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Prognostic Significance of C-Reactive Protein in Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is the sixth most prevalent type of cancer worldwide. One of the most investigated potential biomarkers in this context is C-reactive protein (CRP), a constant biomarker and an acute segment reactant related to inflammation and tissue injury.

Aims and Objectives: This systematic review and meta-analysis aim to investigate the role of CRP as a potential biomarker for predicting prognosis in OSCC, specifically in terms of overall survival (OS) and disease-free survival (DFS).

Methodology: This systematic review (ID: CRD42022344744) has been registered with the International Prospective Register of Systematic Reviews (PROSPERO). We conducted a systematic literature search using PubMed, Scopus, and Google Scholar. From this search, 638 studies were initially identified. The PRISMA flow diagram was then developed to guide study selection, and Version 5.3 of the Review Manager (RevMan) software was used to do the meta-analysis.

Results: Our systematic review and meta-analysis included articles that completely satisfied our inclusion and exclusion criteria. In our meta-analysis, the forest plot model calculates a combined Hazard ratio of more than 1.5 (1.85 for DFS and 1.97 for OS), suggesting a poor prognosis for OSCC patients regarding DFS and OS, particularly in those with high CRP.

Conclusions: A high CRP level was found to be a significant indicator of poor prognosis compared to OSCC cases with low CRP levels, in terms of patients' overall survival and disease-free survival. Thus, these findings suggest that CRP may be a potential marker for predicting prognosis.

Keywords: biomarker, carcinogenesis, C-reactive protein, diagnosis, oral cancer, prognosis

Introduction

Globally, oral squamous cell carcinoma (OSCC) is the sixth most prevalent type of cancer. Crucial and main risk factors for developing OSCC are heavy alcohol, smoking, betel nut chewing, infection, as well as human papillomavirus (HPV).[1-3] The most vital predictors for prognosis in patients include lymph node metastasis and tumor size. Potential biomarkers are required to predict prognosis and improve patients' quality of life through therapeutic approaches.[4-6] One of the most investigated potential biomarkers in this context is C-reactive protein (CRP), a chronic biomarker and an acute segment reactant related to inflammation and tissue injury. Raised CRP has been linked to poor prognosis in patients with a variety of solid tumours, including lung, breast, and renal cell carcinoma. Numerous evaluations and investigations have been conducted to determine the prognostic association between CRP and oral cancer.[7-10]

CRP levels fluctuate daily and progressively rise with age, blood pressure, coffee, alcohol, and smoking.[11-13] The production of CRP in hepatocytes is regulated by pro-inflammatory cytokines, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). TNF-α levels and CRP expression are positively correlated.[14-17] CRP has been traditionally used as a crucial biomarker for infection. Previous studies on cardiovascular disease have provided evidence of its role in the inflammatory process, including the host response and infection, which involves apoptosis, primarily through the production of IL-6 and cytokines such as tumour necrosis factor, and facilitates phagocytosis by releasing nitric oxide.[18-20] It was very early appreciated that CRP can function as an opsonin.[7,21-24] CRP plays a crucial role in host defence against infection, in which Opsonisation is one of the mechanisms.[25]

CRP plays a vital role in the body's immune defense, particularly by initiating the complement cascade. It also eliminates autoantigens, which are widespread throughout the body. CRP promotes this clearance by binding to Fc receptors and activating the complement pathway on the surface of phagocytic immune cells. Various theories have been proposed; systemic inflammatory reactions mediated by CRP and different white blood cell types are essential in conditions such as tumor cell death, low-oxygen environments (hypoxia), and localized tissue damage. Consequently, both CRP and leukocyte subtypes are widely recognized as key biomarkers for evaluating systemic inflammation.[26-33]

The liver produces CRP, an acute-phase protein, when inflammatory cytokines, particularly IL-6, increase significantly during infection. CRP is a non-specific biomarker widely used to indicate systemic inflammation, including infections. Significantly increased levels of CRP are often detected in inflammatory conditions such as osteoarthritis. Additionally, CRP serves as an essential clinical indicator for cardiovascular events, including unstable angina, thrombosis-related complications, and systemic inflammatory activity. In contrast, modest elevations in CRP are more frequently associated with autoimmune diseases like systemic lupus erythematosus, scleroderma, Sjögren's syndrome, polymyositis, and other long-term inflammatory disorders. Multiple diagnostic approaches are used to measure CRP concentrations in clinical settings. These techniques include visual agglutination, rapid immunodiffusion, and immune-turbidimetry. Among the earliest and most commonly employed methods is the latex agglutination assay. This technique involves latex beads coated with goat-derived IgG antibodies specific to human CRP. When exposed to a CRP-positive sample, these particles aggregate, producing visible clumping within two minutes. This allows for quick and semi-quantitative assessment of CRP levels.[30-33] In certain primary malignancies like oesophageal cancers, hepatocellular cancers, colorectal cancers, cervical cancers, bladder cancers, as well as in advanced stages of any cancers or any microbial infections, can lead to systemic inflammation, and the serum level of CRP plays a vital role as both a direct and indirect indicator of this inflammatory response.[11,20,33-36]

Numerous investigations have examined the relationship between pro-inflammatory cytokines and blood levels of acute-phase proteins, specifically CRP, in patients with oral squamous cell carcinoma.[37,38] These investigations have consistently shown that CRP concentrations rise significantly during the active phase of the disease. Based on this observation, CRP has been proposed as a potential biomarker for OSCC and may also assist in identifying cases of local recurrence in head and neck malignancies.[18,37-39]

Furthermore, IL-6 enhances the interaction between CRP and tumor cells, possibly contributing to the lysis of malignant cells. As such, increased CRP levels could

reflect tumor-associated tissue damage and the broader inflammatory response mounted by the host against the tumor microenvironment.[16,40] Therefore, by doing a systematic review and meta-analysis, we aimed to determine the elevated CRP as a potential biomarker for prognostic prediction in OSCC in terms of overall survival (OS) and disease-free survival (DFS).

Systematic review

This systematic review (ID: CRD42022344744) has been registered with the International Prospective Register of Systematic Reviews (PROSPERO). The most recent Meta-Analyses and Preferred Reporting Items for Systematic Reviews (PRISMA) criteria were used in reporting this systematic study.[41]

• The focus question was–Can CRP play a prognostic biomarker role in OSCC?

• PECO Criteria–This sub-heading includes

• Population (P)–OSCC patients for whom CRP has been evaluated.

• Exposure (E)–States the cut-off value of C-reactive protein.

• Comparison (C)–of <5 and ≥5 of CRP value

• Outcome (O)–Value of HR (hazard ratio) with a 95% confidence interval (CI) as an effect size measure for the variables' overall survival and disease-free survival.

• We conducted a systematic literature search using PubMed, Scopus, and Google Scholar. The systematic review search topic was registered in 2022. Search was performed by December 2022-2024, using the following keywords: “CRP” OR “C-REACTIVE PROTEIN” AND ‘BIOMARKERS' AND “PREDICTION” AND “PROGNOSIS” AND “ORAL CANCER” OR “OROPHARYNGEAL SQUAMOUS CELL CARCINOMA” OR “ORAL SQUAMOUS CELL CARCINOMA” OR “HEAD AND NECK SQUAMOUS CELL CARCINOMA”.

• After searching and screening, all potentially associated studies were evaluated for their contents, followed by exclusion and inclusion criteria, and data were extracted.

Inclusion criteria

I. Cohort studies that reported the prognostic value of CRP for survival (OS, DFS) and clinic-pathological factors in OSCC, such as tumour size, histological grade, clinical stage, or N status.

II. Research articles written in English.

III. Research in which pre-operative levels of CRP have been evaluated by univariate analysis.

IV. Studies in which the cut-off value of CRP was taken as ≥5.

Exclusion criteria

I. Studies in which HR of DFS and OS was not directly mentioned or could not be calculated using estimation methods.

II. Review articles of CRP.

III. Secondary or metastatic cases of OSCC.

Data were extracted from all the eligible studies for systematic review and Meta-analysis and retrieved under the following headings

I. Demographic data concerning population, survival rates, and ethnicity during the follow-up.

II. Information on tumours (sample size, lymph node invasion, TNM staging, and histological grading).

III. Experiments involving materials, study design, and meeting CRP cut-off requirements.

IV. Data on survival and clinic-pathological factors that include univariate analysis of CRP and HR data for OS and DFS with matching 95% CIs, respectively.

V. Publication information, such as the author's name, the year of publication, and journal titles.

The Newcastle-Ottawa scale (NOS) was used in the included studies to assess the risk of bias. Selection, outcome, and comparability were all employed to measure study qualities.[42] NOS score ≥7 is commonly accepted as “good quality” in meta-analyses. Calibration ensures consistent and reproducible scoring. RevMan 5.3 software version was used to perform the meta-analysis of the accumulated studies from selected articles. A forest plot was generated using the OSCC patient survival data (HR and 95% CI) to illustrate the association between CRP and its prognostic role in OSCC, expressed in terms of OS and DFS. The inverse-variance approach was used to meta-analyze pooled estimates. This random-effects approach considers the potential for distinct underlying findings between research subgroups (i.e., variations in oral subsides associated with geographical regions or the intrinsic variability of the experimental procedures). Heterogeneity was assessed using RevMan 5.3 software, where a p-value less than 0.10 and an I-squared value greater than 50% indicate the presence of considerable heterogeneity across the studies. An observed HR>1 suggests that the direction of the effect tends to favour poor prognosis in the research

group exposed to raised or elevated CRP levels.

Results

PRISMA chart description: Records identified from various databases, PubMed (n=21), Scopus (n=606), and Google Scholar (n=11). A total of 638 articles were identified. Five hundred ninety-two articles were removed before screening, as they did not align with the topic's specificity and were duplicates. The remaining 46 articles were then screened, and five were excluded as review articles. So, 41 articles reports sought for retrieval. Among these 25 studies were removed as they did not mention the prognostic outcome of CRP. The eligibility of the remaining sixteen items was then evaluated. However, the following factors led to the exclusion of 12 studies. Reasons for exclusion: 1) Missing HR data in 5 studies. 2) The CRP cut-off value did not meet the inclusion criteria (≥5 mg/L) in 6 studies. 3) HR reported for recurrence only, not overall survival, in 1 study. Although it has been observed that these 12 studies reviewed were supportive of the increased value of CRP in predicting a poor prognosis for OSCC cases, the details provided in the manuscript did not meet the inclusion criteria. Therefore, these studies were excluded. Lastly, findings of the remaining four studies were included to assess the contribution of CRP to OSCC prognosis in terms of OS and DFS, and a systematic review and meta-analysis were conducted. Which entirely satisfy our inclusion and exclusion criteria, as shown in Figure 1. The complete clinical data, including histological grading, TNM staging, lymph node status, and HR values, have been summarized in Table 1. All four studies you listed, from Taiwan and Austria, performed univariate analysis to examine the predictive role of C-reactive protein (CRP) in OSCC. A total of three out of four studies were conducted in Taiwan, while the other was conducted in Austria. All four articles reported the prognostic outcome associated with CRP and included the key characteristics of HR and 95% CI values–an overview of all the selected articles and prognostic outcome-giving studies related to CRP and OSCC. All studies had NOS scores between 7 and 8 (Table 2). Three papers received a NOS score of "7," while one study received an overall score of eight. The quality of the included retrospective cohort studies was evaluated using the Newcastle-Ottawa Scale in three domains: outcome (0-3 points), comparability (0-2 points), and selection (0-4 points). Nine is the highest possible score. Studies with a score of 6-9 are often regarded as high-quality. Therefore, all studies included in our systematic review and meta-analysis had overall good NOS scores.

The risk of selection bias is low in relation to the individual domains. Regarding all the included studies, all have successfully reported at least six months of follow-up with the Hazard ratio value.

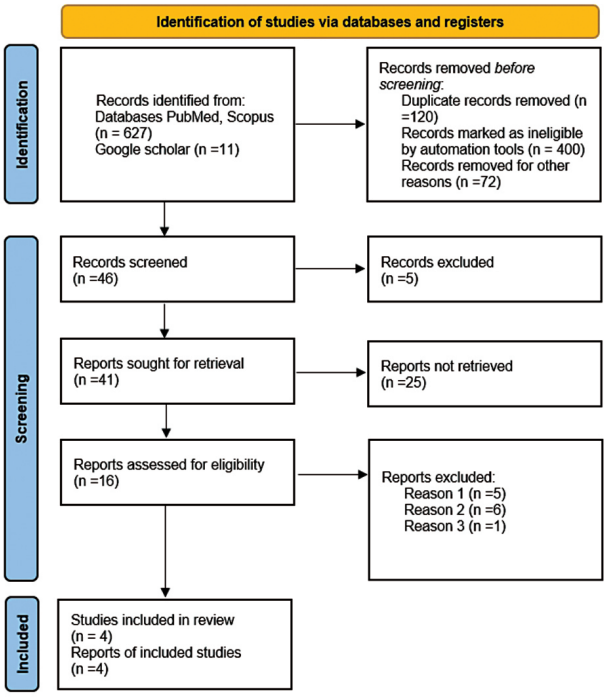

Figure 1: PRISMA 2020 flow diagram for systematic review. (Showing literature search and study selection for the present systematic review)

Meta-analysis outcome

The HR and 95% CI observed in our included studies were combined to investigate the relationship between CRP and OSCC. If the 95% Confidence Interval (CI) for the HR>1, the result is statistically significant. In cancer prognosis of OSCC and its relation to CRP, an HR>1 means the event is more likely to occur in the exposed group (OSCC cases). While HR>1 indicates a higher probability of recurrence in disease-free survival and a higher risk of mortality (overall survival).

In our meta-analysis, the forest plot model calculates a combined Hazard ratio of more than 1.5 (1.85 for DFS and 1.97 for OS), suggesting a poor prognosis for OSCC patients regarding DFS and OS (Figures 2 and 3). Figure 2 shows in DFS (Meta-analysis), very low heterogeneity

Table 1: Description of study articles included finally in the systematic review and meta-analysis.

SN	Year	Author	Nation	Sample size	M: F	Median Age	Predominant Site	Follow up	TNM staging	Histological staging	Number of cases analyzed: CRP	CRP vs. T				CRP Vs. N				CRP vs. HR (95%CI)	
												<5		≥5		<5		≥5		DFS	OS
												E	A	E	A	E	A	E	A		
1	2012	Huang SF	Taiwan	142	133:9	52.06	Buccal Mucosa 67 (47.2%)	3 Years	I-37 II-28 III-12 IV-65	Well/ Moderate-117 Poor-25	109*	50	36	9	14	70	16	13	10	2.888 (1.625-5.135)	2.526 (1.245-5.136)
2	2017	Tai SF	Taiwan	343	318:25	52.21	Tongue 132 (38.5%)	6 Months -6years	I-76 II-66 III-43 IV_a-133 IV_b-25	Well-107 Moderate-192 Poor-44	343	181	68	29	65	192	56	57	38	1.902 (1.302-2.778)	2.235 (1.393-3.585)
3	2018	Graupp M	Austria	197	146:1	58.9	Tongue 197 (100%)	Long-term cohort study (Up to 13 Years	I-22 II-29 III-28 IV-118	N.A.	150**	31	35	36	48	23	43	52	59	1.454 (0.949-2.227)	1.616 (1.026-2.546)
4	2019	Dante D.P.	Taiwan	246	225:21	53	Tongue 106 (43%)	6-72 Months	I-63 II-51 III-35 IV-97	Well-66 Moderate-150 Poor-29 Undifferen-tiated-1	246	134	51	20	41	152	33	41	20	1.714 (1.029-2.854)	1.879 (0.981-3.599)

Abbreviations'*- M: F- Male: Female Ratio, CRP: C- reactive protein, OS: Overall-survival, DFS: Disease-free survival, SZ: Sample-Size, Tumor Stage, N-Lymph Node, CI: Confidence Interval, HR: Hazard Ratio, NA: Not Available, *(33 patients excluded due to not available data on CRP), **(47 patients excluded due to not available data on CRP). N_0, N_1 – Early (E). N_2, N3- Advance (A) and T_0, T_1- E (Early), T_2, T_3, T_4, T_{4a}, T_{4b}, T_{4c}- Advance (A).

Table 2: Studies of quality assessment by the Newcastle-Ottawa scale.

Study	Selection	Comparability	Outcome	NOS Score
SF.Huang *et al* (2012), Taiwan	● ● ● ●	● ●	● ○ ○	7
S.F.Tai *et al* (2017), Taiwan	● ● ● ●	● ●	● ○ ○	7
M.Graupp *et al* (2018), Austria	● ● ● ●	● ●	● ○ ●	8
Dante De Paz *et al* (2019), Taiwan	● ● ● ●	● ●	● ○ ○	7

● Point rewarded; ○ no point rewarded

was observed with Tau^2=0.01, Chi^2=3.63, p<0.00001. I^2=17%. The overall effect is obtained as Z=4.78. The combined HR value in this figure is calculated as 1.85 (1.44-2.39) with a 95% CI. The findings revealed a strong correlation and an increase in the HR value of DFS, indicating a poor prognosis. HR=1.8 DFS, which means that patients with high CRP have an 80% higher risk of recurrence or progression of OSCC than those with lower CRP.

Figure 3 shows the overall survival (meta-analysis), which shows zero heterogeneity (Tau^2=0.00) with a combined value of HR obtained as 1.97(1.50-2.58), with a confidence interval. Chi^2=1.49 and p-value (p<0.00001) with an overall effect; Z=4.91, I^2=0.00. The result also states that an increase in HR value (OS) is associated with the worst prognosis in OSCC patients. The statistical analysis was performed using RevMan software version 5.3 for meta-analysis.

Discussion

The studies included in our review support the prognostic value of elevated CRP (≥5 mg/L) in OSCC, linking it to advanced tumor stage, nodal involvement, and reduced survival outcomes. Despite some heterogeneity in methodology and cut-off values in the broader literature, a consistent trend suggests that CRP is a low-cost, easily measurable, and clinically relevant biomarker for risk stratification and treatment planning in OSCC.

S.F. Huang *et al.,*[7] conducted a retrospective study involving 142 patients diagnosed with OSCC. The cut-off value for CRP was set at ≥5 mg/L. The average age of the patients was 52.06 years, with the majority being men. The tongue (35.2%) and buccal mucosa (47.2%) were the most often occurring primary tumour sites. Early pathological tumor status was noted in 92 patients, while 50 presented with advanced disease. CRP levels were measured using an auto-analyzer. The study reported HR of DFS and

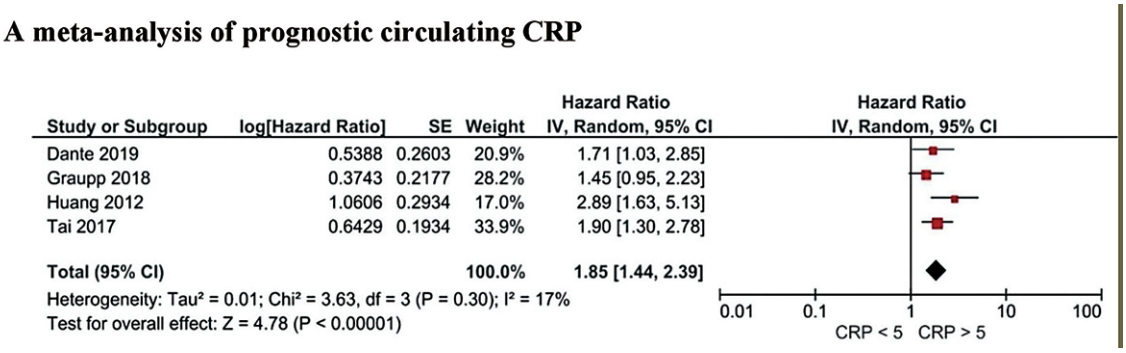

Figure 2: Forest plot for survival outcome of up-regulated CRP in OSCC patients. (Disease-Free Survival).

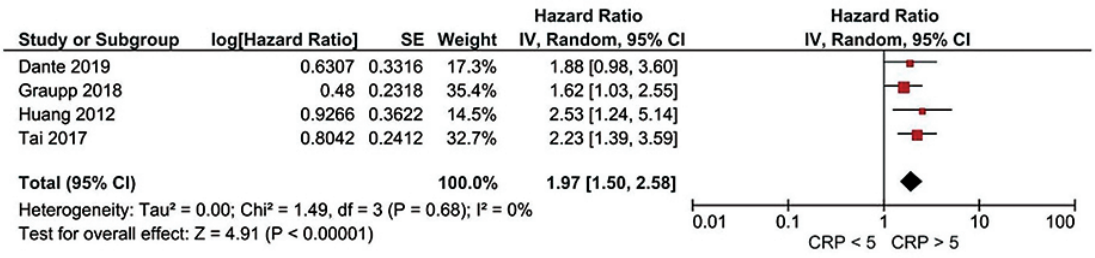

Figure 3: Forest plot of survival outcome associated with CRP &OSCC patients. (Overall Survival).

OS and suggested that elevated preoperative CRP levels serve as a significant prognostic biomarker in OSCC, particularly in relation to lymph node metastasis, tumor recurrence, and advanced tumor stage.

Graupp *et al.,*[12] analyzed 197 patients with tongue OSCC, focusing on OS and DFS as the primary outcome measures. Males comprised the majority (n=146), with a mean age of 58.9 years. Of the individuals in the group, 112 had advanced disease and 85 had early-stage tumours. Patients with CRP ≥5 mg/L included 36 with early-stage and 48 with advanced-stage tumors. Positive lymph node involvement was seen in 59 of these patients. The study found a significant association between elevated CRP and poor survival, with an HR of 1.616 (95% CI: 1.026-2.456) and an HR of 1.45 for disease-free survival DFS, establishing CRP as a cost-effective, clinically relevant prognostic biomarker in tongue SCC.

Tai *et al.,*[43] included 343 OSCC patients with CRP ≥5 mg/L as the cutoff. We used an auto-analyzer (Hitachi, Tokyo) to measure CRP levels. The most frequently affected areas were the buccal mucosa (n=126) and the tongue (n=132). The majority of patients (n=318) were male. The distribution of tumour stages was as follows: Stage I (n=76), Stage II (n=66), Stage III (n=43), and Stage IV (n=158). There was a strong correlation between advanced pathogenic nodal status (p=0.006) and lymphatic invasion (p=0.068), as well as elevated CRP levels (≥5 mg/L). The HR was 2.235 (95% CI: 1.393-3.585) for OS and 1.902 (95% CI: 1.302-2.778) for DFS. The authors concluded that CRP is an essential biomarker for prognosis, particularly effective in buccal cancer, potentially linked to areca nut and tobacco use.

Dante De Paz *et al.,*[13] assessed 246 OSCC patients (225 males and 21 females) with CRP levels ≥5 mg/L, which was defined as the threshold. The mean age was 53 years. Tumors were most commonly located in the tongue (n=106), followed by buccal mucosa (n=83). Among patients with CRP levels ≥5 mg/L, 20 were in the early stages and 41 were in the advanced stages. The median follow-up period was 24 months (6-72 months). The HR for DFS was 1.714 (95% CI: 1.029-2.854), and for OS, it was 1.879 (95% CI: 0.981-3.599). The study concluded that CRP significantly correlates with poor prognosis in OSCC and may inform treatment modifications and adjuvant therapy strategies.

Several additional studies have demonstrated a correlation between elevated CRP and poor prognosis in OSCC. Still, they were excluded from our systematic analysis because they did not meet the inclusion criteria, primarily due to the absence of hazard ratio (HR) reporting or inconsistent CRP cut-off values. For instance, Khandavilli *et al.,*[1] Kruse *et al.,*[2] Anderson *et al.,*[3] Kawasaki *et al.,*[4] and Blatt *et al.,*[5] found a significant association between elevated CRP and OSCC. Still, they were excluded because they did not report HR for OS or DFS, which is essential for meta-analysis. Other studies were excluded because they used CRP cut-off values inconsistent with the ≥5 mg/L threshold defined in our inclusion criteria. Farhan *et al.,*[10] used a cut-off of 10 mg/L. The readings reported by Chen *et al.,*[6] had a cut-off of ≤5 mg/L, and Peter *et al.,*[9] applied a threshold of <2 mg/L. Similarly, Grimm *et al.,*[8] employed a CRP cut-off of ≥1.1 mg/dL, Matsuki *et al.,*[14] did not adhere to the ≥5 mg/L standard, and Aarstad *et al.,*[15] used a threshold of 1 mg/L. Chen *et al.,*[44] focused exclusively on recurrent OSCC cases and provided HR values only for recurrence, not OS or DFS, and were therefore excluded. These exclusions were necessary to ensure methodological consistency and improve the reliability of the prognostic implications derived from CRP levels in OSCC. Some systematic reviews also supported the significance of CRP in OSCC, as seen in Rivera *et al.,*[45] who identified CRP among 41 significant prognostic biomarkers associated with early mortality in OSCC patients. Machado *et al.,*[46] suggested that systemic inflammation in patients can be measured by CRP. Stec-Martyna *et al.,*[47] suggested that CRP serves as a sensitive indicator of inflammation and, to some extent, cellular damage; its kinetics differ significantly depending on the underlying condition.

However, it is essential to note that many studies have used different cut-off values for CRP, which limits its overall predictive capacity in relation to OSCC. Our systematic review included only studies that used a CRP cut-off value of ≥5 to ensure more consistent and reliable results. Despite the variation in cut-off values across the literature, the evidence suggests that elevated CRP levels are associated with a poor prognosis in OSCC.

Limitations & future perspectives

As with any retrospective study, our analysis has certain limitations. Notably, the follow-up period was

relatively short, which may affect the strength of long-term prognostic conclusions. To address this, future prospective studies with a minimum follow-up duration of five years are warranted. Another critical limitation lies in the inconsistency of CRP cut-off values used across different studies. For improved standardization and comparability, adopting the internationally recognized CRP cut-off value of ≥5 mg/L is essential. Furthermore, to validate and generalize the prognostic utility of CRP in OSCC, well-designed, multi-institutional studies conducted across diverse populations and geographic regions are highly recommended.

Conclusions

After a thorough and careful review of various studies involving CRP and OSCC, this meta-analysis and comprehensive systematic review found that an increase in CRP levels of ≥5 is associated with poor outcomes in OSCC patients. The elevation in the Hazard ratio of OS and DFS suggests a poor prognosis in these patients.In studies conducted in Taiwan and Austria, most OSCC cases were of tongue carcinoma, followed by buccal mucosa carcinoma, as observed in the present review. The CRP test has advantages over other biomarkers, as it is inexpensive, rapid, and repeatable. However, further studies with a 5-year follow-up are required to confirm the prognostic capacity of CRP as a biomarker for predicting the prognosis of OSCC.

Conflict of Interest

The authors declare no conflict of interest.

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