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Elevated C-reactive Protein Levels and Malignant Transformation Risk in Patients With Oral Mucosal Diseases

Jeong-Hyun Kang

Department of Dental Education, Yonsei University College of Dentistry, Seoul, Korea

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ABSTRACT

Introduction and aims: Chronic inflammation is recognised as a hallmark of cancers. This multicentre cohort study investigated the influence of elevated serum C-reactive protein (CRP) levels on the malignant transformation risk of oral inflammatory diseases and lesions with malignant potential utilising the Observational Medical Outcomes Partnership Common Data Model.

Methods: This retrospective, observational cohort study included the data from 9 medical centres. CRP levels recorded within 30 days of oral diseases diagnosis were analysed. A meta-regression identified 0.269 mg/dL as the optimal threshold for predicting malignancy. Patients were classified into elevated CRP (CRP ≥ 0.269 mg/dL) and control (CRP < 0.269 mg/dL) groups. Cox proportional hazard models were applied to estimate risk of developing oral squamous cell carcinoma (OSCC), followed by 1:1 and 1:2 propensity score matching and pooled meta-analyses.

Results: In total, 10029 individuals with oral diseases and available CRP data were included, comprising 4142 and 5887 in the elevated CRP and control groups, respectively. Overall, 204 individuals (2.03%) progressed to OSCC, with higher incidence in the elevated CRP group (2.32%) compared with controls (1.83%). Elevated CRP was significantly associated with increased OSCC risk in both 1:1 (HR = 1.79 [95% CI 1.08-2.95]), and 1:2 propensity score matching models (HR = 1.55 [95% CI 1.01-2.38]).

Conclusions: Elevated CRP levels, indicative of systemic inflammation, were linked to an increased risk of malignant progression in patients with inflammatory oral conditions and lesions with malignant potential. Understanding the role of inflammation may help assess OSCC risk and improve prevention.

Introduction

Oral cancer is the 18th most prevalent malignancy globally and is characterised by a relatively poor 5-year survival rate.[1,2] This poor prognosis is primarily due to delayed diagnosis, which often results in advanced-stage presentation and limited therapeutic options. The majority of oral cancers are oral squamous cell carcinoma (OSCC), which frequently arises from precancerous lesions, known as oral potentially malignant disorders (OPMDs), including a range of oral mucosal abnormalities such as oral leukoplakia, erythroplakia, erythroleukoplakia, oral lichen planus (OLP), oral lichenoid lesions, and oral submucous fibrosis (OSF), which each exhibit different degrees of malignant potential.[3-5] Reported transformation rates vary by lesion type, with oral leukoplakia, OLP, and1 OSF carrying risks of approximately 9.8%, 1.14% to 1.40%, and 1.9 to 9.0%, respectively.[6-9]

Timely detection of early stage OSCC and identification of risk factors for malignant transformation of OPMDs are essential to prevent cancer development and to enable less invasive treatments. Even after malignant transformation, minimal resection may help preserve oral function and aesthetics. A number of clinical factors have been associated with an increased risk of malignant transformation in patients with OPMD, including female sex, tobacco use, heterogeneous lesion textures, larger lesion size, and anatomical high-risk sites such as the ventral tongue surface.[10]

E-mail address: irene85@yuhs.ac
Jeong-Hyun Kang: http://orcid.org/0000-0001-7124-8693
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Nonetheless, substantial gaps remain in the understanding of specific serum or histopathological biomarkers and the molecular pathways which drive these transformation mechanisms.

Chronic inflammation has been recognised not only as a hallmark of established cancers, but also as a contributor to early stage of carcinogenesis. Beyond localised tissue responses, inflammation can produce systemic changes that promote malignant transformation. C-reactive protein (CRP), a well-known acute phase protein synthesised by the liver in response to inflammatory stimuli, has been linked to an increased risk for various cancers, including melanoma and colorectal, lung, and breast cancer.[11-13] Elevated CRP levels have also been associated with worse clinical outcomes in patients with cancer.[14,15]

Even though limited in scale, one previous cross-sectional study reported higher CRP levels in individuals with oral leukoplakia and primary OSCC compared to healthy control.[16] In addition, research exploring the involvement of circulating autoantibodies in the dysplastic changes in oral epithelium and progression of OPMDs to OSCC has suggested a potential role of systemic inflammation in cancer development.[17,18] Despite these findings, no large-scale longitudinal investigation has yet assessed whether elevated CRP levels are predictive marker of malignant transformation in OPMD patients over time.

To the best of the knowledge, the precise clinical importance and role of CRP in OPMD-related malignant transformation remain unclear. This multi-centre cohort study investigated the association between baseline CRP levels and the risk of progression from OPMD to OSCC using the Observational Health Sciences and Informatics network tools for the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) to ensure standardised analysis across institutions.

Materials and methods

Data sources

This multicentre, retrospective, cohort study utilised real-world clinical data from patients diagnosed with various forms of OPMD and other inflammatory oral diseases and lesions, including oral stomatitis, oral mucositis, OLP, oral leukoplakia, and OSF, across 9 medical centres in South Korea. All institutions converted their electronic health records in to the OMOP-CDM version 5.3.1. The participating centres were as follows: (1) Ajou University Medical Center CDM (AUMC), (2) Ewha Womans University Medical Center (EUMC), (3) Wonkwang University Hospital (WKUH), (4) Daegu Catholic University Medical Center (DCMC), (5) Soonchunhyang University Hospital Seoul (SCHSU), 6() Soonchunhyang University Hospital Bucheon (SCHBC), (7) Soonchunhyang University Hospital Cheonan (SCHCA), (8) Gyeongsang National University Hospital (GNUH), and (9) Chungam National University Hospital (CHNUH).

All databases comprised de-identified, patient-level data, standardised with OMOP-CDM vocabularies to facilitate network-wide analysis through a distributed research network.[19,20] Data extraction and statistical analysis were conducted using ATLAS version 2.7.6, via the FEEDER-NET platform, a Korean health data platform based on OMOP-CDM. Ethical approval for this research protocol was exempted by the Institutional Review Board (IRB) of the tertiary University Hospital (AJIRB-EX-2024-103). All participating medical centres are part of the Research Border Free Zone of Korea, which allows IRB exemption at the coordinating centre when working with CDM data.

Patient selection

Eligible patients for this retrospective, observational, comparator cohort study were adults aged over 18 years who had received either clinical or histological diagnoses of lichen planus, stomatitis, oral mucositis, oral leukoplakia, or OSF. Diagnoses were based on the 10th version of the International Classification of Disease (ICD-10) diagnostic codes. including L43, K12.1, K12.3, K13.2, and K13.5, respectively. The index date was defined as the date of the first recorded diagnosis of an oral lesion.

As the study utilised the OMOP-CDM, disease classification relied on ICD-10 diagnostic codes, which do not contain detailed clinical, etiological, or histopathological information. Accordingly, oral stomatitis (K12.1) and oral mucositis (K12.3) were not interpreted as strictly distinct clinicopathological entities but were considered part of a broader spectrum of inflammatory oral mucosal conditions.

Exclusion criteria included the following: (1) prior history of head and neck cancer to avoid confounding due to malignancy recurrence, (2) diagnosis of OSCC within 1 month of the index date to prevent misclassification and re-diagnosing the same lesion, (3) age under 19 years, and (4) absence of CRP laboratory data in the observation window.

Determining the optimal CRP cut-off value

To identify the most efficient CRP threshold for predicting malignant transformation, CRP levels recorded within 30 days of the index date were analysed. This phase was conducted solely for identifying the cut-off value and was independent from the exposure assignment used in the Cox regression analyses. Patients were classified based on whether they progressed to OSCC during follow-up, with OSCC defined using the ICD-10 diagnosis codes C01-C06.9, C14, and D00.

Data from 9 medical centres, with adequate sample sizes, including AUMC, EUMC, WKUH, DCMC, SCHSU, SCHBC, SCHCA, GNUH, and CHNUH were pooled. A univariate meta-regression was performed using cubic splines in R (version 4.1.3; R Development Core Team, Vienna, Austria) via the 'splines' package, assessing nonlinear relationships between CRP levels and standardised mean differences (SMD) related to OSCC transition. Segmented regression analysis was subsequently applied in R using the 'segmented' package to identify inflection points. The derived optimal cut-off value was determined as 0.269 mg/dL (Supplementary Figure 1).

Cohort definitions and study design

For analysis, data from 7 medical centres with sufficient case numbers, including AUMC, WKUH, DCMC, EUMC, SCHBC, SCHCA, and GNUH, were included. The specific timeframe for each medical centre is listed in Supplementary Table 1.

To avoid circularity in exposure definition and risk estimation, the optimal CRP threshold of 0.269 mg/dL was derived via regression analysis using data from 9 centre within a 30-day peri-diagnostic window. This multicentre dataset was used to enhance the robustness and generalisability of the estimated cut-off, particularly given the use of spline-based meta-regression to identify a nonlinear inflection point. The 30-day peri-diagnostic window was selected to standardise the timing of CRP measurements relative to the index date, thereby minimising variability in measurement timing across patients.

In contrast, the prognostic validity was further evaluated through Cox proportional hazards models using a longitudinal dataset from 7 centres with a 180-day observation window to define sustained inflammatory exposure. To represent the baseline inflammatory state prior to therapeutic interventions for OPMD or the emergence of malignant transformation, the earliest CRP recording within a 180-day window, spanning 90 days before and after the index date, was selected for each patient. The target cohort included individuals with CRP values consistently at or above 0.269 mg/dL, whereas the comparator cohort included those with CRP values consistently below 0.269 mg/dL within a 90-day before and after the index date. Individuals were included only if all CRP values in this 180-day window met the threshold criteria. Patients with CRP levels crossed the threshold in either direction within the window period were excluded to preserve group clarity. This approach minimised the influence of transient fluctuations and ensured stable exposure classification. Follow-up continued until either a diagnosis of OSCC or the end of observation, whichever occurred first (Figure 1).

Propensity score matching and statistical analysis

To reduce for baseline discrepancies between the target and comparator cohorts, large-scale propensity score (PS) matching was employed to minimise potential confounding from imbalanced baseline covariates. Covariates included age, sex, comorbidities, medication history within 365 days prior to study entry, and the Romano's Adaptation of the Charlson comorbidity index.[21] Matching was performed using 1:1 or 1:2 PS matching with a 0.2 caliper on the logit scale, employing a greedy matching algorithm.

PS matching in 1:1 and 1:2 ratios was conducted to assess the impact of elevated CRP on subsequent OSCC incidence among patients diagnosed with white and red oral lesions. Cox proportional hazard regression was employed to estimate hazard ratio (HR) for OSCC between the 2 cohorts. Two-sided P-value < .05 were considered statistically significant.

The same analytical procedures were independently executed across all 7 databases using standardised R software version 4.4.4. Results were then synthesised via meta-analysis. Effect estimates were pooled, using inverse-variance weighting based on between-study variance. Inter-study heterogeneity was evaluated using Higgins' I^2 statistic, with values over 50% indicating notable heterogeneity.[22] When significant heterogeneity was present across studies, a random effects model with a restricted maximum-likelihood estimator was employed, otherwise, a common-effects model was applied. Final effect estimates were presented as HR with 95% confidence intervals (CIs). All statistical analyses were performed using the 'meta' and 'metafor' packages in, with all significance tests being 2-tailed, and $P < .05$ considered statistically significant.

Subgroup and sensitivity analyses

To assess the robustness of the study findings, several sets of subgroup and sensitivity analyses were performed. Subgroup analyses stratified participants by age, those younger than 60 years and those aged 60 years or older, sex, and medical

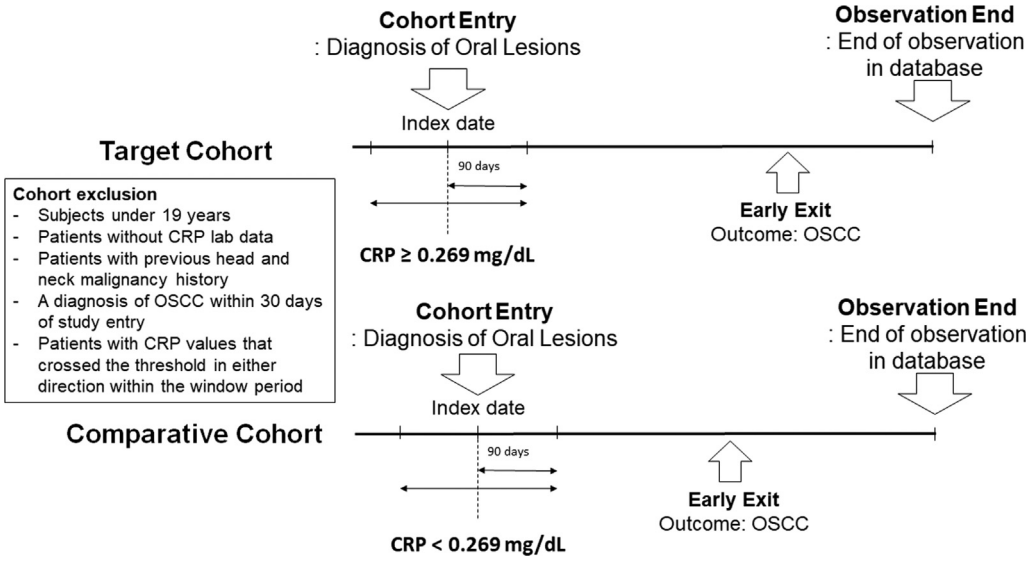

Fig. 1 – Schematic diagram illustrating cohort construction.

centres location, Seoul and Gyeonggi metropolitan or none Seoul and Gyeonggi metropolitan regions. Sensitivity analyses excluded influential outlier studies through Baujat plot diagnostics, to evaluate their contribution to heterogeneity and pooled effect estimates within 95% CIs.[23] All tests of significance were 2-tailed, with $P < .05$ was considered statistically significant.

Results

Prevalence of malignant transformation

In total, 10029 individuals with available CRP laboratory data and a diagnosis of various red and white oral lesions, including oral stomatitis, OLP, oral leukoplakia, and OSF were identified across the 7 databases, including AUMC, WKUH, DCMC, EUMC, SCHBC, SCHCA, and GNUH. Among these, 204 individuals (2.03%) experienced malignant transformation to OSCC. When analysed by specific category, malignant transformation occurred in 11 of 646 (1.70%) for OLP, 47 of 4530 (1.03%) for stomatitis, 100 of 4417 (2.26%) for oral mucositis, 45 of 434 (10.4%) for oral leukoplakia, and 1 of 2 (50.0%) for OSF (Table 1). The target cohort (CRP ≥ 0.269 mg/dL) included 4142 individuals, with elevated CRP levels within a 180-day window period. The comparator cohort (CRP < 0.269 mg/dL) comprised 5887 individuals during the same period. Within these cohorts, 96 (2.32%) and 108 (1.83%) in the target and comparator cohort progressed to OSCC (Figure 2A).

To reduce intergroup heterogeneity, 1:1 and 1:2 PS matching analyses were performed. After PS matching, 3268 and 4439 individuals were included in the 1:1 and 1:2 PS matching models, respectively. In the 1:1 PS matching model, 98 individuals (3.00%) experienced malignant transformation including 55 (3.37%) and 43 (2.33%) in the target and comparator cohorts, respectively (Figure 2B). In the 1:2 PS matching model 118 individuals (2.66%) progressed to OSCC, with 55 (3.37%) and 63 (2.25%) in the target and comparator cohorts, respectively (Figure 2C).

Baseline characteristics of the matched cohort of 1:1 and 1:2 PS matching were summarised in Tables 2 and 3, respectively. Following large-scale PS matching, hypertension emerged as the most prevalent comorbidities aside from malignancy, and anti-rheumatic drugs were the most commonly prescribed medication prior to cohort entry (Tables 2 and 3).

Impact of elevated CRP levels on malignant transformation potential in patients with OPMD

To mitigate heterogeneity between the target and comparator cohorts, both 1:1 and 1:2 PS matching analysis were applied. The I^2 statistic was 0% for the crude model without PS matching as well as 1:1 and 1:2 PS matching model, indicating no significant heterogeneity across datasets. Therefore, common-effect models were applied for the meta-analysis.

The meta-analysis demonstrated a consistent association between elevated CRP levels and increased OSCC risk. In the crude model, the HR was 1.40 (HR = 1.40, [95% CI 1.05-1.86], I^2 = 0%) (Figure 3A). After 1:1 PS matching, the HR increased to 1.79 (HR = 1.79 [95% CI 1.08-2.95] I^2 = 0%) (Figure 3B), and in the 1:2 PS matching model, the HR was 1.55 (HR = 1.55 [95% CI 1.01-2.38] I^2 = 0%) (Figure 3C and Table 4).

Subgroup and sensitivity analyses

To enhance the reliability of the findings, multiple subgroup and sensitivity analyses were performed to validate findings regarding the impact of elevated CRP on malignant transformation risk in patients with diverse types of oral lesions.

Subgroup analyses, stratified by age, sex, and geographic region revealed patterns consistent with the primary results. In age-stratified analysis, elevated CRP was associated with an increased risk of OSCC in both individuals aged under 60 years (HR, 1.00, 95% CI [0.64-1.57], I^2 = 8.4%) (Supplementary Figure 2A) and those aged 60 years or older (HR, 1.61, 95% CI [1.08-2.41], I^2 = 0%) (Supplementary Figure 2B). However, the association was more prominent in the groups aged 60 years or older. Sex-stratified analysis demonstrated similar trends, with elevated CRP linked to increased risk in males (HR, 1.19, 95% CI [0.62-2.29], I^2 = 0%) (Supplementary Figure 3A) and females (HR, 1.72, 95% CI [0.86-3.44], I^2 = 10.6%) (Supplementary Figure 3B), although females showed more remarkable association. Regional stratification analysis revealed consistent effects in the Seoul/Gyeonggi metropolitan hospitals (HR, 1.15, 95% CI [0.73-1.80], I^2 = 35.6%) (Supplementary Figure 4A) and those in other nonmetropolitan regions (HR, 1.60, 95% CI [1.11-2.31], I^2 = 0%) (Supplementary Figure 4B). Therefore, females and older adults, lived in nonmetropolitan areas exhibited stronger associations between elevated systemic inflammation levels and the incidence of OSCC.

Table 1 – Malignant transformation rates in each OPMD category.

	Cases			Malignant transformation cases		
	CRP ≥ 0.269 mg/dL	CRP < 0.269 mg/dL	Total	CRP ≥ 0.269 mg/dL	CRP < 0.269 mg/dL	Total
Lichen planus (L43)	152	494	646	3 (1.97%)	8 (1.62%)	11 (1.70%)
Stomatitis (K12.1)	2368	2162	4530	29 (1.22%)	18 (0.83%)	47 (1.04%)
Oral mucositis (K12.3)	1444	2973	4417	39 (2.70%)	61 (2.05%)	100 (2.26%)
Oral leukoplakia (K13.2)	177	257	434	25 (14.1%)	20 (1.78%)	45 (10.4%)
Oral submucous fibrosis (K13.5)	1	1	2	0	1 (100%)	1 (50.0%)
Total	4142	5887	10029	96 (2.32%)	108 (1.83%)	204 (2.03%)

%, malignant transformation rate.

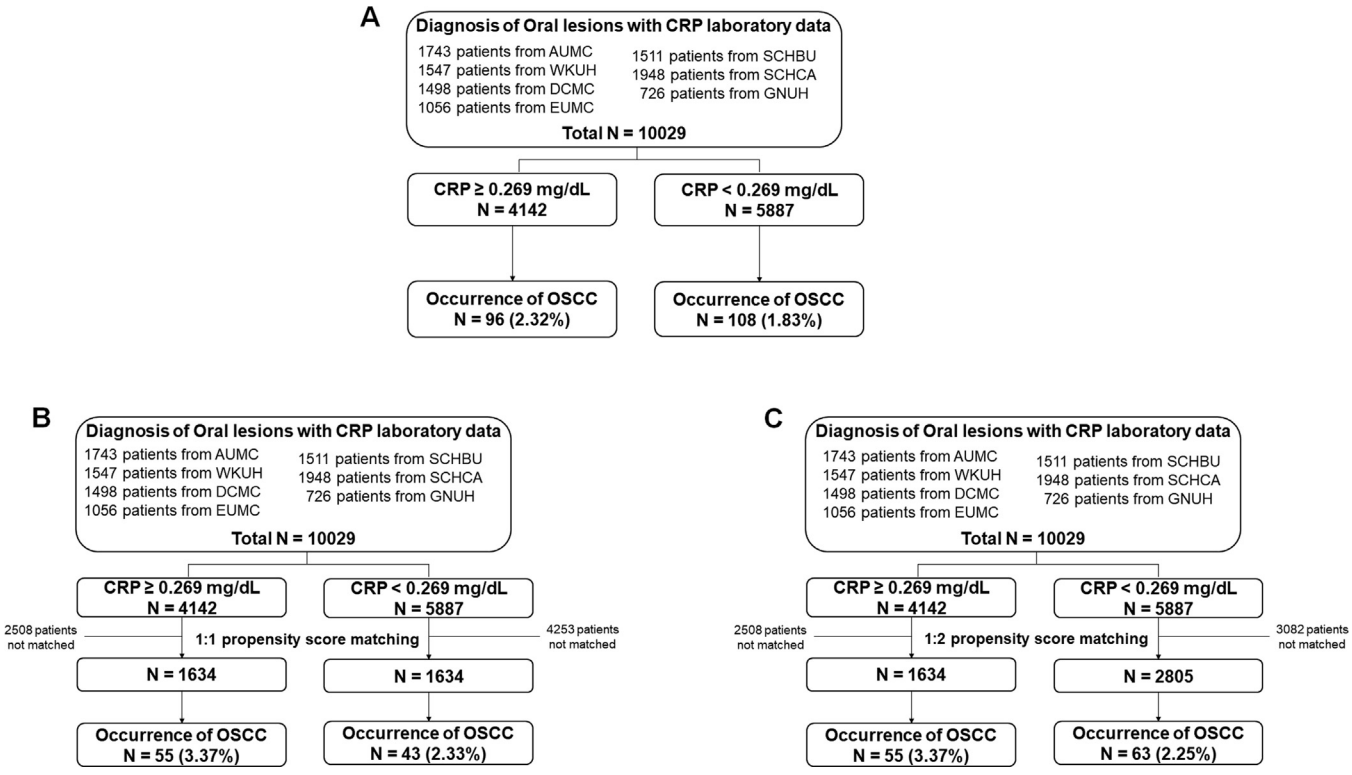

Fig. 2 – Participant selection flowchart. A, Before PS matching. B, After 1:1 PS matching. C, After 1:2 PS matching.

Baujat plot analysis (Supplementary Figure 5A) identified SCHBA as a significant contributor to heterogeneity and pooled effect size. Exclusion of this medical centre slightly increased the pooled HR (HR, 1.81, 95% CI [1.18-2.25], I^2 = 0%) (Supplementary Figure 5B). These subgroups and sensitivity analysis consistently support the primary findings that elevated systemic inflammation, indicated by higher CRP levels, is associated with an increased risk of malignant transformation in patients with OPMD. The observed regional variation may be attributed to the demographic structure in nonmetropolitan areas in Korea, where a higher proportion of older residents is present due to declining birth rates in South Korea.

Discussion

Numerous clinical risk factors have been proposed as contributors to the malignant transformation of OPMD and other inflammatory oral conditions, however, the precise biomarkers and specific molecular mechanisms remain unclear. Although prior research has explored the associations between both local and systemic inflammation and malignant progression or survival outcomes related to various precancerous lesions, the specific contribution of systemic inflammation in OPMD and other inflammatory oral conditions has not been elucidated. Hence, this study addressed this gap by investigating whether elevated serum CRP levels, a well-established indicator of systemic inflammation, were associated with an increased risk of malignant transformation to OSCC in OPMD patients, leveraging the Observational Health Sciences and Informatics network and the OMOP-CDM framework.

The novel insight from this multicentre, observational, retrospective, comparator cohort study was the potential role of systemic inflammation in the malignant transformation of diverse oral conditions to OSCC, particularly among females and older adults. Although systemic inflammation has been implicated in early tumorigenesis in various cancers, such as melanoma, colorectal, lung, and breast cancer,[11-13] our findings suggested that a similar mechanism may be operative in oral precancerous conditions. Chronic inflammation promotes the sustained production of reactive oxygen and nitrogen species, contributing to oxidative damage affecting cellular membranes, protein peroxidation, and DNA damage, ultimately this cascade of molecular damage causes oncogenic transformation.[24-26] Inflammatory mediators such as cytokines and matrix metalloproteinases, not only initiate early carcinogenic process but also support tumour progression, through local invasion and distant metastasis.[27] Previous studies have identified elevated levels of pro-inflammatory cytokines and metalloproteinases as potential biomarkers of malignant transformation in OPMD and recurrence in OSCC.[16] Moreover, systemic inflammatory profiles have been correlated with oral lesion severity and progression, reinforcing the link between systemic inflammation and oral carcinogenesis.[16] Despite this, large-scale, longitudinal cohort studies confirming the association in oral cancer have been lacking, with this study providing novel evidence supporting this link.

The role of the immune system in the initiation, progression, and dissemination of cancer is well established.[28] Elevated

Table 2 – Baseline characteristics of overall participants before and after 1:1 PS matching.

Characteristic	Before PS adjustment			After 1:1 PS matching		
	CRP ≥ 0.269 mg/dL %	CRP < 0.69 mg/dL %	SMD	CRP ≥ 0.269 mg/dL %	CRP < 0.69 mg/dL %	SMD
Age group						
20-24	4.57	3.86	0.037	4.10	4.86	−0.026
25-29	4.84	4.93	−0.0057	3.92	4.82	−0.048
30-34	7.03	6.30	0.031	8.82	6.53	0.088
35-39	5.92	8.05	−0.088	5.52	8.32	−0.11
40-44	7.07	9.39	−0.087	8.61	9.61	−0.036
45-49	6.47	10.09	−0.14	8.72	8.68	−0.004
50-54	8.22	11.77	−0.12	9.10	10.46	−0.048
55-59	8.77	12.05	−0.11	11.13	12.18	−0.035
60-64	8.96	10.1	−0.036	10.14	10.75	−0.020
65-69	8.50	8.44	0.0025	9.39	7.19	0.074
70-74	8.45	6.183	0.095	7.87	7.10	0.035
75-79	7.60	4.60	0.13	6.75	5.28	0.062
80-84	6.27	3.08	0.15	6.15	4.78	0.062
Gender: Female	47.46	62.26	0.058	53.79	57.40	−0.074
Medical history: General						
Acute respiratory disease	13.19	4.39	0.310	6.24	7.13	−0.031
Depressive disorder	3.20	2.94	0.058	5.03	3.25	0.023
Diabetes mellitus	9.42	5.35	0.017	6.86	7.70	−0.026
Gastroesophageal reflux disease	12.03	14.79	0.16	12.27	17.46	−0.146
Hyperlipidaemia	8.97	11.92	0.11	11.98	14.32	−0.056
Hypertensive disorder	19.0	13.58	−0.07	16.57	17.60	−0.027
Renal impairment	8.11	3.23	0.042	4.00	5.84	−0.03
Medical history: Cardiovascular disease						
Heart disease	10.875	9.94	−0.30	11.08	13.25	−0.063
Ischemic heart disease	5.10	5.80	0.073	5.41	7.86	−0.045
Medical history: Neoplasm						
Malignant neoplastic disease	14.93	6.00	−0.005	10.627	9.08	0.057
Medication use						
Agents acting on the renin-angiotensin system	12.35	9.99	0.085	11.81	12.81	−0.039
Antibacterial for systemic use	57.55	34.81	0.48	40.4	44.6	−0.086
Antidepressants	21.213	10.63	0.29	13.69	15.34	−0.051
Antiepileptics	9.863	9.38	0.015	9.56	12.34	−0.066
Antirheumatic products	53.84	35.58	0.39	40.00	44.24	−0.089
Antineoplastic agents	13.83	7.013	0.21	9.63	9.78	−0.0088
Antithrombotic agents	29.53	17.89	0.28	21.33	24.41	−0.075
Beta blocking agents	9.94	7.84	0.007	8.87	10.40	−0.051
Calcium channel blockers	14.81	9.40	0.083	12.54	13.30	−0.024
Diuretics	19.89	7.071	0.16	12.67	12.46	0.0057
Drugs for acid related disorders	65.21	50.14	0.38	50.44	55.88	−0.115
Drugs for obstructive airway diseases	27.63	19.27	0.32	20.69	23.87	−0.079
Drugs used in diabetes	10.96	6.84	0.21	6.73	9.16	−0.080
Immunosuppressants	4.91	3.44	0.15	2.52	3.82	−0.032
Lipid modifying agents	13.14	13.95	0.16	13.40	15.20	−0.06
Opioids	33.79	17.86	0.30	21.46	25.68	−0.094
Psycholeptics	29.16	21.79	0.35	23.01	27.21	−0.100
Psychostimulants, agents used for ADHD and nootropics	1.50	1.48	0.18	2.67	0.77	0.040

CRP, C-reactive protein; PS, propensity score; SMD, standardised mean difference.
Values are presented as proportion of the participants (%).

cancer risk has been observed in individuals with autoimmune conditions, such as systemic lupus erythematosus (SLE), cutaneous lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, and systemic sclerosis.[29-33] Notably, patients with SLE have demonstrated increased susceptibility to head and neck cancers, including OSCC,[34,35] as well as epithelial dysplasia among those with OPMD.[18,36] In parallel, inflammatory conditions of the oral cavity have been associated with increased systemic inflammatory burden, further supporting the interplay between local and systemic inflammation.[37,38] The increased cancer susceptibility may stem from chronic inflammatory environment and impaired immune regulation related to autoimmune conditions, potentially facilitating malignant transformation in oral tissues.

Table 3 – Baseline characteristics of overall participants before and after 1:2 PS matching.

Characteristic	Before PS adjustment			After 1:2 PS matching		
	CRP ≥ 0.269 mg/dL %	CRP < 0.69 mg/dL %	SMD	CRP ≥ 0.269 mg/dL %	CRP < 0.69 mg/dL %	SMD
Age group						
20-24	4.70	3.95	0.038	4.1	4.36	−0.0040
25-29	4.84	4.93	−0.00571	3.92	5.06	−0.060
30-34	7.03	6.30	0.031429	8.3	6.07	0.089
35-39	5.92	8.05	−0.08833	3.88	7.62	−0.11
40-44	7.07	9.39	−0.08714	8.61	8.99	−0.014
45-49	6.76	10.31	−0.1325	8.82	9.82	−0.040
50-54	8.16	11.46	−0.115	9.74	10.34	−0.026
55-59	8.91	11.79	−0.09714	10.63	11.26	−0.024
60-64	9.23	10.70	−0.04857	10.63	10.89	−0.010
65-69	8.50	8.44	0.0025	9.39	8.14	0.036
70-74	8.21	6.10	0.0875	7.56	6.60	0.038
75-79	6.88	4.65	0.103333	7.12	5.90	0.052
80-84	6.37	3.76	0.121429	7.10	4.99	0.093
85-89	2.93	1.88	0.0725			
Gender: Female	47.46	62.26	−0.31	53.79	57.34	−0.071
Medical history: General						
Acute respiratory disease	13.19	4.39	0.31	6.24	6.44	−0.01
Depressive disorder	3.20	2.94	0.017	4.30	4.04	0.002
Diabetes mellitus	9.42	5.35	0.16	6.86	8.14	−0.05
Gastroesophageal reflux disease	14.28	14.54	−0.0025	12.84	17.09	−0.12
Hyperlipidaemia	8.34	11.01	−0.066	10.95	12.35	−0.022
Hypertensive disorder	19.00	13.58	0.15	16.57	17.13	−0.013
Lesion of liver	4.44	1.47	0.16	3.45	2.83	0.03
Renal impairment	8.11	3.23	0.22	4.32	5.95	0
Osteoarthritis	2.44	2.24	0.0088	4.78	3	0.073
Pneumonia	9.03	1.38	0.35	1.4	2.6	−0.02
Medical history: Cardiovascular disease						
Heart disease	10.88	9.94	0.051	11.08	12.83	−0.05
Ischemic heart disease	5.10	5.8	−0.0050	5.41	7.64	−0.039
Cerebrovascular disease	2.10	2.92	−0.012	3.50	3.90	−0.023
Medical history: Neoplasm						
Malignant neoplastic disease	16.42	6.20	0.33	11.33	9.80	0.057
Medication use						
Agents acting on the renin-angiotensin system	12.35	9.99	0.085	11.81	12.49	−0.026
Antibacterial for systemic use	57.55	34.81	0.48	40.40	43.10	−0.054
Antidepressants	21.21	10.63	0.29	13.69	15.46	−0.053
Antiepileptics	9.86	9.38	0.015	9.56	12.69	−0.074
Antirheumatic products	53.84	35.58	0.39	40.00	44.11	−0.085
Antineoplastic agents	13.83	7.01	0.21	9.625	9.25	0.0088
Antithrombotic agents	29.53	17.89	0.28	21.325	23.78	−0.058
Beta blocking agents	9.94	7.84	0.007	9.16	10.50	−0.049
Calcium channel blockers	14.81	9.40	0.18	12.54	13.275	−0.023
Diuretics	18.75	6.91	0.36	12.3	12.05	0.0063
Drugs for acid related disorders	65.21	50.14	0.32	50.44	55.71	−0.11
Drugs for obstructive airway diseases	26.84	19.15	0.19	20.93	23.83	−0.07
Drugs used in diabetes	10.96	6.84	0.16	6.73	9.425	−0.09
Immunosuppressants	6.13	4.24	0.083	4.013	5.729	0
Lipid modifying agents	13.77	15.26	−0.029	14.29	16.56	−0.073
Opioids	33.79	17.86	0.37	21.46	24.94	−0.080
Psycholeptics	29.17	22.32	0.17	23.10	27.00	−0.093
Psychostimulants, agents used for ADHD and nootropics	1.50	1.48	0.042	2.67	1.07	0.037

CRP, C-reactive protein; PS, propensity score; SMD, standardised mean difference.
Values are presented as proportion of the participants (%).

This multicentre, retrospective observational cohort study is the first to utilise the OMOP CDM framework and a defined CRP levels to investigate the association between systemic inflammation and malignant transformation potential in patients with OPMD and other inflammatory oral conditions. The standardised CDM-based distributed network model, enables robust, large-scale PS matching across multiple institutions, while preserving patient privacy by sharing only

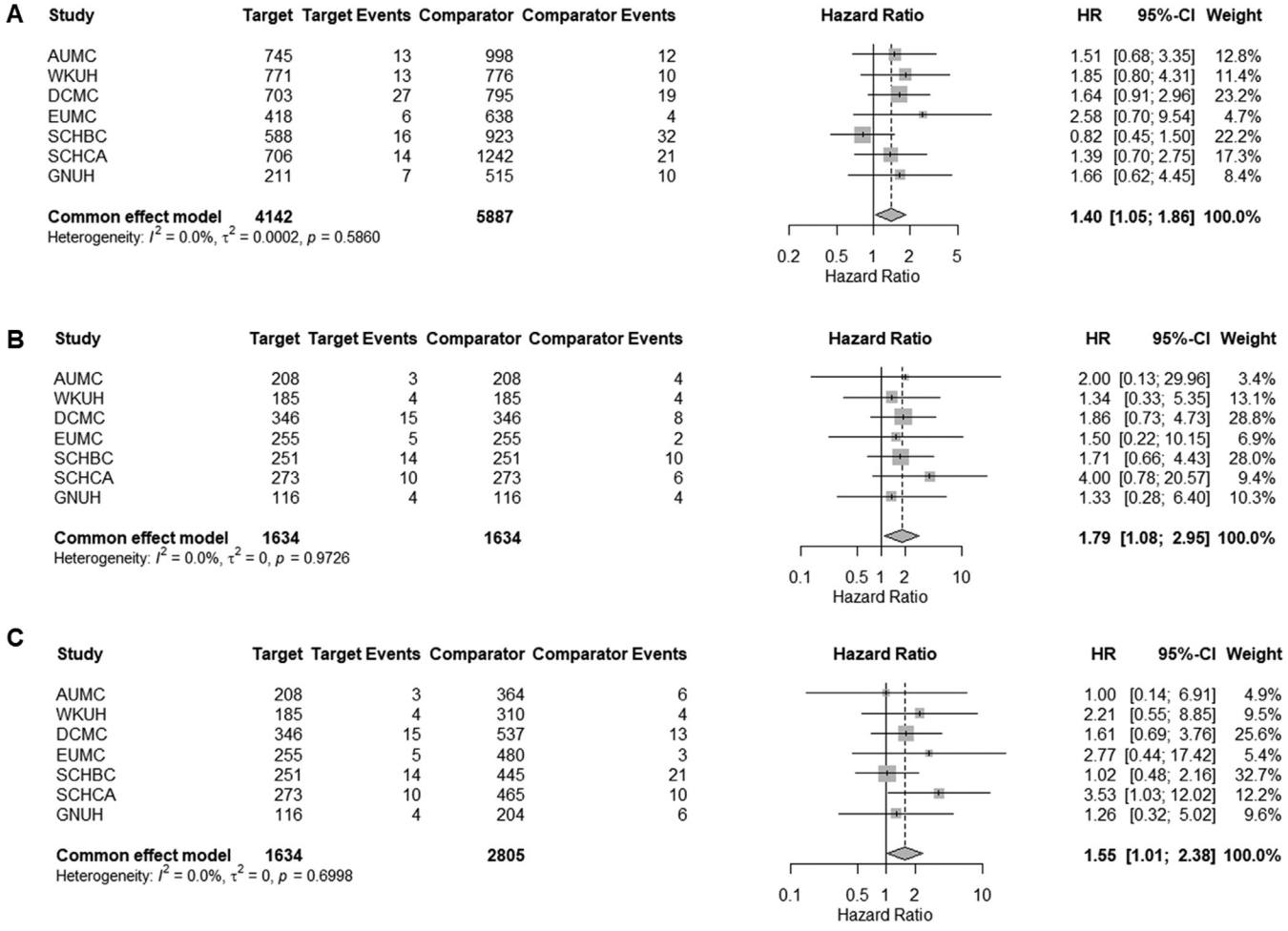

Fig. 3 – Meta-analysis of OSCC risk associated with elevated serum CRP levels. A, Before PS matching. B, After 1:1 PS matching. C, After 1:2 PS matching.

algorithms and protocols rather than personal health data.[39] Despite the real-world nature of the data, the use of extensive PS matching helped to minimise bias from confounding baseline covariates.

Limitations

However, this study has several limitations that must be acknowledged. First, the CDM lacked clinical and health-behaviour related variables including specific lesion site, tobacco and alcohol use, and family history of cancer, all of which are known to affect malignant transformation risk of OPMD. To mitigate this, large-scale propensity score matching was performed by incorporating a comprehensive range of comorbidities and medication histories as proxy indicators to indirectly adjust for these underlying health behaviours. Furthermore, to validate the stability of the findings, multiple sensitivity analyses were conducted, including subgroup evaluations and the exclusion of medical centres

Table 4 – Risk of malignant transformation in patients with OPMD according to serum CRP levels.

	Group	Subjects (n)	Person-years (PY)	OSCC incidence cases	Incident rate (per 1000 PY)	HR (95% CI)
No PS matching	CRP < 0.269	5887	32,921	108	3.28	Reference
	CRP ≥ 0.269	4142	23,489	96	4.09	1.40 (1.05-1.86)
1:1 PS matching	CRP < 0.269	1634	7020	38	5.41	Reference
	CRP ≥ 0.269	1634	6555	55	8.39	1.79 (1.08-2.95)
1:2 PS matching	CRP < 0.269	2805	11,994	63	5.25	Reference
	CRP ≥ 0.269	1634	6555	55	8.39	1.55 (1.01-2.38)

CI, confidential interval; CRP, C-reactive protein; HR, hazard ratio; PS, propensity score.
Estimated from the Cox proportional hazards model to estimate HRs an 95% CIs.

exhibiting high heterogeneity. The consistent association observed between elevated CRP and OSCC transformation across these diverse analytical frameworks suggests that the predictive value of systemic inflammation remains robust, even when indirect methods are utilised to account for unmeasured confounders. Second, the absence of histological data, including number of patients with epithelial dysplasia, limited the biological and molecular characterisation of oral lesions. The reliance on ICD-10 diagnostic codes assigned during routine clinical care means the cohort reflects real-world clinical management patterns rather than risks stratified by specific pathological grades. In particular, oral stomatitis and oral mucositis, which were identified based on ICD-10 codes, may not represent strictly distinct clinicopathological entities due to the lack of detailed clinical and histopathological information, and were therefore interpreted as part of a broader spectrum of inflammatory oral mucosal conditions. For instance, the codes for stomatitis and oral mucositis is frequently applied to persistent inflammatory lesions clinically monitored for malignant potential. Thirdly, although standardised matching methods minimised confounders, unmeasured institutional variability, such as difference in laboratory quality control standards, may still influence the outcomes. Additionally, given the multicentre nature of the study, variability in diagnostic labelling and coding practices across institutions may have influenced disease classification. Fourth, the use of an aggregated meta-analysis rather than pooled individual-level data may have reduced the granularity of the findings. Finally, although the short biological half-life of CRP may introduce variability, the study design utilised a standardised 180-day window and prioritised data purity by excluding cases with confirmed fluctuations. This conservative approach, supported by a large-scale multicentre cohort of over 10,000 patients, allowed for the identification of a sustained basal inflammatory profile rather than transient noise. Nevertheless, the use of differing time windows for threshold derivation and exposure definition may introduce methodological complexity, although this design was intended to balance temporal standardisation and longitudinal stability. Furthermore, to minimise reverse causality, a 30-day lag period was implemented between OPMD diagnosis and OSCC transformation, ensuring a clear temporal relationship.

Conclusions

In conclusion, elevated CRP levels, a well-known marker of systemic inflammation were significantly associated with an increased risk of malignant transformation in patients with OPMD. CRP should be regarded not as a replacement for localised tissue markers, but as a valuable complementary biomarker reflecting the host's systemic inflammatory state. These findings emphasise the potential pathogenic role of chronic inflammation in promoting oral tumorigenesis, possibly through mechanisms involving aberrant wound healing and sustained epithelial damage. Given the relatively high prevalence of OPMD, an improved understanding of its inflammatory underpinnings may aid in identifying high-risk individuals and refining early detection and more effective management strategies to prevent OSCC.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

Materials described in the study, including relevant raw data, will be accessed to researchers for noncommercial purpose through ATLAS version 2.7.6, provided by FEEDER-NET platform.

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Supplementary materials

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