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Original Research Article

Comparative evaluation of serum homocysteine, CYFRA 21-1 and leptin in newly diagnosed oral squamous cell carcinoma: a hospital-based observational study

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is the predominant malignancy of the oral cavity and is associated with morbidity and mortality. Identification of circulating biomarkers reflecting disease-associated biochemical alterations may facilitate early detection and clinical risk assessment. This study evaluated serum homocysteine, cytokeratin 19 fragment antigen 21-1 (CYFRA 21-1), and leptin concentrations in patients with newly diagnosed OSCC and healthy controls.

Methods: This hospital-based comparative observational study included 126 participants: 63 histopathologically confirmed, treatment-naïve patients with OSCC and 63 age- and sex-matched healthy controls. Serum homocysteine was determined using an automated biochemical analyser, whereas CYFRA 21-1 and leptin were estimated by enzyme-linked immunosorbent assay. Between-group comparisons were performed using Student's independent t-test, and associations among biomarkers were assessed using Pearson's correlation analysis. A p value <0.05 was considered statistically significant.

Results: Serum homocysteine and CYFRA 21-1 concentrations were significantly higher in OSCC patients than in controls (22.87±7.24 vs 12.53±3.01 µmol/l and 4.09±1.40 vs 0.81±0.51 ng/ml, respectively; both p<0.001). Conversely, serum leptin concentrations were significantly lower in OSCC patients (4.16±3.17 vs 11.04±5.83 ng/ml; p<0.001). Homocysteine demonstrated a significant positive correlation with CYFRA 21-1, whereas leptin showed significant inverse correlations with both biomarkers.

Conclusion: Newly diagnosed OSCC was characterized by elevated serum homocysteine and CYFRA 21-1 and reduced leptin concentrations. This differential biomarker profile supports their potential utility as complementary circulating markers in OSCC and warrants further prospective investigation.

Keywords: Biomarkers, CYFRA 21-1, Homocysteine, Leptin, Oral squamous cell carcinoma

INTRODUCTION

OSCC is the most common malignancy of the oral cavity, accounting for nearly 90% of all oral cancers. It is a major contributor to cancer-related morbidity and mortality worldwide and remains a significant public health concern, particularly in developing countries such as India. Despite advances in diagnostic techniques and treatment modalities, the overall five-year survival rate has shown only modest improvement over the past few decades. This is largely because most patients are diagnosed at an advanced stage, when the disease has already invaded surrounding tissues or metastasized to the regional lymph nodes. The high prevalence of tobacco smoking,

smokeless tobacco use, betel quid and areca nut chewing, alcohol consumption, poor oral hygiene, and human papillomavirus (HPV) infection substantially increases the burden of OSCC in South Asian populations. Therefore, identifying reliable biomarkers that facilitate early diagnosis and provide prognostic information has become an important priority in oral cancer research.[1–8]

Accumulating evidence indicates that metabolic alterations play a pivotal role in the initiation and progression of cancer.[9–12,24–27] One-carbon metabolism, which is essential for DNA synthesis, methylation reactions, and cellular proliferation, is frequently disrupted in malignant cells. Homocysteine, a sulfur-containing amino acid formed during methionine metabolism, has emerged as a potential biomarker of these metabolic disturbances. Elevated serum homocysteine concentrations have been associated with oxidative stress, DNA damage, impaired DNA methylation, and genomic instability, all of which contribute to carcinogenesis. Although hyperhomocysteinaemia has traditionally been linked to cardiovascular and neurological disorders, recent studies suggest that altered homocysteine metabolism may also play an important role in the development and progression of several epithelial malignancies, including OSCC.[9–13]

In addition to metabolic biomarkers, tumour-associated epithelial markers have gained considerable attention for their potential clinical utility. Cytokeratin 19 fragment antigen 21-1 (CYFRA 21-1), a soluble fragment of cytokeratin 19 released during epithelial cell degeneration and tumour cell turnover, has been extensively investigated as a non-invasive biomarker in epithelial cancers. Increased serum CYFRA 21-1 levels have been associated with a greater tumour burden, advanced clinical stage, lymph node involvement, and poor prognosis in patients with OSCC. Because serum estimation is simple and minimally invasive, CYFRA 21-1 has considerable potential as an adjunctive marker for disease diagnosis, prognosis, and therapeutic monitoring.[14–19]

Leptin, a 16-kDa adipokine predominantly secreted by adipose tissue, regulates energy homeostasis, appetite, immune responses, inflammation, and angiogenesis. Beyond its physiological functions, leptin influences several cellular signalling pathways involved in tumour growth, proliferation, and survival. Altered circulating leptin levels have been reported in various malignancies and are believed to reflect changes in nutritional status, systemic inflammation, and cancer-associated metabolic disturbances.

In patients with OSCC, reduced serum leptin concentrations may be indicative of tumour-related cachexia and progressive nutritional decline, making leptin a potentially valuable biomarker for assessing disease severity and prognosis.[20–27]Although several studies have independently evaluated homocysteine, CYFRA 21-1, or leptin in oral cancer, relatively few have investigated their combined diagnostic and prognostic significance in newly diagnosed patients with OSCC. Simultaneous assessment of these biomarkers may provide a more comprehensive understanding of the metabolic, inflammatory, and epithelial alterations associated with oral carcinogenesis and may improve the accuracy of disease detection and risk stratification.[13,17,18,23,32–35]

Therefore, the present study was undertaken to compare serum homocysteine, CYFRA 21-1, and leptin levels between newly diagnosed, treatment-naïve patients with oral squamous cell carcinoma and age- and sex-matched healthy controls. In addition, the study evaluated the relationship among these biomarkers to determine their potential utility as non-invasive indicators for diagnosis, prognostic assessment, and monitoring of disease progression in patients with OSCC.

METHODS

Study design and setting

This hospital-based comparative observational study was conducted in the Departments of Biochemistry and Medical Oncology, SMS Medical College and Attached Hospitals, Jaipur, Rajasthan, India. The study was carried out over a period of 12 months, from April 2025 to March 2026, after obtaining approval from the Institutional Ethics Committee (Ref. No. 407/MC/EC/2025, dated 24 April 2025). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, the Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017), and the New Drugs and Clinical Trials Rules (2019). Written informed consent was obtained from all participants before enrolment.

Study population

A total of 126 participants were enrolled in the study. The study group comprised 63 newly diagnosed, histopathologically confirmed, treatment-naïve patients with OSCC attending the Department of Medical Oncology. The control group included 63 apparently healthy age- and sex-matched individuals without any evidence of malignancy or chronic systemic illness. Controls were recruited from hospital visitors and individuals attending routine health check-ups.

Inclusion criteria

The following participants were included in the study.

Patients aged 18 years or older with newly diagnosed, histopathologically confirmed OSCC. Patients who had not received surgery, chemotherapy, radiotherapy, or any other cancer-specific treatment before sample collection. Individuals who were willing to participate and provided written informed consent. Age- and sex-matched healthy volunteers without clinical evidence of oral malignancy.

Exclusion criteria

Participants were excluded if they had recurrent or previously treated oral squamous cell carcinoma, any other malignancy. Acute or chronic inflammatory disorders. Chronic liver disease, renal disease, cardiovascular disease, or autoimmune disorders, pregnancy or lactation. Current treatment with vitamin B12, folic acid, corticosteroids, or immunosuppressive drugs. Refusal to provide informed consent.

Sample size

The sample size was calculated using OpenEpi software, assuming a 95% confidence level, 80% study power, and an effect size derived from previously published studies evaluating serum biomarkers in patients with oral squamous cell carcinoma. Based on these assumptions, the minimum required sample size was 126 participants, comprising 63 newly diagnosed OSCC cases and 63 age- and sex-matched healthy controls. Eligible participants were recruited consecutively during the study period until the predetermined sample size was achieved.

Clinical evaluation

A detailed clinical history was obtained from all participants using a structured case record form. Demographic characteristics, tobacco and alcohol consumption, relevant medical history, and clinical findings were recorded. Anthropometric measurements, including height, weight, and body mass index (BMI), were measured using standard techniques. Clinical staging of OSCC was performed according to the TNM classification system based on clinical examination and histopathological evaluation.

Blood sample collection

After an overnight fast, approximately 5 ml of venous blood was collected from each participant under strict aseptic precautions. Blood samples were allowed to clot and were subsequently centrifuged at 3000 rpm for 10 minutes to separate the serum. The separated serum samples were aliquoted into sterile microcentrifuge tubes and stored at −80°C until biochemical analysis to prevent degradation of analytes.

Biochemical analysis

Serum homocysteine concentrations were estimated using a fully automated biochemical analyzer following the manufacturer's recommended protocol and standard laboratory quality control procedures.

Serum CYFRA 21-1 and leptin concentrations were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions. All assays were performed in duplicate under identical laboratory conditions to minimize analytical variability. Internal quality control procedures were followed throughout the analytical process to ensure accuracy and reproducibility of the results.

Statistical analysis

Data were entered into Microsoft Excel and analysed using the Statistical Package for the Social Sciences (SPSS) software, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages.

Comparisons between OSCC patients and healthy controls were performed using Student's independent t-test for continuous variables. Pearson's correlation coefficient was used to assess the relationship among serum homocysteine, CYFRA 21-1, and leptin levels in patients with OSCC. A two-tailed p value of less than 0.05 was considered statistically significant.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee, SMS Medical College and Attached Hospitals, Jaipur (Ref. No. 407/MC/EC/2025; approval dated 24 April 2025). Written informed consent was obtained from all participants before enrollment. Confidentiality of participants' information was maintained throughout the study, and all laboratory investigations were performed exclusively for research purposes without imposing any additional financial burden on the participants.

RESULTS

A total of 126 participants were included in the study, comprising 63 newly diagnosed, histopathologically confirmed, treatment-naïve patients with OSCC and 63 age- and sex-matched healthy controls. Baseline demographic characteristics, anthropometric measurements, tumour stage, and serum biomarker concentrations were evaluated and compared between the two groups.

Baseline demographic and clinical characteristics

The demographic and clinical characteristics of the study population are summarized in Table 1. The mean age of patients with OSCC was 47.70±11.00 years, while that of the control group was 48.27±10.51 years. The difference was not statistically significant (p=0.387), confirming appropriate age matching between the groups.

The gender distribution was identical in both groups, with males accounting for 79.36% (n=50) and females for 20.64% (n=13), reflecting the male predominance observed in the present study population. Anthropometric assessment demonstrated significantly lower height, body

weight, and body mass index among patients with OSCC than among healthy controls (all p<0.001). Furthermore, clinical staging revealed that Stage IV disease constituted the largest proportion of cases (47.62%), followed by Stage II (23.81%), Stage III (20.63%), and Stage I (7.94%), indicating that most patients were diagnosed at an advanced stage of the disease (Table 1).

Serum homocysteine levels

Patients with OSCC exhibited significantly higher serum homocysteine concentrations than healthy controls (Table 2). The mean serum homocysteine level was 22.87±7.24 µmol/l in the OSCC group compared with 12.53±3.01 µmol/l in the control group (p<0.001).

Serum homocysteine values ranged from 7.23 to 46.80 µmol/l in patients with OSCC and from 3.00 to 21.20 µmol/l among controls. Overall, circulating homocysteine concentrations were approximately 1.8-fold higher in patients with OSCC.

Serum CYFRA 21-1 levels

Serum CYFRA 21-1 concentrations were markedly elevated in patients with OSCC compared with healthy controls (Table 3).

The mean concentration was 4.09±1.40 ng/ml in patients with OSCC and 0.81±0.51 ng/ml in controls, representing a highly significant difference (p<0.001). The observed concentrations ranged from 1.14 to 7.31 ng/ml in the OSCC group and from 0.20 to 2.40 ng/ml in the control group. On average, serum CYFRA 21-1 levels were approximately five-fold higher among patients with OSCC.

Table 1: Baseline demographic and clinical characteristics of the study participants.

Variables	OSCC patients (n=63)	Healthy controls (n=63)	P value
Age (years), mean±SD	47.70 ± 11.00	48.27 ± 10.51	0.387
Sex, n (%)			
Male	50 (79.36)	50 (79.36)	—
Female	13 (20.64)	13 (20.64)	—
Height (m), mean±SD	164.86 ± 8.83	170.04 ± 6.85	<0.001
Weight (kg), mean±SD	57.40 ± 11.55	69.98 ± 11.37	<0.001
BMI (kg/m²), mean±SD	21.05 ± 3.52	24.06 ± 2.66	<0.001
Clinical stage, n (%)-OSCC patients only			
Stage I	5 (7.94)	—	—
Stage II	15 (23.81)	—	—
Stage III	13 (20.63)	—	—
Stage IV	30 (47.62)	—	—

Table 2: Comparison of serum homocysteine, CYFRA 21-1, and leptin levels between patients with oral squamous cell carcinoma and healthy controls.

Biomarker/Parameter	OSCC patients (n=63)	Healthy controls (n=63)	P value
Homocysteine (µmol/l)			
Mean±SD	22.87±7.24	12.53±3.01	<0.0001
Minimum	7.23	3.00	
Maximum	46.80	21.20	
CYFRA 21-(ng/ml)			
Mean±SD	4.09±1.40	0.81±0.51	<0.0001
Minimum	1.14	0.20	
Maximum	7.31	2.40	
Leptin (ng/ml)			
Mean±SD	4.16±3.17	11.04±5.83	<0.0001
Minimum	0.36	2.13	
Maximum	16.00	22.00	

Table 3: Pearson correlation coefficients among serum homocysteine, CYFRA 21-1 and leptin in newly diagnosed patients with OSCC.

Variables	Pearson's r	P value
Homocysteine vs CYFRA 21-1	0.955	<0.001
Homocysteine vs Leptin	−0.769	<0.001
CYFRA 21-1 vs Leptin	−0.795	<0.001

Serum leptin levels

In contrast, serum leptin concentrations were significantly lower in patients with OSCC than in healthy controls (Table 2). The mean serum leptin level was 4.16±3.17 ng/ml in the OSCC group compared with 11.04±5.83 ng/ml in the control group ($p<0.001$). Serum leptin concentrations ranged from 0.36 to 16.00 ng/ml in patients with OSCC and from 2.13 to 22.00 ng/ml among controls. Overall, patients with OSCC demonstrated an approximately 62% reduction in circulating leptin levels relative to healthy individuals.

Correlation analysis of serum biomarkers

Pearson's correlation analysis demonstrated significant associations among the investigated biomarkers (Table 3). Serum homocysteine showed a very strong positive correlation with CYFRA 21-1 ($r=0.955$), indicating that higher homocysteine concentrations were closely associated with increased serum CYFRA 21-1 levels. Conversely, serum leptin exhibited strong inverse correlations with both homocysteine ($r=-0.769$) and CYFRA 21-1 ($r=-0.795$), suggesting that lower leptin concentrations were associated with higher levels of these biomarkers. The observed relationships are illustrated in the scatter plots, which demonstrate a strong positive linear association between serum homocysteine and CYFRA 21-1, together with inverse linear relationships between serum leptin and both homocysteine and CYFRA 21-1 (Figures 2–4).

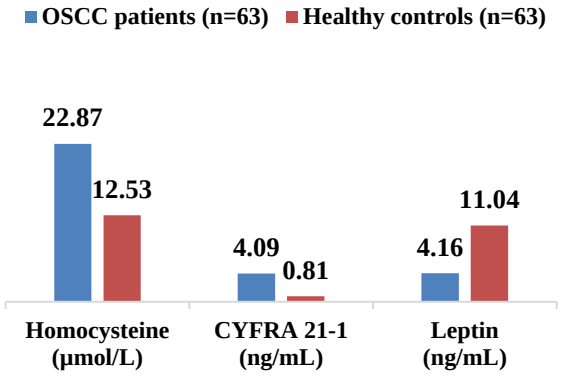

Figure 1: Comparison of serum biomarkers in OSCC patients and healthy controls.

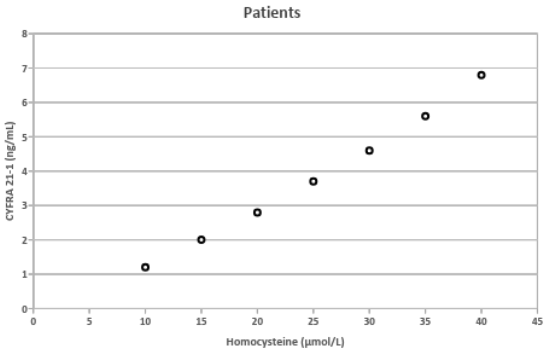

Figure 2: The correlation between serum homocysteine and CYFRA 21-1 concentrations in newly diagnosed patients with oral squamous cell carcinoma.

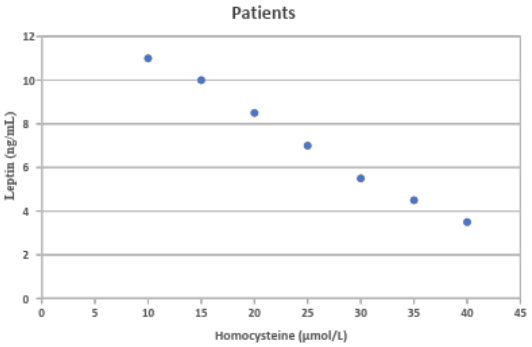

Figure 3: The correlation between serum homocysteine and leptin concentrations in newly diagnosed patients with oral squamous cell carcinoma.

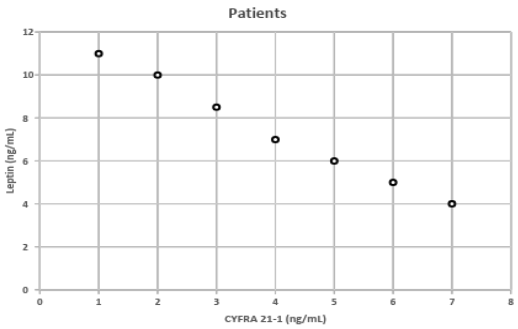

Figure 4: The correlation between serum CYFRA 21-1 and leptin concentrations in newly diagnosed patients with oral squamous cell carcinoma.

Overall findings

The present study identified distinct alterations in serum biomarker profiles among patients with newly diagnosed oral squamous cell carcinoma. Compared with healthy controls, patients with OSCC exhibited significantly higher serum homocysteine and CYFRA 21-1 concentrations, together with markedly lower serum leptin levels. Furthermore, the strong positive association between homocysteine and CYFRA 21-1, coupled with the inverse relationship between leptin and both biomarkers, underscores the close interplay between metabolic dysregulation, epithelial tumour activity, and nutritional status in oral squamous cell carcinoma. These findings support the potential utility of combined biomarker assessment as a complementary approach for the evaluation of patients with OSCC.

DISCUSSION

The present hospital-based comparative observational study evaluated serum homocysteine, cytokeratin 19 fragment antigen 21-1 (CYFRA 21-1), and leptin concentrations in newly diagnosed, treatment-naïve patients with oral squamous cell carcinoma (OSCC) and compared them with those of age- and sex-matched healthy controls. The findings demonstrated significant alterations in all three biomarkers, with markedly elevated serum homocysteine and CYFRA 21-1 levels and significantly reduced serum leptin concentrations in patients with OSCC. Furthermore, serum homocysteine exhibited a strong positive correlation with CYFRA 21-1, whereas leptin showed significant inverse correlations with both biomarkers. These observations suggest that metabolic dysregulation, epithelial tumour activity, and nutritional status are closely interconnected in OSCC and may collectively reflect disease burden and biological behaviour.[1–35]

The demographic characteristics of the study population were comparable between the two groups, with no significant differences in age or sex distribution, thereby minimizing the influence of these potential confounding variables. The predominance of male patients observed in the present study is consistent with the well-established epidemiology of OSCC, particularly in the Indian subcontinent, where tobacco smoking, smokeless tobacco use, betel quid chewing, and alcohol consumption remain the principal risk factors for oral carcinogenesis. Similar demographic patterns have been consistently reported in studies from India and other South Asian countries.[1–8,32,33]

Patients with OSCC demonstrated significantly lower body weight and body mass index than healthy controls. These findings are consistent with the metabolic consequences of malignancy and may be attributed to reduced oral intake secondary to pain, dysphagia, impaired mastication, systemic inflammation, and cancer-associated cachexia. Nearly half of the patients presented with Stage IV disease, highlighting the persistent challenge of delayed diagnosis in OSCC. Advanced-stage presentation is frequently associated with greater nutritional compromise, poorer treatment outcomes, and reduced survival, underscoring the importance of early detection and timely intervention.[1,5,8,23,24,32,33]

A major finding of the present study was the significant elevation of serum homocysteine concentrations in patients with OSCC. Homocysteine is a central intermediate in one-carbon metabolism and plays a critical role in DNA synthesis, methylation, and cellular proliferation. Dysregulation of homocysteine metabolism has been implicated in oxidative stress, endothelial dysfunction, impaired DNA repair, and epigenetic alterations, all of which contribute to carcinogenesis. Nutritional deficiencies, particularly of folate and vitamin B_{12}, which are common among patients with oral cancer, may further impair homocysteine metabolism and lead to its accumulation. The elevated serum homocysteine observed in the present study therefore supports its potential role as a biomarker of metabolic derangement associated with OSCC.[9–13,24–27]

The present findings are consistent with previous reports demonstrating increased serum homocysteine concentrations in patients with oral and head-and-neck malignancies. Earlier studies have suggested that elevated homocysteine reflects increased cellular turnover, altered methylation pathways, and nutritional deficiencies associated with malignant transformation. Although the underlying mechanisms require further elucidation, the available evidence supports the contribution of disturbed one-carbon metabolism to oral carcinogenesis. The findings of the present study further reinforce the potential clinical utility of serum homocysteine as an adjunctive biomarker in OSCC.[11–13,32–35]

Serum CYFRA 21-1 concentrations were also significantly higher in patients with OSCC than in healthy controls. CYFRA 21-1, a soluble fragment of cytokeratin 19, is released into the circulation during epithelial cell apoptosis and tumour cell turnover. Since OSCC originates from stratified squamous epithelium, progressive tumour growth is accompanied by increased cytokeratin degradation, resulting in elevated circulating CYFRA 21-1 levels. Consequently, serum CYFRA 21-1 has been widely investigated as a marker of tumour burden, disease progression, and treatment response.[14–19]

The markedly elevated serum CYFRA 21-1 concentrations observed in the present study corroborate earlier reports describing its diagnostic and prognostic significance in OSCC. Previous studies have demonstrated positive associations between CYFRA 21-1 levels and tumour stage, lymph node metastasis, and disease recurrence. Although stage-wise biomarker analysis was beyond the scope of the present investigation, the predominance of advanced-stage disease among the study participants may

partly explain the high circulating CYFRA 21-1 concentrations observed. These findings further support the role of CYFRA 21-1 as a valuable non-invasive biomarker for assessing tumour burden in patients with OSCC.[15–19,32–35]

Unlike homocysteine and CYFRA 21-1, serum leptin concentrations were significantly reduced in patients with OSCC. Leptin is an adipocyte-derived hormone involved in the regulation of appetite, energy homeostasis, immune function, and inflammatory responses. Circulating leptin levels are influenced by adipose tissue mass, systemic inflammation, and nutritional status. Therefore, the reduced leptin concentrations observed in the present study most likely reflect the metabolic and nutritional deterioration associated with advanced malignancy rather than tumour-specific secretion.[20–24]

Previous investigations evaluating leptin in OSCC have reported inconsistent findings, with some studies demonstrating increased tissue expression despite reduced circulating concentrations. These discrepancies may be explained by differences in tumour stage, body composition, ethnicity, sample size, and analytical methodology. Nevertheless, the present findings support the concept that serum leptin primarily reflects cancer-associated nutritional compromise and may provide complementary information regarding the metabolic status of patients with OSCC.[21–24,32–34]

An important strength of the present study was the demonstration of significant correlations among the investigated biomarkers. Serum homocysteine showed a very strong positive correlation with CYFRA 21-1, suggesting that metabolic disturbances become more pronounced with increasing tumour activity. In contrast, serum leptin exhibited strong inverse correlations with both homocysteine and CYFRA 21-1, indicating that worsening nutritional status is associated with greater metabolic abnormalities and increased tumour burden. These findings suggest that the three biomarkers represent complementary biological processes involved in OSCC rather than isolated pathological events.[13,17,18,23–26,32–35]

From a clinical perspective, the combined assessment of serum homocysteine, CYFRA 21-1, and leptin may provide greater diagnostic and prognostic value than the evaluation of any single biomarker alone. While homocysteine reflects disturbances in one-carbon metabolism, CYFRA 21-1 serves as an indicator of epithelial tumour turnover, and leptin provides insight into the nutritional and metabolic consequences of malignancy. Simultaneous evaluation of these biomarkers may therefore facilitate a more comprehensive assessment of disease status and potentially improve risk stratification in patients with OSCC.[13,17,18,23,32–35]

The present study has several strengths. Only newly diagnosed, histopathologically confirmed, treatment-naïve patients were included, thereby eliminating the confounding effects of surgery, chemotherapy, or radiotherapy on serum biomarker concentrations. The inclusion of age- and sex-matched healthy controls enhanced the validity of intergroup comparisons, and all biochemical analyses were performed using standardized laboratory protocols with appropriate quality control procedures.

Certain limitations should also be acknowledged. This was a single-centre study with a relatively modest sample size, which may limit the generalizability of the findings. The cross-sectional design precludes the establishment of causal relationships between biomarker alterations and disease progression. In addition, longitudinal follow-up was not performed to evaluate post-treatment changes or the prognostic value of these biomarkers for recurrence and survival. Future multicentric prospective studies involving larger patient cohorts and long-term follow-up are warranted to validate these findings and establish clinically relevant diagnostic and prognostic cut-off values.

CONCLUSION

The present study demonstrated significant alterations in serum homocysteine, CYFRA 21-1, and leptin levels among newly diagnosed, treatment-naïve patients with oral squamous cell carcinoma. Compared with age- and sex-matched healthy controls, patients with OSCC exhibited significantly elevated serum homocysteine and CYFRA 21-1 concentrations, whereas serum leptin levels were markedly reduced.

In addition, the strong positive correlation between homocysteine and CYFRA 21-1 and the inverse relationship of leptin with both biomarkers suggest that metabolic disturbances, epithelial tumour activity, and nutritional impairment are closely interconnected in the pathophysiology of OSCC. These findings indicate that the combined assessment of serum homocysteine, CYFRA 21-1, and leptin may provide a more comprehensive evaluation of disease status than the use of individual biomarkers alone.

Their estimation is minimally invasive, relatively simple, and has the potential to complement conventional diagnostic approaches by improving early detection, facilitating prognostic assessment, and aiding disease monitoring. Although the present study provides valuable evidence supporting the clinical relevance of these biomarkers, its findings should be interpreted in light of the single-centre, cross-sectional design and relatively limited sample size.

Larger multicentre prospective studies with longitudinal follow-up are required to validate these observations, establish clinically meaningful reference ranges and diagnostic cut-off values, and determine their predictive

value for treatment response, recurrence, and survival. Such investigations may further clarify the role of these biomarkers in the routine clinical management of patients with oral squamous cell carcinoma.

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