Preoperative C-Reactive Protein to Albumin Ratio and Oral Health in Oral Squamous Cell Carcinoma Patients

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Research Article

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Abstract

Background The C-reactive protein to albumin (CRP/alb) ratio can predict early mortality of a hospitalized patient. We evaluated factors that influence the preoperative CRP/alb ratio in oral squamous cell carcinoma (OSCC) patients and in particular clarified the role of oral health to this ratio.

Materials and Methods Data from surgically treated OSCC patients were collected retrospectively. Patient 3-month mortality was recorded. The outcome variables were preoperative CRP/alb ratio, CRP level, and alb level. The studied predictors were total number of teeth, periodontal stability, marginal bone loss, tumour stage, T-class, lymph node status, and site. The statistical significance of age, sex, comorbidity combination of age and disease history (Charlson Comorbidity Index [CCI]), smoking, and alcohol history for outcome variables were evaluated.

Results A total of 159 patients were included in the study. The early mortality was 3.8%. CRP/alb was higher in these patients than in those who survived. The only independent variables for CRP/alb changes were CCI and heavy alcohol use. The CRP/alb ratio was significantly lower in non-heavy alcohol users (odds ratio [OR] 0.114, 95% confidence interval [CI] 0.024-0.541; adjusted p=0.006) than in other patients. Patients with CCI 0-1 were more likely to have a lower CRP/alb ratio than patients with CCI ≥5 (OR 0.033, 95% CI 0.004-0.284; adjusted p=0.002).

Conclusions The CRP/alb ratio was high in OSCC patients with combined comorbities of age and disease history and in patients with heavy alcohol use. Oral health or tumour-related variables did not independently affect the CRP/alb ratio. The CRP/alb ratio appears suitable for prediction of OSCC patient early survival.

Background

The predominant type of oral cancer is oral squamous cell carcinoma (OSCC), which comprises 90% of all oral carcinomas [1]. The main risk factors for the development of OSCC are alcohol consumption and tobacco smoking [2]. The survival rate of patients with OSCC depends on many factors, such as age, gender, diagnosis time, socioeconomic background, and tumour, node, and metastasis (TNM) classification [3]. In particular, the OSCC survival rate is highly dependent on cancer staging [4]. Disease-specific survival beyond 3 years is approximately 70% in patients with stage-I tumours, whereas in stage III/IV OSCCs only 60% patients survive beyond 3 years [4].

It has been suggested that in a malignant tumour, inflammatory cells act as early intrinsic defence mechanisms to resist the tumour. However, chronic inflammation results in tumour angiogenesis and DNA damage, which both increase C-reactive protein (CRP) levels [5, 6]. OSCC patients with larger tumours and more advanced tumour stages have reduced overall survival when increased CRP levels are present [7, 8]. Thus, the CRP level is considered to increase the prognostic power in OSCC patients.

In addition to CRP, the chronic phase protein albumin (alb) is an indicator of the patient's nutritional and inflammatory status [9, 10]. Systemic inflammation, followed by a decrease in alb level, results in poor performance, weight loss, and nutritional deficiency, all of which negatively affect the prognosis of patients with cancer [11]. Serum alb levels are lower in patients with oral pre-malignancy and oral malignancy compared with healthy individuals. In addition, increased salivary alb levels have been observed in patients with oral pre-malignancy and oral malignancy compared with healthy individuals [12].

CRP is an acute-phase infective and inflammatory process protein. An increase in CRP production and diminished alb as a negative acute-phase protein are most often associated with chronic disease [13, 14]. The ratio of CRP/alb correlates particularly well with the modified early warning score (MEWS), which is associated with a poorer outcome in many systemic diseases [14]. Fairclough et al., 2009 observed in a follow-up study of 300 patients that the CRP/alb ratio was generally better than MEWS as a predictor of death in younger patients [14]. The CRP/alb ratio is a novel inflammation-based prognostic score and has shown outstanding prognostic value in tumours such as those of the liver or lung [15–17]. The CRP/alb ratio is comparable or even superior to other inflammation-based prognostic scores in predicting prognosis [15–17].

Oral health and particularly the infectious load of periodontitis may have systemic effects [18]. There are some studies on the associations between oral health and serum alb levels [18–20]. The role of oral microbes is associated with the inflammatory process itself and cancer risk [21], and the relationship between periodontal status and cancer prognosis has been evaluated. The mortality of orodigestive cancers increases according to the severity of periodontitis [22]. Additionally, the periodontal pathogen *Porphyromonas gingivalis* has been presented as a biomarker for microbe-associated risk of death [22].

The purpose of the present study was to evaluate the factors that influence preoperative CRP and alb levels and particularly the CRP/alb ratio in patients with OSCC. We also focused on the role of oral health. We hypothesized that the CRP/alb ratio differs between OSCC patients.

Materials And Methods

Patient material

Patient records from the 3-year period between January 2016 and December 2018 at the Head and Neck Centre, Helsinki University Hospital, Helsinki, Finland were evaluated. Our search was based on data from the multidisciplinary head and neck tumour board of Helsinki University Hospital, which covers data of all primary diagnosed OSCC patients.

Data on OSCC patients and tumours, laboratory values, radiological dental status, information on smoking and alcohol consumption habits, and early overall survival were collected retrospectively.

Inclusion and exclusion criteria

Patients with a primary OSCC diagnosis who received surgical treatment for the malignancy were included. An additional inclusion criterion was the availability of a digital panoramic radiography (DPR) of dentate patients. Patients with additional malignancy, previous head or neck malignancy, previous radiotherapy in the region of head or neck, preoperative acute infection, and missing preoperative CRP or alb values or incomplete information on smoking or alcohol consumption were excluded.

Study design

The primary outcome variable was CRP/alb ratio before treatment. Additional outcome variables were CRP level (mg/l) and alb (g/l) levels before treatment. The lowest value of CRP that could be obtained by laboratory tests was < 3 mg/l.

Predictor variables related to oral health were periodontal stability, marginal bone loss, and number of teeth. Patients were grouped according to number of teeth, which included third molars and excluded dental implants. In assessing periodontal status, unerupted teeth, teeth without sound supragingival tissue remaining (crown affected by caries), and teeth floating in parts of the jaw affected by the tumour were excluded.

Tumour-related predictor variables included prognostic stage group (i.e. cancer severity), tumour size, patient lymph node status, and tumour site. The prognostic stage group was defined according to the Oral Cavity cancers - AJCC 8th Edition into two subgroups (stage 0-II and stage III-IV) [23]. Correspondingly, tumour size was defined according to T categorization as Tis-2 (Tis, T1, or T2) or T3-4 (T3 or T4). Pathological lymph node status was categorized as N0 and N1 or more.

Explanatory variables were age, gender, smoking, heavy alcohol use, and Charlson Comorbidity Index (CCI) [24], which combines comorbidity for age and disease history. Patients were divided into three CCI groups as follows: 0–1 points, 2–4 points, and ≥ 5 points [24]. Patients were stratified by smoking habit into the following two groups: non-smokers (i.e. non-smokers and former smokers who have been in cessation ≥ 5 years) and current and former smokers (i.e. who have been in cessation < 5 years) [25]. Alcohol use was determined according to the Finnish Current Care Guidelines consumption limits for heavy alcohol use: ≥23 doses (i.e. ≥287.5 g of alcohol) per week for men and ≥ 12 doses (i.e. ≥150 g alcohol) per week for women as suggested by Finnish working group [26].

Patient early mortality (3 months) overall survival was recorded. Associations between the CRP/alb ratio and early mortality was reported.

Radiological analyses for periodontal status

Dental panoramic radiograph images (Instrumentarium Dental™ Orthopantomograph™ OP200 or Orthopantomograph® OP300) were reviewed by an oral radiologist (M.M.G.) twice at 6-month intervals. For discordant results, the more severe status was used for the study.

Periodontal status was evaluated for periodontal stability and marginal bone loss. Stability was defined according to alveolar marginal crest and described as stable if a corticated alveolar marginal crest was radiologically identifiable (i.e. presence of a corticated crestal lamina dura). When present, marginal bone loss was classified as not present, mild, moderate, or severe [27]. Marginal bone loss was determined by tertile as follows: maximum bone loss extending to cervical third (mild), maximum bone loss extending to the middle third (moderate), or maximum bone loss extending to the apical third (severe) (Fig. 1). Edentulous patients were included as patients with periodontal stability without marginal bone loss.

Statistical analysis

Associations between patient cancer severity status, clinical data, periodontal status and CRP/alb, CRP, and alb were assessed with the Chi-squared test, Fisher's exact test, and logistic regression analysis. Hosmer and Lemeshow goodness-of-fit test was used to assess logistic regression analyses. Before conducting multiple logistic regression analyses, Cramer's V test was used to detect possible multicollinearity of categorical explanatory variables. Bivariate screening for variables was used to assess inclusion in the multivariable model using a cut-off value of $p < 0.05$. The significance level was set at 0.05. SPSS 25.0 (IBM Corp, Armonk, NY) was used for statistical analyses.

Results

Patient material

From a total of 305 evaluated patients, 159 OSCC patients who received surgical treatment for primary tumour were included in the final analyses (Fig. 2). Most patients were male (51.6%). Median age was 66.0 years. Most patients were non-smokers (50.3%) and did not have a history of heavy alcohol use (82.4%). The most common primary tumour site was tongue (44.0%), followed by gingiva or palate (34.0%), floor of the mouth (15.7%), and cheek (6.3%). Median values for the studied laboratory variables were the following: CRP < 3 mg/l, alb 38.00 g/l, and CRP/alb 0.05 (mg/l)/(g/l) (Table 1).

In all, 6 patients died during the first postoperative three months (3.8%). The cause of death was cardiovascular in 3 patients, respiratory infection or respiratory complication in 2 patients and 1 patient died while receiving palliative cancer care. The CRP/alb ratio was higher in these patients compared to surviving patients (Table 2).

Smokers had significantly higher CRP levels ($p = 0.036$) and higher alb levels ($p = 0.026$) than non-smokers (Table 3). Patients with a history of heavy alcohol use had significantly higher CRP levels ($p = 0.001$) and a higher CRP/alb ratio ($p = 0.016$) compared with the other patients. Patients with a higher CCI score more often had lower alb levels ($p < 0.001$) and a higher CRP/alb ratio ($p < 0.001$). Associations between explanatory variables and CRP/alb ratio are shown in Table 4.

Primary tumour sites differed significantly when considering alb levels ($p = 0.027$) (Table 5). Patients with floor of the mouth tumours had the highest alb levels compared with other regions. T-class was

significantly associated with CRP levels (p = 0.030). Patients with larger tumours more often had higher CRP than patients with less extensive tumours. Differences were also significant between total number of teeth and CRP/alb ratio (p = 0.009) (Table 6). Edentulous patients and patients with 13 to 24 teeth more often had a lower CRP/alb ratio than other patients.

Multiple logistic regression analysis included heavy alcohol use and CCI for CRP/alb ratio (Table 7). The CRP/alb ratio was significantly lower in patients with no history of heavy alcohol use (odds ratio [OR] 0.114, 95% confidence interval [CI] 0.024–0.541; adjusted p = 0.006) than in patients with history of heavy alcohol use. In addition, patients with CCI 0–1 were more likely to have lower CRP/alb ratio than patients with CCI ≥ 5 (OR 0.033, 95% CI 0.004–0.284; adjusted p = 0.002).

Discussion

We evaluated the factors that influence preoperative CRP and alb levels and the CRP/alb ratio in OSCC patients. We also evaluated the role of oral health. We hypothesized that the CRP/alb ratio differs between OSCC patients, which was confirmed in this study. Although numerous factors were associated with CRP and alb and CRP/alb, heavy alcohol use and high CCI were found to be the only independent variables for CRP/alb increase.

CRP/alb scores in OSCC patients have been considered as promising predictive markers for patients with OSCC in addition to tumour staging [28]. A previous study on OSCC patients treated with concomitant radio-chemotherapy showed that CRP and alb predicted patient long-term survival [29]. However, even in this selected patient population, only radiotherapy combined with chemotherapy remained significant in multivariate analyses. While early mortality was low in the present population (3.8%), the CRP/alb ratio was higher in these patients than survivors. Thus, the CRP/alb ratio seems to be more appropriate for assessing early prognosis of OSCC patients.

Heavy alcohol use and smoking also increased preoperative CRP, as shown previously [30, 31]. Imhof et al. 2001 found that men's alcohol consumption showed a U-shaped association with mean CRP values. In their study, non-drinkers and heavy drinkers had higher CRP concentrations than moderate drinkers [31]. In this patient population, only 1 out of 28 heavy alcohol users had liver cirrhosis. According to our results, heavy alcohol use is therefore a notable factor that increases CRP levels in OSCC patients. Even if smokers more often had higher CRP than non-smokers, they also had higher alb values. Thus, no effect of smoking was found on the CRP/alb ratio.

Systemic inflammation in cancer patients is considered to relate to prognosis. Various mechanisms are involved in inflammation cascades during OSCC development and progression. Tumour growth, invasion, or both can cause inflammation via necrosis, tumour hypoxia, or local tissue damage [32–34]. Inflammatory cells related to the tumour and tumour cells related to tumorigenic inflammatory cytokines, such as tumour necrosis factor, interleukin (IL) IL-1, IL-6, and vascular endothelial growth factor [32–34] can induce invasion, growth, and tumour metastasis [32–34]. CRP production increases as a response to these stimuli mediators and has been shown worsen inflammatory status and advance progression of

the oral cancer [7, 8, 35]. Thus, it is consistent that tumour extent is associated with CRP levels as confirmed in the present study.

Hypoalbuminemia is a prognostic marker of survival in the general population and in many pathological settings, mainly due to malnutrition and inflammation [36, 37]. Our results are consistent with previous findings. Higher CCI was associated with lower alb levels. However, it should be noted that a single effect of patient age was not found. Somewhat surprisingly, the number of teeth was also not associated with alb levels.

We chose periodontal stability, marginal bone loss, and total number of teeth as measurements of the level of periodontitis and dental health. Patients that had tooth loss had a significantly higher CRP/alb ratio than patients without tooth loss, but the difference was non-significant in multivariate analysis. Thus, even if OSCC patients often require further dental care as shown in the present study, these findings do not affect the CRP/alb ratio.

The frequent findings of periodontitis in our results are worth considering. Stable periodontal status was observed in only half of the patients and marginal bone loss was frequent. Radiotherapy and chemotherapy have an impact on oral health and the oral cavity should be as free of infection as possible before these oncological treatments. In addition, surgical procedures for OSCC often extend to tooth-bearing regions of the oral cavity. Thus, an individual treatment plan by dentists and oral and maxillofacial surgeons is appropriate to reduce local infections and address other considerations during OSCC treatment, and to promote further rehabilitation of occlusion and jaw function. Appropriate oral and dental care should be included in the OSCC treatment plan to improve the patient’s quality of life.

A larger number of patients with additional data from treatment strategies is required to clarify the clinical relevance of the CRP/alb ratio in specific OSCC patient subgroups. In addition, hs-CRP was not recorded, thus the significance of micro infection burden could not be assessed. An additional limitation is that we estimated periodontal status based on radiological findings alone and cariological status or dental-care habits were not analysed.

In summary, even if a number of factors are associated with the CRP/alb ratio in oral cancer patients, only the comorbidity combination of age and disease history and heavy alcohol use increased the CRP/alb ratio in OSCC patients independently. Consideration of these predictive variables are warranted when assessing early postoperative prognosis of a patient with OSCC.

List Of Abbreviations

albumin (alb)

C-reactive protein (CRP)

C-reactive protein to albumin (CRP/alb)

Charlson Comorbidity Index (CCI)

confidence interval (CI)

interleukin (IL)

modified early warning score (MEWS)

oral squamous cell carcinoma (OSCC)

tumour, node, and metastasis (TNM)

Declarations

Ethical approval and consent to participate

The study was approved by the Internal Review Board of the Head and Neck Centre, Helsinki University Central Hospital, Finland (HUS/66/2018). The Internal Review Board of the Head and Neck Centre waived the requirement of informed consent due to the retrospective nature of this study. The guidelines of the Declaration of Helsinki were followed in this study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that they have no competing interests

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Authors' contributions

AK: Data curation, formal analysis, investigation, visualization, writing – original draft. JU: Conceptualization, methodology, project administration, supervision, writing – review & editing. MM-G: Investigation, methodology, writing – review & editing. SK: writing – review & editing. JS:Conceptualization, formal analysis, methodology, project administration, supervision, validation, writing – review & editing. All authors read and approved the final manuscript.

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Not applicable

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Tables

Due to technical limitations, table 1,2,3,4,5,6,7 is only available as a download in the Supplemental Files section.

Figures

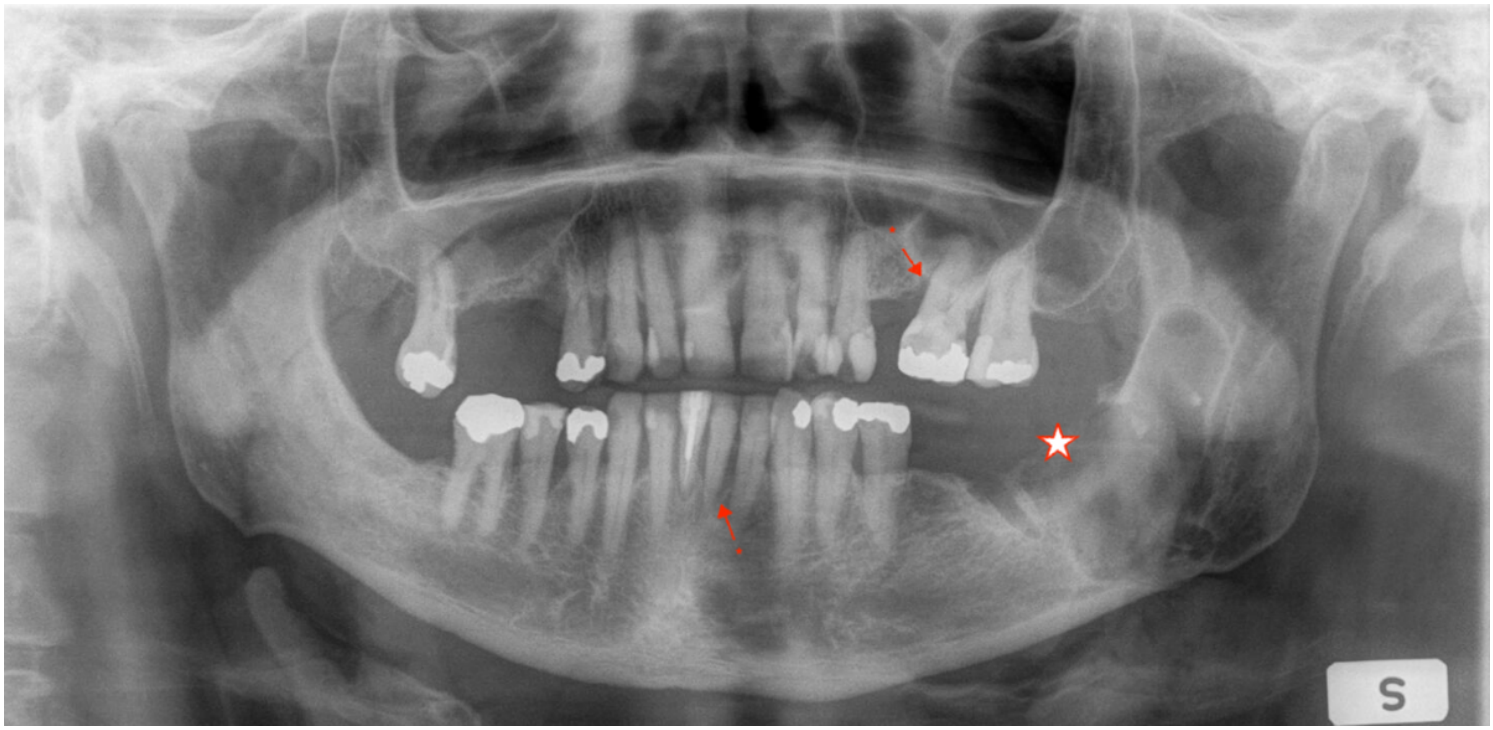

Figure 1

Panoramic tomography of a patient with missing teeth and periodontal instability, with severe marginal bone loss (up to apical third of the roots, marked with *). On the left there is also tumour-induced bone destruction (star), which in this case does not involve a dentate area of the mandible.

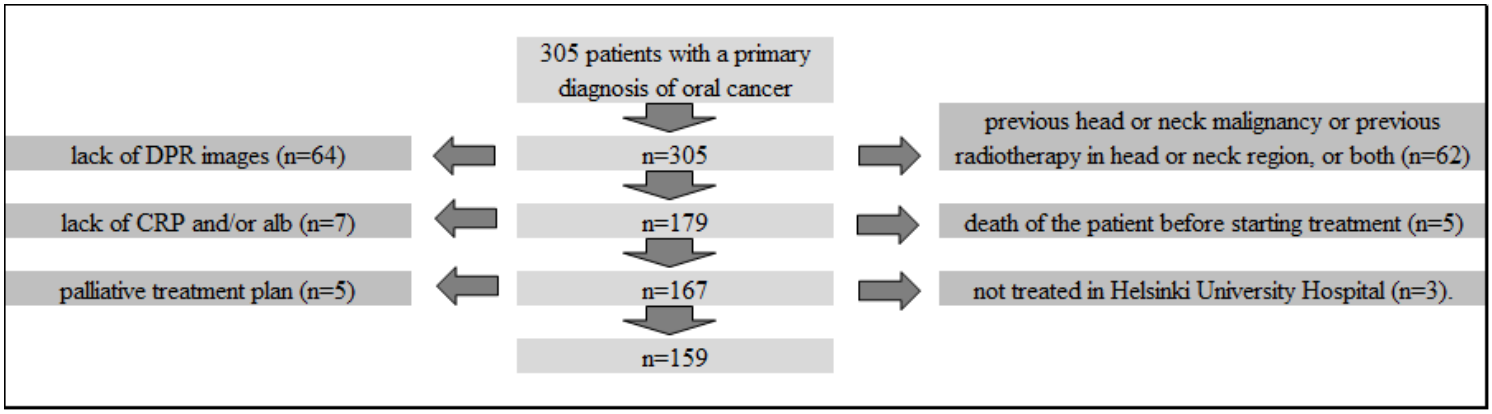

Figure 2

In all remaining 159 patients, requisite data on smoking and alcohol consumption were available. Thus, 159 patients were included in the final analyses.

Supplementary Files

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