4-5 mm) and/or the emergence of new periodontal pockets of 4 mm or more following radiation therapy (14). Untreated periodontitis can lead to chronic inflammation and ultimately result in tooth loss (16). Loss of teeth in patients with HNC increases the risk of malnutrition, weight loss (WL), and cachexia, which in turn reduces their likelihood of a more prolonged survival chance (17, 18, 19). Similarly, WL may significantly influence the prognosis of periodontal disease by reducing appropriate immune responses and treatment tolerance. In this context, Sales-Peres et al. conducted research that linked WL to an increase in gingival bleeding, which peaked six months after bariatric surgery (20).

Multiple inflammation markers have been examined for prognostic classification and toxicity prediction in patients with HNC. The most often examined indicators are C-reactive protein (CRP) and albumin (ALB). Chronic inflammation, such as periodontitis, triggers a widespread increase in inflammatory cytokines, leading to elevated CRP levels (21). Any increase in CRP levels is consistently associated with a decrease in ALB levels, owing to the inhibitory effects of CRP on ALB synthesis in the hepatocytes. Furthermore, reduced ALB production in the liver during long-term inflammation suggests a prolonged state of tissue catabolism due to nutrient deficiency, leading to weight loss (18). Kshirsagar et al. conducted a study investigating the relationship between periodontitis and blood levels of CRP and ALB. The results revealed a strong correlation between severe periodontitis and decreased serum ALB levels (22). Therefore, periodontitis can alter CRP and ALB levels in blood, with levels proportional to disease severity. Nevertheless, when periodontitis is absent, HNC-related and RT- or CCRT-induced varying degrees of inflammation may also contribute to the development of periodontitis, especially in individuals exposed to substantial radiation doses in their periodontal tissues (23). Confirming this remark,

Sakai et al. found that cancer patients had considerably higher rates of periodontitis (81.0 vs. 52.7%, p < 0.01) and severe periodontitis (44.0 vs. 12.4%, p < 0.01) compared to those in the national survey (24).

A significant correlation exists between body weight and periodontitis. Periodontitis, a manifestation of inadequate oral health, can lead to weight loss. On the other hand, involuntary weight loss or being underweight can substantially heighten the likelihood of developing osteoporosis and experiencing tooth loss owing to the increased susceptibility to periodontitis. In a comprehensive investigation of a large Korean cohort, Song et al. found that individuals with a body mass index (BMI) below 18.5 kg/m², indicating underweight status, had a significantly increased risk of periodontitis and tooth loss (25).

Recently, Topkan et al. introduced a new scoring system for immune, inflammation, and nutritional status, known as the CARWL scores. This system integrates the CRP-to-ALB ratio (CAR) and significant weight loss (SWL), defined as involuntary weight loss > 5% in the previous 6 months (26). In the first-of-its-kind study, the authors demonstrated that this scoring system was highly efficient at stratifying stage IIIC patients into three groups with significantly distinct survival outcomes, which appeared to outperform the current American Joint Committee on Cancer (AJCC) staging framework. However, the novel CARWL scoring system, despite its robust performance, has not been evaluated for its efficiency in predicting RIP rates after RT or CCRT in HNC patients. Accordingly, this retrospective cohort study aimed to assess the predictive ability of pretreatment CARWL scores for the development of RIP in patients with LA-HNC who had no evidence of periodontitis before CCRT.

MATERIALS AND METHODS

Study population, ethics, and consent

This retrospective cohort analysis strictly adhered to the principles outlined in the Declaration of Helsinki and its subsequent revisions. Before gathering patient data, the research design (Project No. DKA19/39A) underwent a thorough audit and received approval from the Institutional Assessment Board of Baskent University. Every eligible patient provided their written informed consent before initiating the indicated therapy. This authorization allowed analysis of blood tests and pathology

specimens and the sharing of study findings via academic publications or congress presentations.

The Department of Radiation Oncology and the Dentistry Clinics at Baskent University's Adana Research and Treatment Center collaborated to design the current research. A retrospective search of the medical records of LA-HNC patients who received CCRT and completed oral and dental examinations before and after treatment was conducted, spanning from February 2010 to January 2024 (Figure 1). Although both investigations were performed at the same institution, the present dataset was assembled independently of our previously published 2024 cohort (27), and no patients from that series were included in this analysis. The current study population was limited exclusively to patients with complete baseline and follow-up periodontal assessments. To determine the exact rates of RIP and their correlation with CARWL score groups, all participants in this study were required to have documented evidence of no periodontitis before the commencement of CCRT. To be qualified for the study, patients were required to meet the following criteria: ≥ 18 years of age, have histopathologic confirmation of squamous cell carcinoma, have locally advanced disease according to the 8th edition of the AJCC's cancer staging criteria (T1-2N1-3M0 or T3-4N0-3M0), have no prior history of other cancers, have not undergone systemic chemotherapy or RT in the HNC region, and have accessible complete blood count and biochemistry test results before CCRT. Additional study qualifications included access to dental and panoramic radiographic examination records before and after CCRT completion. Patients who had a prior history of jaw surgery, documented tumor or lymph node invasion in the mandible or maxilla, or osteoradionecrosis of the jaws were not included in the study. The research protocol also deemed patients using steroids or other immunosuppressive medications ineligible. To minimize the potential influence of preexisting inflammatory and immunological conditions and medication use on outcomes, individuals with chronic systemic immune or inflammatory illnesses were also excluded from the analysis.

Oral examinations and management

We evaluated all patients with oral and dental screening, including clinical and radiographic examinations. An experienced maxillofacial surgeon (ES) and a periodontist (SB) conducted dental examinations before CCRT, adhering to the guidelines of the American Dental Association (ADA) and the US Food and Drug

Administration (FDA) (28). Each patient underwent radiographic examinations with panoramic scans, following the manufacturer's instructions (J. Morita, Veraviewepocs 2D, Kyoto, Japan). We used illuminated and explorer mirrors to examine all teeth for dental caries, adhering to World Health Organization guidelines (29).

The periodontal examination included evaluations of plaque and gingival bleeding scores, probing depth, mobility, and periodontal attachment loss. Plaque accumulation was assessed using the Silness–Löe Plaque Index on the buccal surfaces of all teeth. Probing depth (PD), bleeding on probing (BOP), and clinical attachment level (CAL) were recorded at six sites per tooth (mesiobuccal, buccal, distobuccal, mesiolingual, lingual, distolingual) using a UNC-15 periodontal probe with ≤2 mm controlled insertion force. Whole-mouth periodontal scores (plaque, BOP, PD, and CAL) were calculated as the mean of all measured sites, and the percentage of sites with BOP was also documented. All periodontal examinations were performed by a single experienced periodontist, ensuring methodological consistency (30). Two methods were employed to assess gingival inflammation. The Gingival Index was used to determine gingival inflammation for each tooth (31), with scores ranging from 0 (normal gingiva) to 3 (severe inflammation). The Gingival Index was used to assess the buccal surface of each tooth. To evaluate the presence of inflammation in the gums, we use a method called gingival BOP. During both exams, all teeth were thoroughly checked on six surfaces. The score was obtained by inserting a periodontal probe no more than 2 mm into the sulcus at the gingival border, namely at the mesiobuccal line angle, and then advancing it down the buccal surface to the distobuccal line angle. We documented the presence (1) or absence (0) of blood after inspecting each tooth in a quadrant. The bleeding-on-probing score was determined by summing the number of teeth with bleeding areas for each person. The assessment of probing depth and loss of attachment included the use of a UNC-15 periodontal probe at six specified areas on each tooth. These locations were the mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual sites. Two measurements were taken at each probing location. Initially, measurements were taken of the distance between the free gingival margin and the cementoenamel junction. Subsequently, the distance between the free gingival margin and the pocket base was measured, with the pocket depth as the second measurement. The loss of attachment was calculated by subtracting the original measurement from the second measurement when the free gingival margin was located above the cementoenamel junction, and by

adding the two measurements when the free gingival margin was located below this junction.

RIP was defined in strict accordance with the 2018 AAP/EFP Classification of Periodontal and Peri-Implant Diseases and Conditions. Periodontitis was diagnosed based on: (i) clinical attachment loss (CAL) at ≥2 non-adjacent teeth, or (ii) interdental CAL ≥3 mm with probing depth ≥4 mm at ≥2 teeth, confirmed by radiographic evidence of alveolar bone loss. Staging and grading were performed according to the official consensus framework. Notably, dental caries, endodontic pathology (periapical lesions), and non-periodontal causes of tooth mobility were excluded from the case definition. The previous reference to Miller's recession classification, which is a gingival recession index rather than a mobility scale, was removed. Consequently, the endpoint was limited exclusively to periodontal disease. All RIP cases were re-evaluated and re-tabulated according to this standardized definition, and the overall results remained unchanged (32,33).

The periodontist also emphasized the importance of oral hygiene and provided instructions on self-care for the patients. The periodontist removed plaque and calculus from patients with gingivitis to improve oral hygiene and optimize oral health, and addressed superficial tooth decay by applying fillings. It is important to note that no patient presented with periodontitis at baseline, and the complete baseline periodontal status of all patients is provided in Supplementary Table S1.

Assessment of C-reactive protein-to-albumin ratio and significant weight loss

For each patient, CRP and serum ALB levels were obtained from laboratory records on day 1 of CCRT (27). CRP was measured in mg/L using an immunoturbidimetric assay (ISO 15189–accredited core laboratory, Baskent University), and ALB was recorded in g/dL and converted to g/L (×10) before analysis. The CAR was calculated as CRP (mg/L) ÷ ALB (g/L). Body weight was abstracted from clinic scale measurements whenever available. The 6-month pre-CCRT weight target was −180 days (acceptable window: −195 to −165 days). If no clinic record existed in that interval, a patient-reported weight was recorded and flagged. Percent weight loss was calculated as

$$\%WL = [(Weight_{-6mo} - Weight\text{-}baseline) / Weight_{-6mo}] \times 100,$$

with positive values indicating loss. A sensitivity analysis excluding self-reported weights yielded results consistent with the main analysis. SWL is defined as a

reduction in weight of more than 5% during the previous 6 months, according to the Delphi criteria established by Fearon et al. (34).

Chemoradiotherapy protocol

In January 2010, our Department of Radiation Oncology adopted intensity-modulated radiotherapy (IMRT) as the standard treatment for patients with LA-HNC. The radiotherapy technique used for all patients in this study was simultaneous integrated boost IMRT (SIB-IMRT) (35). To enhance the accuracy of target volume delineation, co-registered computed tomography (CT), 18F-FDG PET/CT, and magnetic resonance imaging (MRI) datasets were routinely utilized. The oral cavity was contoured in accordance with the EORTC Head and Neck Cancer contouring guidelines (36), encompassing the mucosal surfaces of the anterior and posterior oral cavity, including the buccal mucosa, gingiva, oral tongue (excluding the base), floor of mouth, and hard palate, while excluding the teeth, mandible, and maxilla. All contours underwent peer review during the institutional radiotherapy plan–quality assurance process, and DVHs were exported directly from Eclipse for quantitative analysis. For analytical purposes, the MOCD was extracted from dose–volume histograms (DVHs) generated in the Eclipse Treatment Planning System (Varian Medical Systems, version 15.6).

The prescribed SIB-IMRT doses for the high-risk, intermediate-risk, and low-risk planning target volumes (PTVs) were 70 Gy, 59.4 Gy, and 54 Gy, respectively, delivered in 33 daily fractions over 5 days per week. In addition to IMRT, three cycles of concurrent cisplatin (80 mg/m²) were administered every 21 days. Following completion of CCRT, all patients were instructed to receive two additional cycles of adjuvant chemotherapy with cisplatin and 5-fluorouracil. Antiemetic prophylaxis, nutritional supplementation, and other supportive care were provided in accordance with institutional protocols.

Follow-up dental examination

The protocol described in the “baseline oral examination” section was followed, and further oral and dental exams were conducted according to the set schedule or as decided by clinical indications. The patients' clinical and radiological examination data were recorded at 1, 3, 6, 9, and 12 months after CCRT, and every 6 months thereafter throughout the follow-up period. The treatment criteria for each patient

were established and presented in accordance with the concepts outlined in the previously mentioned “baseline oral examination” section.

Statistical analysis

The study’s primary objective was to evaluate the association between pretreatment CARWL scores and time to RIP development during follow-up after CCRT in LA-HNC patients without baseline periodontitis. Continuous variables were summarized as medians (range), and categorical variables as frequency percentages. Intergroup differences were assessed using the Chi-square test, Student’s t-test, or Spearman correlation, as appropriate. Receiver operating characteristic (ROC) analysis was initially used to determine an optimal pretreatment CAR cutoff (Youden’s J statistic) for stratifying the cohort by outcome risk. Because RIP could occur at varying follow-up times, the primary analysis employed a Cox proportional-hazards model, and all effect measures are reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). The proportional-hazards assumption was verified using Schoenfeld residuals. To explore potential nonlinearity in the CAR–RIP relationship, restricted cubic splines (three knots at the 10^{th}, 50^{th}, and 90^{th} percentiles) were incorporated into the Cox model, with the p-value for nonlinearity guiding interpretation. To confirm the robustness and directionality of associations, a secondary logistic-regression sensitivity model was also fitted, and its effect estimates are reported as odds ratios (ORs) with 95% CIs. Given the limited number of RIP events (n = 17), ridge-penalized Cox regression was applied to minimize overfitting and small-sample bias. Candidate covariates were prespecified based on clinical relevance: age, sex, T category, N category, smoking status, MOCD, number of concurrent chemotherapy cycles, baseline periodontal status, and CARWL group. To evaluate potential multicollinearity among predictors, variance inflation factors (VIFs) were calculated, and all values were <2.0, indicating acceptable independence among covariates. In addition, a MOCD×CARWL interaction term was tested; because it did not reach statistical significance, it was not retained in the final Cox model. Internal validation was performed using 1,000 bootstrap resampling to estimate bias-corrected C-statistics (Harrell’s C), calibration intercepts, and slopes with accompanying calibration plots. The optimism-corrected model performance, including that of the continuous-CAR spline model, was derived from this bootstrap procedure. All statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant.

To account for potential inflation of type I error from multiple subgroup comparisons, the Bonferroni correction was applied exclusively to analyses involving the three-level CARWL classification (CARWL-0, CARWL-1, and CARWL-2). Because these strata yielded three pairwise contrasts, the adjusted significance level was set at α-adj = 0.05/3 = 0.0167. All Bonferroni-adjusted p-values (p-adj) are reported in tables and figures, and footnotes specify the correction method.

Ethics approval and consent to participate

Before acquiring any information from the patient, the study design was approved by the Institutional Review Board of the Baskent University School of Medicine and complied with the Declaration of Helsinki.

RESULTS

The present study retrospectively reviewed the data of 228 patients with LA-HNC who underwent CCRT. However, only 67 patients met the inclusion criteria, whereas 161 were excluded because they were edentulous or lacked pre- and postoperative dental or periodontal records. As shown in Table 1, the study population comprised 50.7% with oral cavity cancer and 49.3% with nasopharyngeal cancer. The cohort consisted of 70.1% men, with a median age of 56 years (range, 18–75). Histories of smoking and alcohol use were present in 59.7% and 35.8% of patients, respectively. A substantial proportion had advanced primary (56.8%) or nodal (62.7%) disease.

CCRT was generally well tolerated, with 24 cases (35.8%) of grade 3 and 4 cases (6.0%) of grade 4 mucositis, and no treatment-related deaths. The median duration of CCRT was 47 days (range, 45–55 days). Five patients (8.2%) required brief treatment interruptions ($\leq$ 5 days) due to grade $\geq$ 3 radiation-induced mucositis, after which therapy was completed as planned. During CCRT and adjuvant phases, 77.6% and 62.7% of patients completed the planned 2–3 and 1–2 cycles of chemotherapy, respectively. Radiotherapy target volumes encompassed the primary tumor and elective nodal regions, as defined by institutional contouring protocols. Among the 67 patients, 58 (86.6%) received radiation, including level Ib, and 61 (91.0%) had coverage extending to level IIb nodal regions. The MOCD was 50.1 Gy (range, 10.8–61.2 Gy), and 53.7% received $\geq$ 50.1 Gy. The median mandibular dose was 38.4 Gy (range, 11.8–62.4 Gy), and 47.8% received > 38.4 Gy. At a median follow-up of 69.6 months (range, 7.8–146.9 months), 37 patients (55.2%) underwent

1 to 3 tooth extractions, and 17 (25.4%) developed RIP at a median of 10.0 months (range, 5.3–17.1 months). RIP status was absent in 74.6% of cases and present in 25.4 %.

ROC curve analysis identified an optimal CAR cutoff of 3.07 for predicting RIP (AUC = 0.735; sensitivity = 77.2%; specificity = 72.8%; Youden's J = 0.50) (Figure 2). In line with the Delphi consensus by Fearon et al. (34) and the CARWL framework by Topkan et al. (26), SWL was defined as ≥5% body weight loss within 6 months prior to CCRT. Based on these parameters, patients were initially stratified into four CARWL categories: Group 1 (CAR < 3.07 and WL ≤ 5%), Group 2 (CAR < 3.07 and WL > 5%), Group 3 (CAR ≥ 3.07 and WL ≤ 5%), and Group 4 (CAR ≥ 3.07 and WL > 5%). The corresponding incidences of RIP were 11.8% (95 % CI: 5.2 – 24.9 %), 21.4% (95% CI: 8.3 – 43.0 %), 22.7% (95 % CI: 9.9 – 45.2 %), and 38.5 % (95 % CI: 20.2 – 61.4 %), respectively. Because Groups 2 and 3 showed statistically indistinguishable rates (χ^2 = 0.18, p = 0.67) with overlapping confidence intervals, they were merged to create the final three-tier CARWL schema: CARWL-0 (CAR < 3.07 and WL ≤ 5 %), CARWL-1 (CAR < 3.07 and WL > 5% or CAR ≥ 3.07 and WL ≤ 5%), and CARWL-2 (CAR ≥ 3.07 and WL > 5 %).

When analyzed as an ordinal variable, CARWL demonstrated a significant monotonic association with increasing RIP incidence (likelihood-ratio trend test p = 0.006), confirming the validity of its ordered structure. The incidence of RIP increased progressively across CARWL categories,11.8 % vs 20.8 % vs 38.5 % (p = 0.007, omnibus Wald test), indicating a near-doubling of risk with each successive stratum (Figure 3, Table 2). In the multivariable Cox proportional-hazards analysis, adjusted hazard ratios (HRs) for RIP were 1.78 (1.22–3.68) for CARWL-1 and 3.64 (95 % CI: 1.41 – 9.37) for CARWL-2, relative to CARWL-0. The logistic-regression sensitivity model yielded comparable adjusted odds ratios (ORs): 1.82 (95 % CI: 1.32 – 3.84) and 3.58 (95 % CI: 1.35 – 9.45), respectively. For clinical interpretability, adjusted absolute risk differences derived from logistic marginal effects corresponded to + 8.9% (95 % CI: – 4.2 % to +19.3 %) for CARWL-1 and +23.5 % (95 % CI: + 8.6 % to + 37.8 %) for CARWL-2 compared with CARWL-0. All VIFs were < 2.0, confirming the absence of problematic multicollinearity among predictors. The MOCD×CARWL interaction term was not statistically significant (p = 0.53) and was therefore not included in the final multivariable model.

Modeling CAR as a continuous variable with restricted cubic splines confirmed an approximately linear relationship with RIP hazard (p = 0.21 for nonlinearity). The optimism-corrected Harrell's C-statistic (0.72) and calibration slope (0.94) demonstrated good discrimination and minimal overfitting following 1,000 bootstrap validations. Collectively, these model-based contrasts confirm that the risk and hazard of developing RIP increase in a graded, near-linear fashion across ascending CARWL categories, underscoring the prognostic value of the CARWL index in this population.

Given the strong association between MOCD > 50.1 Gy and RIP occurrence, additional analyses were performed to assess this relationship as a continuous variable and to evaluate potential nonlinearity. When modeled continuously within the Cox proportional-hazards framework, MOCD exhibited a consistent, near-linear increase in RIP hazard, without evidence of significant nonlinearity (p for nonlinearity = 0.18). Each incremental 1 Gy increase in MOCD was associated with an adjusted hazard ratio (HR) of 1.09 (95 % CI: 1.03 – 1.17, p = 0.004) for developing RIP, confirming a dose-dependent relationship. The spline-based dose–response curve (Supplementary Figure S1) demonstrated a gradual, monotonic rise in risk across the dose range. For clinical interpretability and to maintain comparability with the existing literature, MOCD was dichotomized at 50.1 Gy in Table 2; however, the continuous-model results reinforce that RIP risk increases proportionally with higher oral-cavity dose exposure.

The final multivariable Cox model demonstrated good discrimination, with a Harrell's C-index of 0.72 (95 % CI: 0.64 – 0.80) obtained through 1,000 bootstrap resamples. Calibration analysis showed close agreement between predicted and observed risks, with a calibration slope of 0.94 and an intercept of − 0.03, indicating minimal overfitting. The calibration plot (Supplementary Figure S2) confirmed excellent model performance across the full range of predicted probabilities. To further assess clinical applicability, decision-curve analysis (DCA) was performed across threshold probabilities from 5 % to 40 %, demonstrating a clear net benefit of the full model relative to treat-all or treat-none strategies (Supplementary Figure S3).

Univariate analyses further identified smoking (p = 0.011), T3–4 stage (p = 0.014), ≥ 2 chemotherapy cycles (p = 0.008), MOCD ≥ 50.1 Gy (p < 0.001), and a higher CARWL group (p = 0.007) as significant predictors of RIP. In the final

multivariable Cox model, CARWL score, T3–4 stage, MOCD ≥ 50.1 Gy, and smoking each retained independent significance (Table 2).

DISCUSSION

Periodontitis is one of the most critical oral diseases and has a characteristic that can cause the most frequent tooth loss if left untreated. Therefore, it is a significant concern due to its impact on the quality of life, especially for patients with LA-HNC treated with CCRT. Inspired by this concern, we planned to investigate, for the first time in the literature, the effect of pretreatment CARWL index on the risk of periodontitis after RT. The study showed that the RIP rate increased significantly from CARWL-0 to CARWL-1 and CARWL-2 (11.8 % vs. 20.8 % vs. 38.5 %; p = 0.007). In addition to this important result, we also found a statistically significant association between RIP and smoking status (p = 0.023), T3-4 stage (p = 0.021), concurrent chemotherapy cycles 2-3 (p = 0.013), and MOCD >50.1 Gy (p < 0.001).

Smoking is a serious factor that significantly affects the health of periodontal tissues (37). Consistent with these data, our study found a statistically significant association between RIP and smoking (p = 0.023). Independent of the inflammatory effects of CCRT, smoking affects the vascularization of gingival tissues, negatively impacting inflammatory and immune responses and the healing capacity of periodontal tissues. In addition, immune and inflammatory cells produce a wide range of inflammatory mediators in response to smoking. For example, studies are reporting that the inflammatory biomarkers C-reactive protein and IL-6 are higher in the plasma of smokers compared to non-smokers (38). The increased risk of periodontal disease in patients irradiated in the head and neck region has generally been associated with hyposalivation and modification of the oral microbiome, and, at the microscopic level, loss of proliferative capacity of oral keratinocytes and increased proinflammatory cytokines have also been reported in a radiation dose-dependent manner (13). For example, in the study by Irie et al., which aimed to review and discuss important issues related to periodontal treatment before and after RT in patients with HNC, 37 scientific articles and their results were reviewed. Periodontal health was reported to be affected by radiation, and tooth loss and advanced periodontal disease are associated with poor periodontal health before the start of RT (39). These results, in parallel with the known harmful effects of smoking, emphasize the importance of

including more meticulous determination of oral health before RT in our routine work in these cancer patients, especially those with a history of smoking.

Another important finding from our study is that the risk of RIP is higher in patients with advanced T stages (T3-4) and those who received 2-3 CRT cycles (p = 0.021 and p = 0.013, respectively). For patients with locally advanced stage III and IV tumors, standard treatment typically involves surgery with reconstruction followed by postoperative RT. When high-risk features are identified during surgery, the treatment is often intensified to include postoperative chemoradiotherapy to improve outcomes and lower the chance of recurrence. In HNCs, the radiation dose usually correlates with the tumor stage. As the stage increases, indicating a more advanced or aggressive tumor, the radiation dose and treatment intensity generally increase to achieve optimal control (40). Higher doses to the jawbone and oral tissues during HNC treatment significantly raise the risk of oral complications, including periodontitis (8). During chemotherapy, drugs can contribute to the development of conditions such as mucositis, xerostomia, gingival bleeding, and periodontitis (41). The extent of these issues depends on factors like cancer type, chemotherapy modality, number of cycles, and the interval between cycles (42). The literature suggests that chemotherapeutic agents may directly affect the buccal mucosa via the circulation or indirectly through saliva secretion (41). Additionally, these drugs can alter salivary flow and its components, such as amylase and immunoglobulin A (IgA), both quantitatively and qualitatively (43). For instance, Azher et al. assessed the oral health of children with acute lymphoblastic leukemia undergoing chemotherapy and found that gingival inflammation was highest during the maintenance phase, followed by the induction therapy with RT and other induction phases (44). Furthermore, increasing radiotherapy dose and the number of chemotherapy cycles in advanced-stage patients appear to exacerbate periodontal tissue damage, thereby increasing susceptibility to RIP after definitive CCRT. These findings suggest a potential additive detrimental effect of concurrent chemoradiotherapy and cumulative chemotherapy exposure on periodontal structures. Beyond treatment-related factors, patient-specific biological and behavioral factors—especially baseline oral hygiene and pre-treatment dental care—may influence periodontal vulnerability during CCRT. Despite all patients receiving standardized professional cleaning before therapy, individual differences in plaque control, gingival inflammation, and oral microbiome composition could affect the host's immune-inflammatory response. Poor plaque control is known to

exacerbate neutrophil-mediated soft-tissue damage, disrupt cytokine expression (e.g., IL-1β, TNF-α), and promote a dysbiotic microbial community that is more prone to radiation-induced mucosal and periodontal breakdown. Variations in pre-treatment periodontal stability may serve as confounders by changing the biological threshold at which radiation and chemotherapy cause connective tissue destruction and alveolar bone loss. Recognizing these patient-specific factors is essential for understanding RIP risk and for developing personalized preventive strategies before CCRT.

One of the key findings of our study was the clear relationship between MOCD and RIP development, consistent with the existing literature. Although the majority of RIP events occurred in patients receiving an MOCD ≥ 50.1 Gy, a few cases were also observed below this threshold, indicating a dose-dependent—but not absolute—risk relationship. In the present cohort, RIP was detected predominantly among patients who received MOCDs ≥ 50.1 Gy, with a median onset time of 10 months after CCRT (37.8 % vs. 13.8 % for MOCD < 50.1 Gy, $p < 0.001$). Radiotherapy exerts cytotoxic effects on both normal and malignant tissues, and direct damage to oral mucosa, gingiva, and alveolar bone frequently accompanies concurrent chemoradiotherapy. Indirect injury may also result from systemic toxicity, inflammation, or vascular compromise secondary to treatment (45). Supporting these findings, Hommez et al. reported that teeth with apical periodontitis received significantly higher radiation doses than those with normal periapical status (37.2 Gy vs. 24.9 Gy; t = 2.823, $p < 0.01$) (46). Similarly, Pathomburi et al. demonstrated that periodontal ligament cell proliferation decreased threefold when the local radiation dose exceeded 42 Gy compared with 20 Gy (47). Mechanistically, irradiation-induced vascular injury initiates a cascade of swelling, capillary degeneration, and necrosis, leading to increased permeability and progressive perivascular fibrosis (48). The accumulation of fibrotic tissue eventually results in capillary stenosis and obliteration, causing reduced vascularity and cellularity of the periodontal ligament, widening of the periodontal space, and thickening or distortion of Sharpey's fibers. Over time, these microstructural alterations contribute to late-onset RIP and the deterioration of periodontal integrity (49).

The most notable result of our study is the meaningful effect of the pretreatment CARWL index on the risk of severe periodontitis after RT. In the present study, we showed that the RIP rate increased significantly from CARWL-0 to CARWL-1 and CARWL-2 (11.8 % vs. 20.8 % vs. 38.5 %; $p = 0.007$). Although

previous studies have shown the effects of the pre-CCRT systemic inflammation index (SIS) (50) and the GLUCAR index on tooth loss after CCRT (27), the impact of any inflammatory mediator on the RIP rate has not been demonstrated. Therefore, although it is difficult to compare the results of our study, understanding the mechanism will be easier when the components of the CARWL index are examined individually. As is known, CRP, one of the components of the CARWL index, is a pentameric plasma protein with homologs that plays a role in the systemic response to inflammation (51). It is regulated by cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) (52), and it is also suggested that CRP may be found in changes in the cellular and molecular components of peripheral blood due to inflammatory changes in periodontal tissues in people with periodontitis. Various studies have demonstrated a positive association between chronic periodontitis and elevated serum CRP levels (53,54), as it is biologically plausible that inflammatory mediators (IL-1, IL-6, and TNF-α) released during periodontitis can stimulate hepatocytes to produce CRP. Similarly, it can be expected that, in the presence of chronic periodontitis, higher serum CRP levels would be observed (51). On the other hand, Kuar et al. examined the effect of another factor, ALB, on chronic periodontitis in 60 patients. They reported that chronic periodontitis was more common in the group with serum ALB levels below 4.815 g/dL ($p < 0.001$), and this was due to an association between low serum ALB levels and periodontal attachment loss (55). Similarly, Ogawa et al reported an inverse independent association between periodontal disease and serum ALB concentrations (56). The last component, significant WL (%), i.e., malnutrition, has also been reported to affect periodontal tissues; for example, nutritional deficiencies have been associated with more rapid tissue deterioration. Thus, dietary abnormalities tend to favor the inflammatory processes involved in periodontal disorders (57). Additionally, malnutrition affects the development of the oral cavity and the progression of oral diseases by altering tissue homeostasis, decreasing resistance to microbial biofilms, and reducing tissue repair capacity (58). When all these data are combined, the difference between CARWL-0 and CARWL-1 and CARWL-2 obtained in our study (11.8 % vs. 20.8 % vs. 38.5 %; $p = 0.007$) would also be an expected result. Because only one patient (1.5%) died before experiencing RIP, the number of competing events was too small to distort the estimated risk of RIP over time materially. Under such circumstances, any bias introduced by treating these deaths as non-informative

censoring is expected to be minimal, so standard Kaplan–Meier estimation and Cox regression provide risk estimates that are effectively equivalent to those obtained from formal competing-risk methods.

Several limitations constrain the present study. First, it relied on retrospective data from a single institution and included a relatively small sample, potentially introducing unintentional selection bias, a common feature of such analyses. The limited cohort size is critical. Because, given the observed RIP incidence of 25.4 % in the final cohort, a conventional rule of thumb (10–15 outcome events per predictor) suggests that approximately 70–105 RIP events, equivalent to a total sample size of roughly 140–210 patients, would be required for a fully powered multivariable model. Consequently, the present findings should be interpreted with caution and warrant validation in larger, prospective cohorts with sufficient statistical power. Furthermore, the lack of a validation cohort may have limited our ability to fully explain our findings, underscoring the need for additional studies in this field. Potential confounding factors related to baseline oral health may also have influenced the observed associations. Although all participants received standardized professional dental cleaning before CCRT, interindividual differences in plaque control, gingival inflammation, and adherence to oral hygiene instructions could have affected the risk of periodontal breakdown during and after therapy. Such variations may modulate local inflammatory responses, shift biofilm composition, and alter mucosal or connective-tissue resilience. While these factors were minimized through uniform pre-treatment dental management, they remain an inherent limitation of retrospective analyses and warrant consideration in future prospective trials. Considering the excluded patients, although detailed comparisons were not feasible, they appeared broadly similar in age and tumor stage distribution to those analyzed. Still, they included a higher proportion of edentulous individuals and patients without baseline dental evaluations. Because these exclusions primarily reflect the availability of oral health documentation rather than oncologic factors, some degree of selection bias is possible, and the generalizability of our findings may therefore be limited to dentate patients with complete periodontal assessments. It is also essential to acknowledge that our study only analyzed data collected on the first day of CCRT treatment. Therefore, it is necessary to recognize that the current CAR cutoff may not precisely identify the optimal threshold for categorizing LA-HNC risk. This is because levels of ALB and CRP can fluctuate considerably during and after concurrent CCRT.

Furthermore, we may have overlooked the possibility of establishing reliable cause-and-effect relationships between a cohort with an elevated CARWL score and cytokine/chemokine levels, nutritional status, and immune-inflammatory markers, such as IL-1, IL-6, and TNF-α. Therefore, it is essential to acknowledge that the findings of this study should be interpreted as exploratory and hypothesis-generating, rather than definitive recommendations, until other well-designed, large-scale research studies addressing these important themes provide supporting data. However, the components of the CARWL index are easily accessible, simple to calculate, cost-efficient, and consistently display specific characteristics. This makes the index a practical biomarker for frequent clinical use. Therefore, despite the limitations mentioned earlier, the newly developed CARWL score can categorize LA-HNC patients into risk groups based on their likelihood of RIP. If further research confirms its effectiveness, the widespread use of this method could enable the careful monitoring of individuals at high risk and the early deployment of preventative measures to prevent periodontitis in its initial stages.

CONCLUSION

RIP is a significant complication that can occur during the treatment of LA-HNC patients. It has poor prognostic value as it increases the risk of tooth loss, osteoradionecrosis, and weight loss. Our research indicates that the newly developed CARWL index is a dependable biomarker that accurately predicts the occurrence rates of RIP in patients with LA-HNC. If future research confirms the results outlined in this study, this new biological marker could represent a breakthrough in identifying individuals at high risk. This could potentially enhance current methods and lead to the development of effective preventive strategies and post-assessment protocols.

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Data availability: Data cannot be shared publicly because it is owned and saved by the Baskent University Medical Faculty. However, for researchers who meet the criteria for access to confidential data, data are available from the Baskent University

Institutional Data Access / Ethics Committee (contact via Baskent University Ethics Committee): contact address, adanabaskent@baskent.edu.tr.

Consent for publication: We ensured that all patients signed an informed consent form before the beginning of the evaluation, either themselves or their legally authorized representatives, for the acquisition and analysis of the patient's sociodemographic, dental, and medical records; blood samples; and publication of the outcomes.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Periodontitis rates according to baseline and treatment characteristics

Characteristics	All patients (*n*= 67)	Periodontitis *n* = 17 (%)	Univariate *p* value	Multivariate *p* value	Multivariate HR (95% CI)
Median age group < 56 years ≥ 56 years	36 31	11 (30.5) 6 (19.4)	0.40	-	-
Gender Female Male	20 47	4 (20.0) 13 (27.7)	0.76	-	-
Smoking status Yes No	40 27	13 (32.5) 4 (14.8)	0.011	0.023	2.07 (1.42-4.08)
Alcohol consumption status Yes No	24 43	6 (25.0) 11(25.6)	1.0	-	-
Type of cancer, N (%) Oral cavity Nasopharynx	34 33	6 (26.1) 8 (24.2)	0.79	-	-
T-stage group 1-2 3-4	29 38	4 (13.8) 13 (34.2)	0.014	0.021	2.27 (1.52-3.84)
N-stage group 0-1 2-3	25 42	5(20.0) 12 (28.5)	0.26	-	-
Concurrent chemotherapy	15	2 (13.3)	0.008	0.013	2.48 (1.65-

cycles 1 2-3	52	15 (28.8)			4.03)
Adjuvant chemotherapy cycles 0 1-2	25 42	5 (24.0) 11 (26.2)	0.39	-	-
MOCD group, N (%) ≤ 50.1 Gy > 50.1 Gy	36 31	5 (13.8) 12 (38.7)	< 0.001	< 0.001	2.98 (1.94-5.67)
CARWL group CARWL-0 (Reference) CARWL-1 CARWL-2	17 24 26	2 (11.8) 5 (20.8) 10 (38.5)	0.007	0.007	- 1.78 (1.22–3.68) 3.64 (1.41 - 9.37)

RIP rates and 95% confidence intervals are determined using exact Clopper–Pearson estimates. Comparisons among the CARWL subgroups (CARWL-0, CARWL-1, and CARWL-2) were adjusted for multiple testing through the Bonferroni method, resulting in an adjusted significance threshold of α-adj = 0.0167 (0.05 / 3). Abbreviations: CCRT: Concurrent chemoradiotherapy; T: Tumor; N: Node; Gy: Gray; MOCD: Mean oral cavity dose.

Table 2. The results of univariate and multivariate analysis depicting the significance level factors of radiation-induced periodontitis

Characteristics	All patients (*n*=67)	CARWL-0 (*n*=17)	CARWL-1 (*n*=24)	CARWL-2 (*n*=26)	*p* value
Median age, years (range)	56 (18-75)	58(43-75)	53 (22-72)	56 (18-69)	0.29
Median age group, years, N (%)					
≥56	36 (53.7)	12 (70.6)	9 (37.5)	15 (57.7)	0.98
<56	31 (46.3)	5 (29.4)	15 (62.5)	11 (42.3)	
Gender, N (%)					
Female	20 (29.9)	5 (29.4)	8 (33.3)	7 (26.9)	0.89
Male	47 (70.1)	12 (70.6)	16 (66.7)	19 (73.1)	
Smoking status, N (%)					
Yes	40 (59.7)	10 (58.8)	14 (58.3)	16 (61.5)	0.97
No	27 (40.3)	7 (41.2)	10 (41.7)	10 (38.5)	
Alcohol consumption status, N (%)					
Yes	24 (35.8)	7 (41.2)	7 (29.2)	10 (38.5)	0.69
No	43 (64.2)	10 (58.8)	17 (70.8)	16 (61.5)	
Median number of pre-CCRT tooth extraction, N, (range)	2 (0-10)	2 (0-10)	2 (0-4)	2 (0-7)	0.59
Type of cancer, N (%)					
Oral cavity	34 (50.7)	7 (41.1)	14(58.3)	13 (50.0)	
Nasopharynx	33 (49.3)	10 (58.9)	10 (41.7)	13 (50.0)	0.34
T-stage group, N (%)	29 (43.2)	8 (47.1)	10 (41.7)	11 (42.3)	0.78
1-2	38 (56.8)	9 (52.9)	14 (58.3)	15 (57.7)	
3-4					
N-stage group, N (%)					
0-1	25 (37.3)	7 (41.2)	9 (37.5)	9 (34.6)	0.63
2-3	52 (62.7)	10 (58.8)	15 (62.5)	17 (65.4)	
Concurrent chemotherapy					

cycles, N (%) 1 2-3	15 (22.4) 52 (77.6)	3 (20.0) 11 (80.0)	5 (20.8) 19 (79.2)	7 (26.9) 20 (73.1)	0.57
Adjuvant chemotherapy cycles, N (%) 0 1-2	25 (37.3) 42 (62.7)	6 (35.2) 11 (64.8)	9 (37.5) 15 (62.5)	10 (38.5) 16 (61.5)	0.81
MOCD, Gy (range)	50.1 (10.8-61.2)	51.7 (13.4-60.2)	48.6 (10.8-59.3)	49.4 (11.4-61.2)	0.51
MOCD group, N (%) ≤ 50.1 Gy > 50.1 Gy	36 (53.7) 31 (46.3)	9 (52.9) 8 (47.1)	12 (50.0) 12 (50.0)	15 (57.7) 11 (42.3)	0.42
Median post-CCRT extracted tooth, N (range)	1 (0-3)	0 (0-1)	1 (0-3)	1 (0-2)	0.79
Post-CCRT tooth extraction, N (%) Absent Present	30 (44.8) 37 (55.2)	9 (52.9) 8 (47.1)	9 (37.5) 15 (62.5)	12 (46.2) 14 (53.8)	0.61
RIP status, N (%) Absent Present	50 (74.6) 17 (25.4)	15 (88.2) 2 (11.8)	19 (79.2) 5 (20.8)	16 (61.5) 10 (38.5)	0.004
Median time from CCRT to periodontitis, mo	10.0 (5.3-17.1)	13.2(10.4-17.1)	11.6 (11.2-14.1)	8.7 (5.3-11.4)	0.28

Abbrevations: CCRT: Concurrent chemoradiotherapy; T: Tumor; N: Node; MOCD: Mean oral cavity dose; Gy: Gray, RIP: Radiation-induced periodontitis, mo: Month.

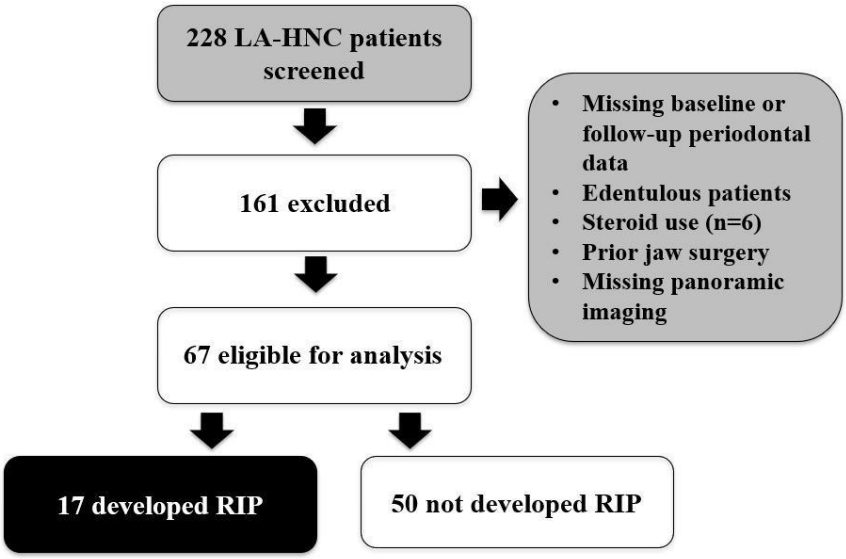

Figure 1. Flowchart illustrating the patient selection process

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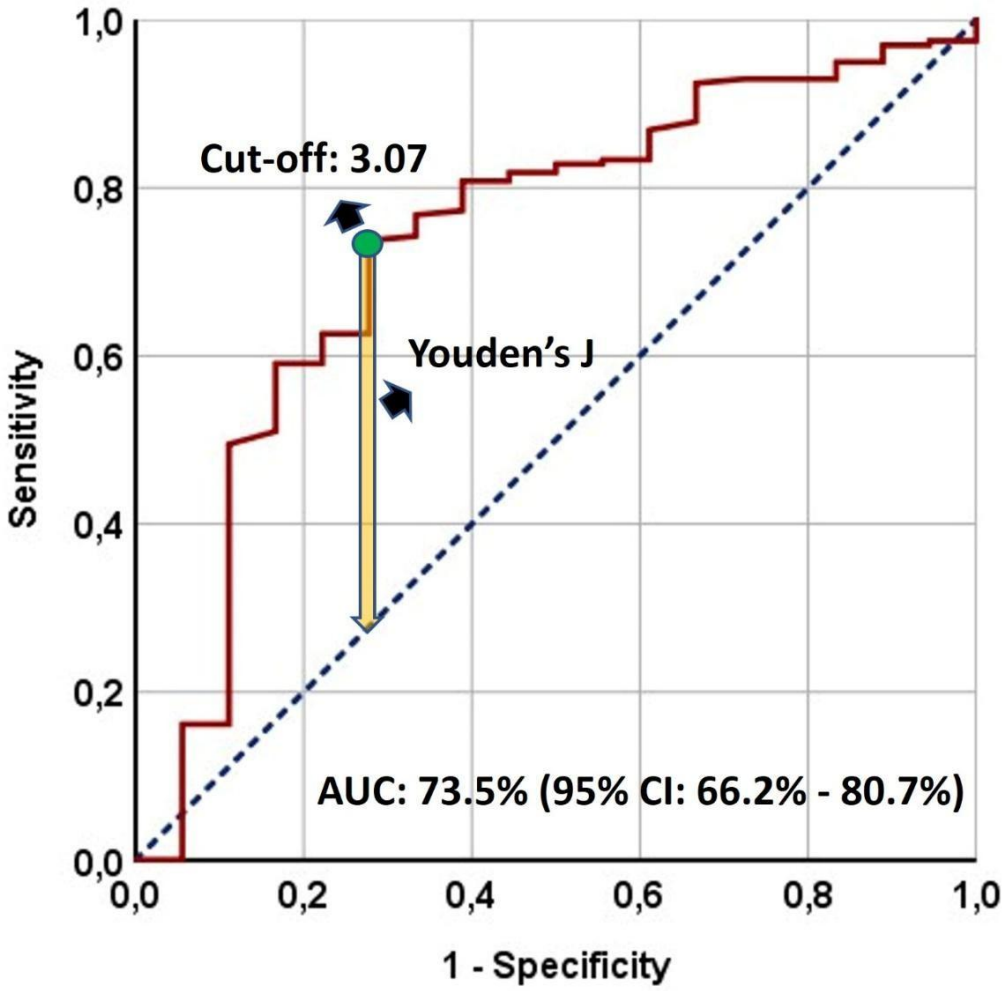

Figure 2. Receiver operating characteristic (ROC) curve of CAR for prediction of RIP. ROC curve analysis identified an optimal CAR cutoff for RIP at 3.07, with an AUC of 73.5%, sensitivity of 77.2%, specificity of 72.8%, and a J-index of 0.50. RIP rates and their corresponding 95% confidence intervals were calculated using exact (Clopper–Pearson) methods. Comparisons among CARWL subgroups (CARWL-0, CARWL-1, and CARWL-2) were adjusted for multiple testing through the Bonferroni method, resulting in an adjusted significance threshold of α-adj = 0.0167 (0.05 / 3). Abbreviations: CAR: C-reactive protein-albumin ratio; RIP: Radiation-induced periodontitis; AUC: Area under the curve; Sens: Sensitivity; Spec: Specificity.

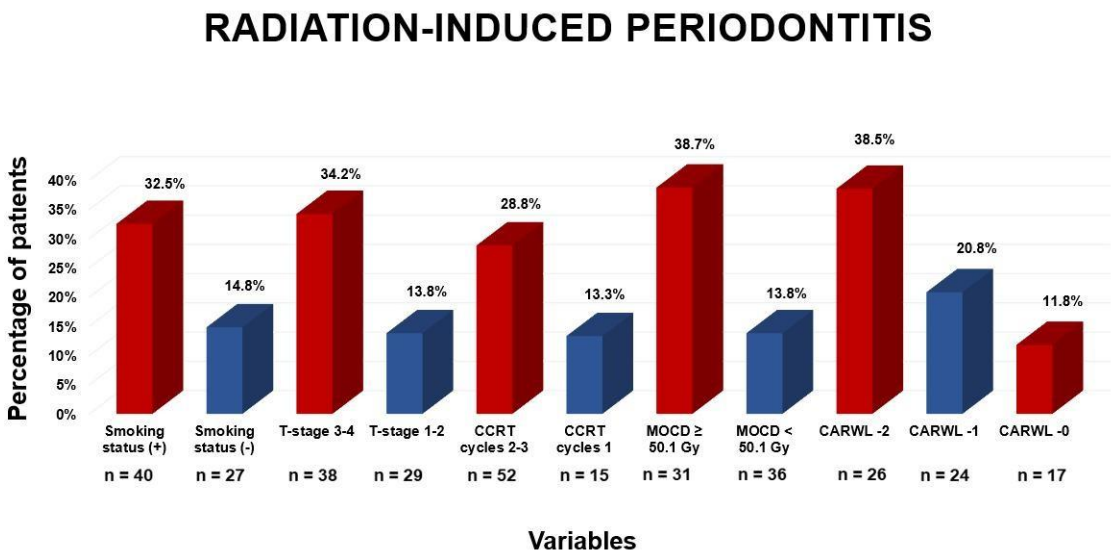

Figure 3. Rates of radiation-induced periodontitis by contributing factors. Bar plots illustrate the proportion of patients who developed RIP based on smoking status, T stage, number of CCRT cycles, MOCD, and CARWL category. The incidence of RIP exhibited a progressive increase across CARWL strata (11.8%, 20.8%, 38.5%; likelihood-ratio trend test $p = 0.006$; omnibus Wald $p = 0.007$), thereby reinforcing the ordered structure of the CARWL index. Abbreviations: T: Tumor; CCRT: Concurrent chemoradiotherapy; MOCD: Mean oral cavity dose; Gy: Gray; CARWL: C-reactive protein to albumin ratio; WL: Weight loss.

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SUPPLEMENTAL DATA

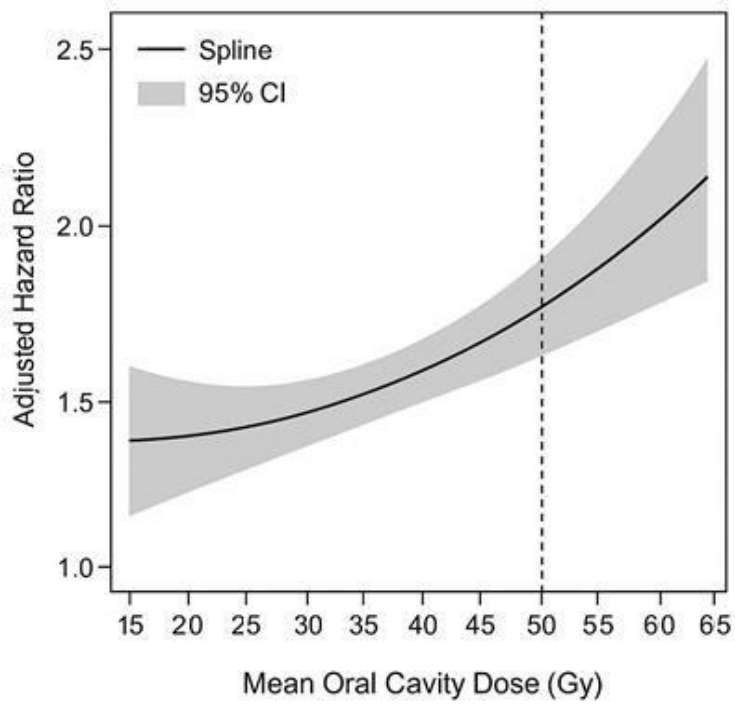

Figure S1. Dose–response relationship between mean oral cavity dose and risk of radiation-induced periodontitis. Restricted cubic spline analysis illustrating the relationship between mean oral cavity dose (Gy) and the adjusted hazard ratio for radiation-induced periodontitis (RIP) derived from the Cox proportional hazards model. The solid line depicts the estimated hazard ratio, while the shaded area shows the 95% confidence interval. The curve indicates a monotonic and nearly linear increase in RIP risk with higher dose exposure (p for nonlinearity = 0.18). The vertical dashed line at 50.1 Gy marks the clinically relevant cutoff point used in categorical analyses.

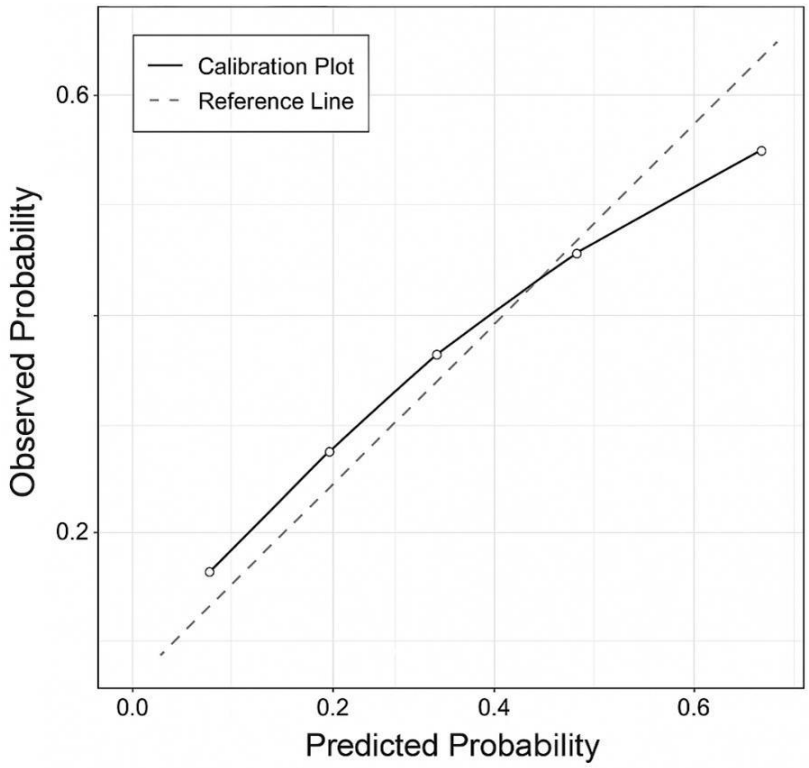

Figure S2. Calibration of the multivariable Cox proportional-hazards model for radiation-induced periodontitis. Calibration plot illustrating the agreement between predicted and observed probabilities of radiation-induced periodontitis derived from the final multivariable model. The diagonal dashed line represents perfect calibration, while the solid line shows the bias-corrected performance of the model after 1,000 bootstrap resamples. The model demonstrated good overall calibration with minimal deviation at the extremes (C-index = 0.72; 95% CI: 0.64–0.80; calibration slope = 0.94; intercept = −0.03).

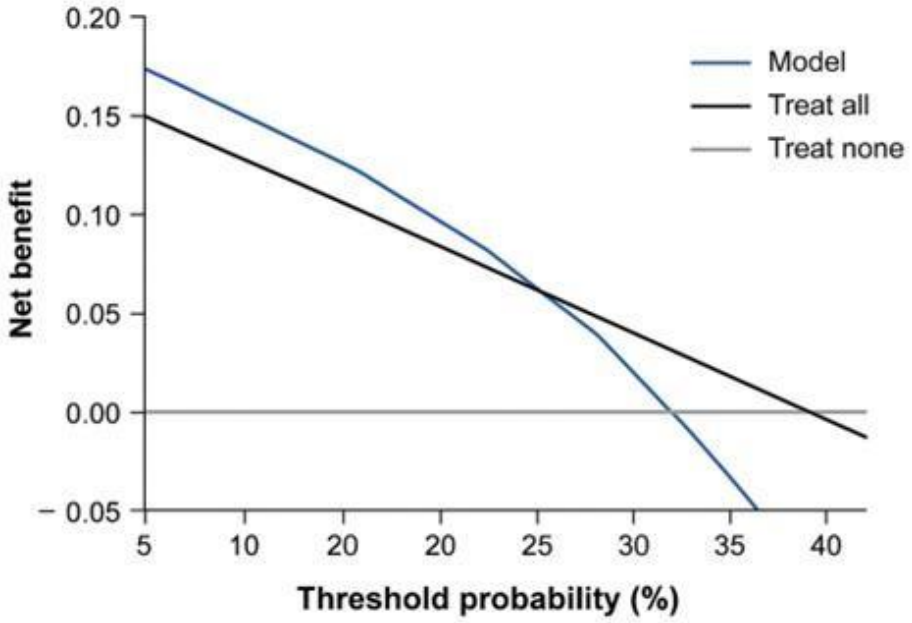

Figure S3. Decision-curve analysis (DCA) for risk prediction of radiation-induced periodontitis. Decision-curve analysis comparing the net clinical benefit of the complete multivariable model (solid blue line) in comparison to the treat-all (black line) and treat-none (gray line) strategies across threshold probabilities of 5% to 40%. The complete model consistently exhibited a superior net benefit across the clinically relevant threshold range, suggesting its potential clinical utility for individualized prediction of radiation-induced periodontitis risk.

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