

## Systematic Review

# Serum ceruloplasmin levels for early detection of oral precancer and oral cancer—a systematic review and meta-analysis

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Serum ceruloplasmin / oral cancer / oral potentially malignant disorder / oral squamous cell carcinoma

**Abstract – Introduction:** Oral squamous cell carcinoma (OSCC) is the most prevalent malignancy of the head and neck region. It frequently develops from oral potentially malignant disorders such as leukoplakia and oral submucous fibrosis, both of which carry a significant risk of malignant transformation. Early detection of OSCC is crucial for improving patient outcomes; however, current diagnostic approaches, including biopsy, are invasive and may lead to patient discomfort and anxiety. Serum ceruloplasmin (SCP), a copper-binding protein with oxidase activity, has shown potential as a less-invasive biomarker in various cancers, including OSCC. OSCC is often preceded by oral potentially malignant disorders (OPMDs); therefore, early detection at this stage is crucial for effective management and improved prognosis. This study combines a systematic review with a meta-analysis to assess serum ceruloplasmin levels for determining whether it can serve as a biomarker for the early detection of OPMDs and OSCC. **Materials and methods** A systematic literature search was conducted using Google Scholar, PubMed, ProQuest, and Scopus databases. Studies included were original human research articles assessing serum ceruloplasmin levels in leukoplakia, oral submucous fibrosis, and oral squamous cell carcinoma, published in English up to 2024. Eight studies that met these criteria were included. The review followed PRISMA guidelines and was registered in PROSPERO. Meta-analysis was conducted using a random-effects model. Forest plots were generated to illustrate SCP levels in the three study groups. **Results:** Serum ceruloplasmin levels demonstrated a progressive increase from normal mucosa to leukoplakia, oral submucous fibrosis, and oral squamous cell carcinoma. Both leukoplakia and oral submucous fibrosis showed significantly higher serum ceruloplasmin levels than normal tissue, suggesting a progressive association between ceruloplasmin concentration and lesion severity. Also, oral squamous cell carcinoma exhibited the highest serum ceruloplasmin concentrations. However, the difference between oral squamous cell carcinoma and oral submucous fibrosis was minimal, indicating overlapping values. **Conclusion:** Elevated serum ceruloplasmin levels may serve as a promising non-invasive biomarker for early detection of oral potentially malignant disorders and oral squamous cell carcinoma. Standardized methodologies and larger-scale studies are warranted to validate serum ceruloplasmin's diagnostic utility.

## Introduction

Oral cancer is the sixth most prevalent cancer in the world, with oral squamous cell carcinoma (OSCC) accounting for over 90% of all malignancies in the oral cavity [1,2]. Because of its high rates of morbidity and mortality, this common cancer that affects the oral cavity poses a serious threat to world health. To improve prognosis and survival rates, early diagnosis and detection are required. According to the European Oral Cancer Foundation, early cancer detection can

result in an 80–90% survival rate [3,4]. The gold standard method for diagnosis of cancer is biopsy, which can cause fear and anxiety in the patients. Consequently, adjuvant diagnostic methods that are noninvasive and cost-effective are beneficial for early detection of OSCC. In this context, the search for reliable biomarkers has gained prominence in recent years, and one such biomarker is serum ceruloplasmin (SCP).

Biomarkers are biological molecules found in tissue, blood, saliva, etc., which help in the prognosis, diagnoses, and prediction of various diseases. Serum biomarkers are specific substances that are released into the serum either by the host

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cell or the malignant cell while combating the cancer. Among various biomarkers, SCP, an acute-phase protein primarily involved in iron and copper metabolism, has emerged as a potential candidate for the detection and prognosis of oral cancer [2,5,6].

Ceruloplasmin (CP) is a glycoprotein, an acute phase reactant, an antioxidant, and a primary copper (Cu) transporting enzyme that is typically synthesized by the liver [5,7]. SCP is a blood protein primarily synthesized in the liver and is responsible for transporting copper throughout the body. It plays a crucial role in copper metabolism and homeostasis. CP carries around 95% of the copper found in the blood plasma. CP, which can only carry iron in a ferric state, has a copper-dependent oxidase activity linked to the potential oxidation of ferrous ( $\text{Fe}^{2+}$ ) ions into ferric ( $\text{Fe}^{3+}$ ) ions. As a result, it helps transport iron in plasma in conjunction with transferrin [8].

CP is known for its antioxidant properties, which play a crucial role in protecting tissues from oxidative damage. However, dysregulated oxidative stress and inflammation are hallmark processes in the pathogenesis of cancer, including OSCC. Elevated levels of SCP have been observed in several malignancies, suggesting its potential role as a biomarker. Studies have indicated that changes in SCP levels might reflect tumor activity, progression, or the body's response to oxidative stress, providing a noninvasive means to assess disease status in oral cancer patients. Its increased expression aligns with inflammatory and hypoxic responses in tumor microenvironments, further cementing its relevance in cancer diagnostics.

Measurement of SCP is used to assess the level of copper in the body, and it can be used in the diagnosis of various conditions, including Wilson's disease and different types of cancer like Hodgkin's lymphoma, oral cancer, etc. [5,6].

Recent studies demonstrate that SCP levels are significantly higher in patients with oral potentially malignant disorder (OPMD) and OSCC compared to healthy controls, underscoring its potential utility in early diagnosis and disease progression monitoring [5,6,9–11].

Hence, this study aims to evaluate whether serum ceruloplasmin can serve as a reliable noninvasive biomarker for distinguishing between normal oral mucosa, OPMDs, and OSCC, and to assess its diagnostic potential through systematic review and meta-analysis.

## Materials and methods

This systematic review was conducted and reported according to the PRISMA 2020 statement. The review was also registered in the International Prospective Register of Systematic Reviews (PROSPERO) database.

## Review question

Can serum ceruloplasmin levels be used as a biomarker for the early detection of oral potentially malignant disorders and oral cancer?

### Eligibility criteria include the following:

#### Inclusion criteria

- Original research assessing SCP in OPMDs such as oral leukoplakia and oral submucous fibrosis, and in OSCC.
- Human studies published in English.
- Studies published up to the year 2024.

#### Exclusion criteria

- Studies involving animals or cancers other than OSCC.
- Studies without a healthy control group.
- Case reports, reviews, editorials, commentaries, conference abstracts, and case series.
- Articles published in languages other than English.

## PICO format

Component	Description
Population	Patients clinically or histologically diagnosed with OPMDs and OSCC
Exposure	Measurement of SCP levels
Comparator	Healthy individuals
Outcome	Evaluation of serum ceruloplasmin as a biomarker for early detection

## Data collection and extraction

A comprehensive search strategy was employed to identify eligible studies. Searches were performed using PubMed, Google Scholar, Scopus, and ProQuest to locate relevant studies published in English until 2024. Keywords such as “serum ceruloplasmin”, “oral cancer”, “oral potentially malignant disorder”, and “oral squamous cell carcinoma” were included. Boolean operators (AND/OR) were used for optimal search combinations. Gray literature was screened manually. Bibliographies of included studies were reviewed to identify additional relevant articles. All searches were conducted by two independent reviewers, with discrepancies resolved through discussion and third-party consultation.

The structured strategy aimed for high sensitivity and specificity, maximizing relevant article retrieval while minimizing irrelevant ones. Studies were selected based on title and abstract screening, followed by full-text review. Two reviewers independently screened titles and abstracts to assess eligibility. Full-text articles were then reviewed to ensure compliance with inclusion criteria. Disagreements were resolved through discussion. In total, eight studies were finalized for inclusion in the review (Fig. 1).

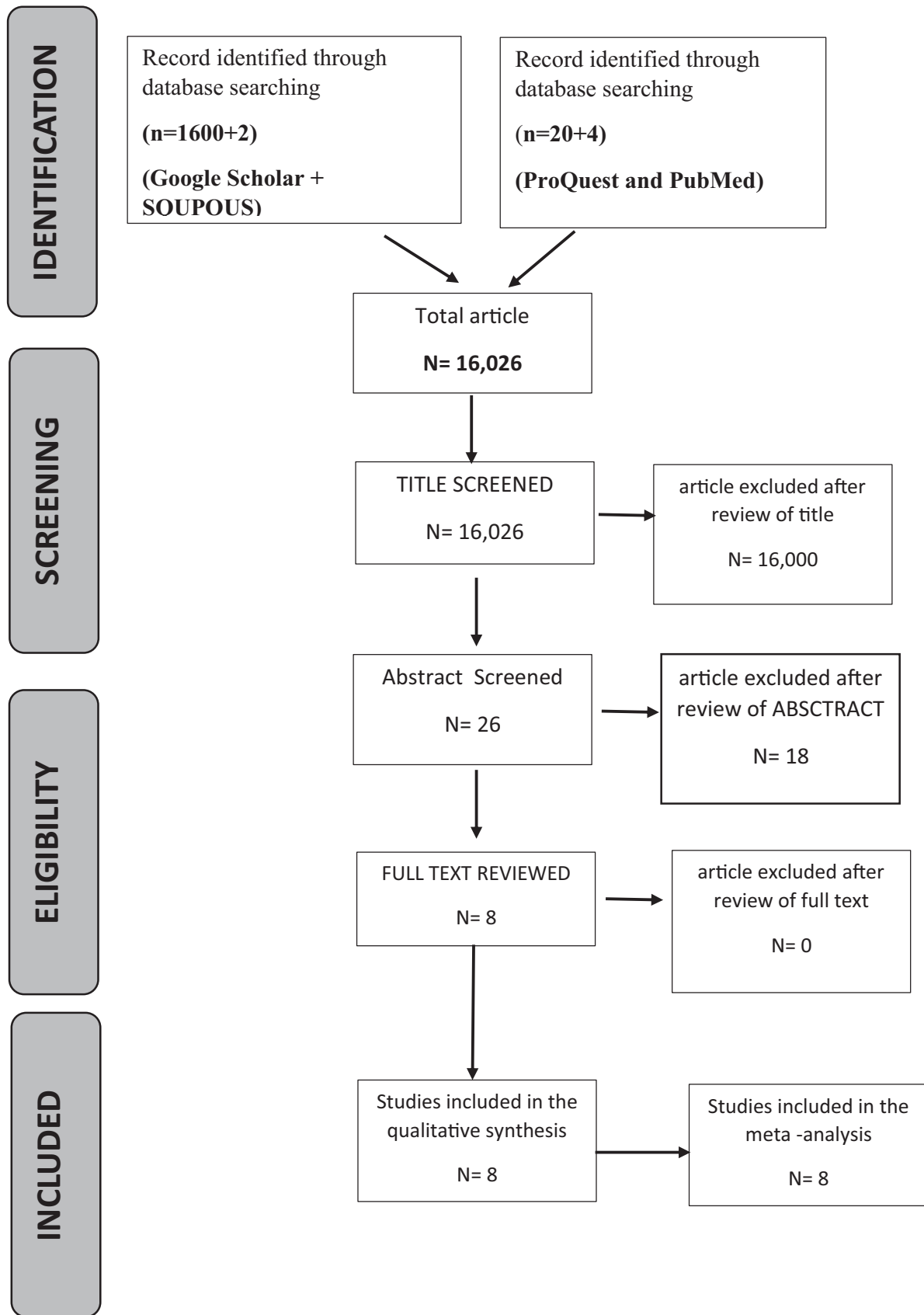


Fig. 1. Flow diagram depicting the process of selection and exclusion of article of each step.

**Qualitative data analysis**

A standardized Excel sheet was developed and validated by MJ and VN to ensure consistent and accurate data extraction (Table I, Table II). The sheet was pre-filled based on established inclusion criteria. All discrepancies were resolved through discussion between the reviewers and the expert.

The following variables were extracted from each selected study: type of study, author and publication year, language of publication, title of the article, study objectives, study population (OPMD and OSCC patients), control group (healthy individuals), sample size, and statistical data (mean and standard deviation).

The data synthesis was carried out in accordance with PRISMA guidelines. Only studies that assessed SCP levels in patients with OPMDs such as oral leukoplakia and oral submucous fibrosis (OSMF), or in oral OSCC, and which conformed to the PICO format, were considered for synthesis. Each study's characteristics were tabulated using a structured Excel sheet to allow systematic comparison of population, intervention, comparison, and outcomes. This enabled effective grouping of studies and facilitated synthesis for further statistical analysis.

A qualitative synthesis was performed across all eight included articles. Specifically, six studies evaluated SCP levels between healthy individuals and leukoplakia patients, four compared healthy controls with OSMF patients, and five assessed SCP levels between healthy individuals and OSCC patients. Additionally, four studies each compared SCP levels between leukoplakia and OSCC and OSMF and OSCC groups. Risk of bias was assessed independently by both reviewers using the Newcastle–Ottawa Scale, and disagreements were resolved through consensus.

**Quantitative data analysis**

To evaluate the pooled effect sizes, a meta-analysis was conducted using RevMan 5 software. A random-effects model was applied with a 95% confidence interval, and a *P*-value ≤ 0.05 was considered statistically significant. A random-effects model was chosen to account for expected variability in study design, population characteristics, and measurement methods across included studies. Forest plots were generated to visualize the mean differences in SCP levels across comparison groups, and funnel plots were used to detect potential publication bias. The *I*<sup>2</sup> statistic was employed to quantify heterogeneity among the studies, helping determine the consistency and robustness of the findings.

**Assessment of certainty of evidence (GRADE framework)**

The certainty of evidence was assessed using the grading of recommendations assessment, development, and evaluation (GRADE) approach. The GRADE system provides a structured and transparent framework to evaluate the quality of evidence and the strength of recommendations in systematic reviews and meta-analyses.

**Table I.** Study characteristics.

SL. NO	Author	Healthy control			Leukoplakia			OSMF			OSCC			
		Year	Sample size	Mean (gm/L)	SD	Sample size	Mean (gm/L)	SD	Sample size	Mean (gm/L)	SD	Sample size	Mean (gm/L)	SD
1	Shahrayne Rashid et al. [12]	2021	90	238.53	51.56	nil	nil	nil	nil	nil	45	361.27	62.89	
2	Aws. W. Abbas et al. [13]	2014	80	311	51.56	48	408	101	nil	nil	nil	nil	nil	
3	Ajay Chandran et al. [9]	2020	100	431.9	19	25	476.8	15.1	25	477.4	14.5	25	477.3	7.4
4	Victor I et al. [14]	2012	40	200	60	0	nil	nil	nil	nil	20	360	200	
5	Manika Singh et al. [15]	2015	150	490.4	68.3	50	930.4	165.6	50	102.16	16.33	50	113.84	17.56
6	Manisha B Patil et al. [16]	2021	100	431.9	19	25	476.8	15.1	25	477.4	14.5	25	477.3	7.4
7	Mathwe O Mampilly et al. [6]	2021	30	317.4	26.5663	10	814.11	101.1768	nil	nil	10	907.12	36.4889	
8	Palak H Shah et al. [17]	2017	300	734.2	243.7	50	800.5	275.23	50	948.9	319.32	50	925.9	265.13

Table showing quantitative analysis of the studies selected for the systematic review.

**Table II.** Study characteristics.

SL. NO	Author	Year	Population	Outcome
1	Shahrayne Rashid et al. [12]	2021	Pakistan	There was increase in value of CP between normal and OSCC <i>P</i> -value
2	Aws. W. Abbas et al. [13]	2014	Iran	There was a substantial increase in serum and saliva ceruloplasmin levels of OLP patients group as compared to controls ( $P < 0.01$ ).
3	Ajay Chandran et al. [9]	2020	India	Serum ceruloplasmin levels were found to be raised in all the three groups including oral leukoplakia, OSMF and OSCC patients as compared to the controls and thus, can be used as a potential biomarker.
4	Victor I et al. [14]	2012	Nigeria	There is an increase in CP levels compared to the normal. Involvement of ceruloplasmin, an angiogenic acute phase protein, in OSCC suggests a role in tumor proliferation.
5	Manika Singh et al. [15]	2015	India	Increased levels of copper and ceruloplasmin ( $<0.05$ ) in patients with OSMF, leukoplakia, and oral cancer was observed when compared with the controls.
6	Manisha B Patil et al. [16]	2021	India	The study revealed that serum ceruloplasmin levels were found to be raised in all three. study groups including oral leukoplakia, OSMF and OSCC as compared to the controls while the results were found to be statistically significant.
7	Mathwe O Mampilly et al. [6]	2021	India	Antioxidants are an important defense system against free radical damage to cells. Ceruloplasmin and selenium levels in serum could be used as disease markers in leukoplakia and squamous cell carcinoma.
8	Palak H Shah et al. [17]	2017	India	The serum ceruloplasmin levels were significantly increased in OSMF, OL and NS groups as compared to healthy control groups.

Evidence was assessed across five key domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each outcome was initially rated based on study design and subsequently downgraded or upgraded according to these domains.

Observational studies were initially considered as low-quality evidence, whereas randomized controlled trials would be considered high-quality evidence. The certainty of evidence was then classified into four levels: high, moderate, low, and very low.

Two independent reviewers (MJ and VN) evaluated the GRADE domains for each outcome, and disagreements were resolved through discussion and consensus.

This combined process of systematic study selection, structured data synthesis, and rigorous statistical analysis ensured the inclusion of only high-quality, relevant studies, strengthening the evidence regarding the role of SCP as a biomarker for early detection of OPMDs and OSCC.

This review was undertaken in light of the numerous studies investigating whether SCP levels could serve as a reliable biomarker for OPMDs and OSCC. Despite these extensive efforts, no systematic review or meta-analysis has comprehensively evaluated SCP levels in this context to establish a definitive association. Recognizing this gap, our systematic review aimed

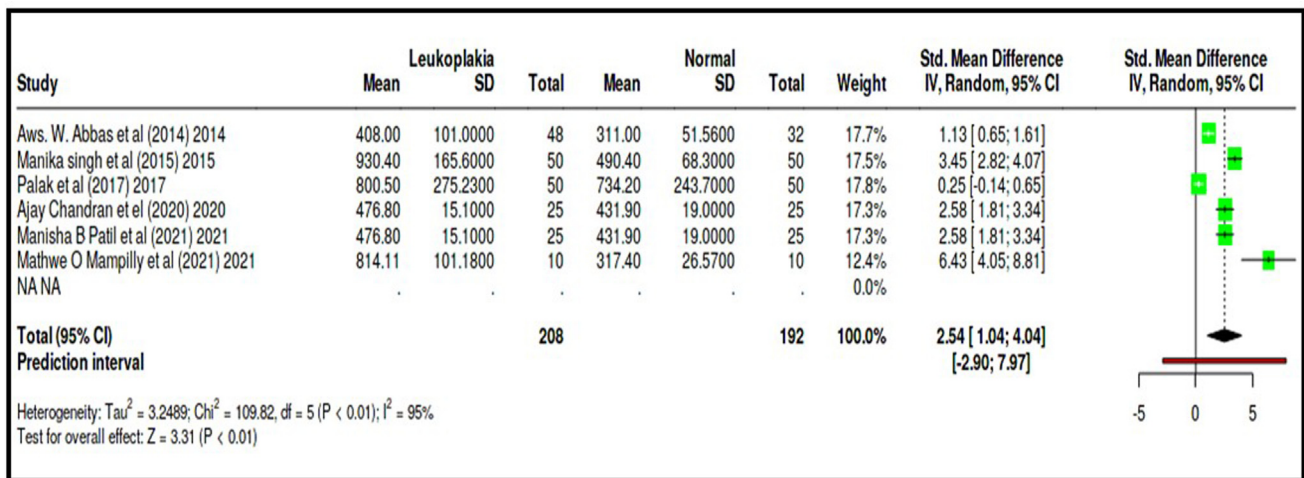
to consolidate and analyze all available data to provide a clearer understanding of SCP's potential as a biomarker. Furthermore, this study seeks to contribute to the development of evidence-based guidelines and management strategies for early detection and intervention in oral precancerous and cancerous conditions.

## Results

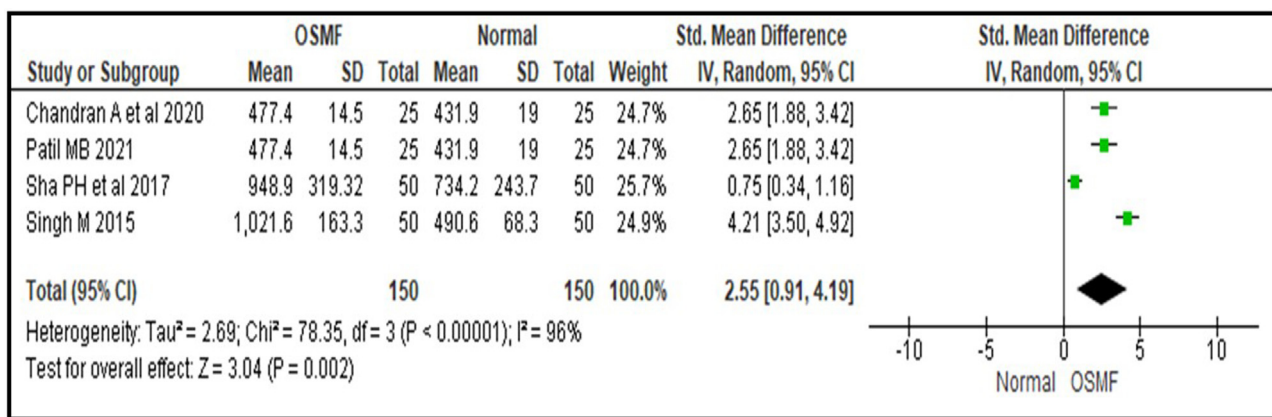
This present systematic review included eight articles that revealed the following evidence. Out of eight, five of the studies were done in the Indian population [6,9,16,17] and the other three studies were done in Pakistan, Iran, and Nigeria.

The studies included participants of both genders to ensure a balanced and comprehensive evaluation of SCP levels in different conditions. Blood samples were collected from all participants using plain vacutainers, which are specifically designed to collect blood without anticoagulants or preservatives. After collection, the samples were subjected to centrifugation at 2000 revolutions per minute (rpm) for 10 min. This centrifugation process allowed for the efficient separation of the serum from the cellular components of the blood.

**Table III.** Showing Forest plot between Normal and Leukoplakia.



**Table IV.** Forest plot between Normal and OSMF groups.



The isolated serum was then analyzed for SCP levels using a diagnostic kit. However, it is important to note that different studies used different diagnostic kits, each with its specific methodology and sensitivity. Despite these variations in the kits used, all studies employed the colorimetric assay technique to determine the concentration of serum ceruloplasmin. This assay relies on a chemical reaction that produces a color change proportional to the concentration of ceruloplasmin in the serum, allowing for precise quantification.

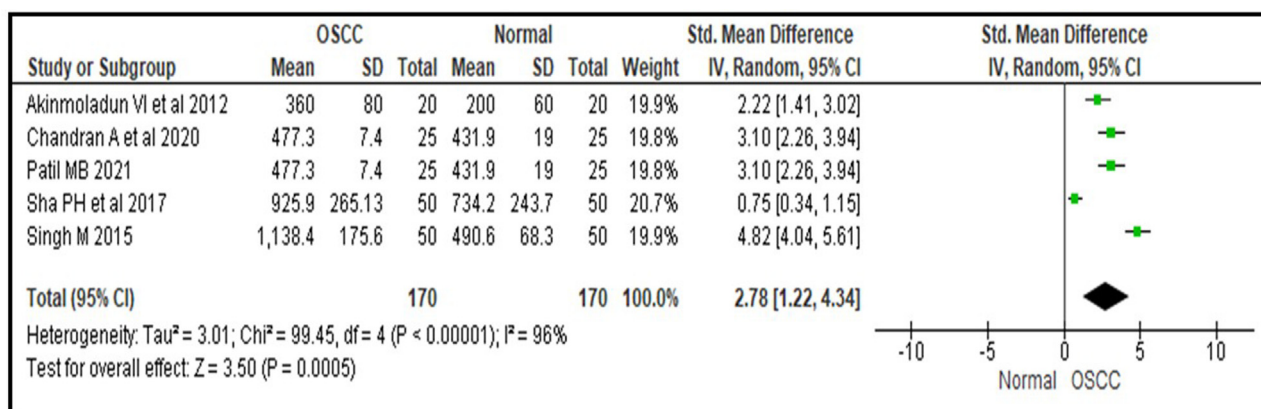
The three distinct groups were identified as healthy individuals, individuals diagnosed with OPMDs, and patients with OSCC. Given the differences in the units used to report SCP levels across various studies, a standardization process was implemented to ensure uniformity. For the convenience of performing a meta-analysis, all SCP levels were converted into milligrams per liter (mg/L). This standardization allowed for accurate comparisons and the identification of trends across different studies.

Risk of bias in individual studies was done. In the assessment, all included studies received a total score of 8, indicating good methodological quality with a low risk of bias.

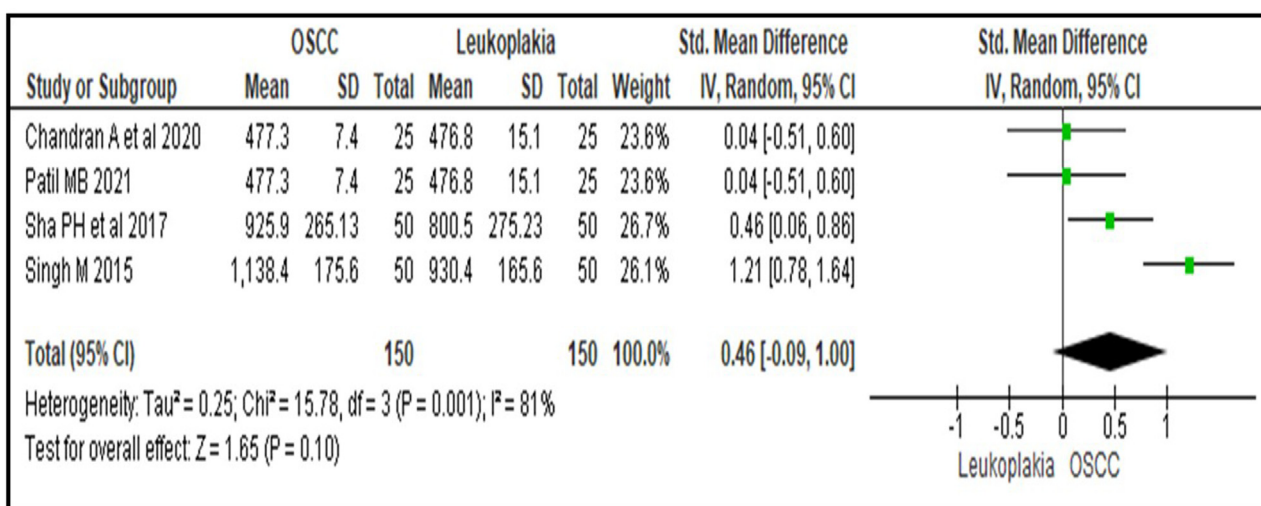
The meta-analysis compared SCP levels in several clinically relevant groups (Tabs. II–VI):

- **Normal vs. Leukoplakia:** Six studies showed significantly higher SCP levels in leukoplakia patients (pooled SMD = 2.54, 95% CI: 1.04–4.04;  $I^2 = 95\%$ ). Despite strong significance, the substantial heterogeneity observed justified the use of a random-effects model.
- **Normal vs. OSMF:** SCP levels were significantly elevated in OSMF patients (pooled SMD = 2.55, 95% CI: 0.91–4.19;  $I^2 = 96\%$ ), again with substantial heterogeneity.
- **Normal vs. OSCC:** A considerable increase in SCP levels was seen in OSCC patients compared to healthy controls (pooled SMD = 2.78, 95% CI: 1.22–4.34;  $I^2 = 96\%$ ), supporting SCP as a marker for malignant progression.

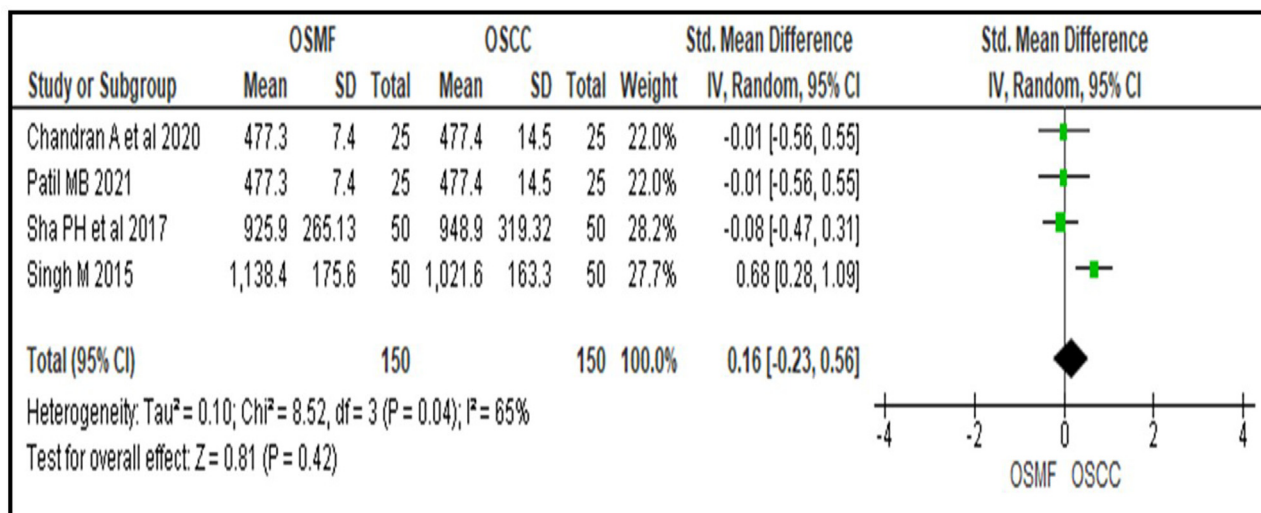
**Table. V.** Forest plot between Normal and OSCC groups.



**Table. VI.** Funnel plot between leukoplakia ad OSCC groups.



**Table. VII.** Funnel plot between OSMF and OSCC groups.



**Table VIII.** GRADE assessment.

Outcome / Comparison	No. of Studies	Study design	Risk of bias	Inconsistency ( $I^2$ )	Indirectness	Imprecision	Publication bias	Overall certainty (GRADE)	Comments
Normal vs. Leukoplakia	6	Observational	Not serious	Serious ( $I^2 = 95\%$ )	Not serious	Not serious	Undetected	MODERATE	Large effect size (SMD = 2.54) upgraded evidence
Normal vs. OSMF	4	Observational	Not serious	Serious ( $I^2 = 96\%$ )	Not serious	Not serious	Undetected	MODERATE	Consistent direction of effect despite heterogeneity
Normal vs. OSCC	5	Observational	Not serious	Serious ( $I^2 = 96\%$ )	Not serious	Not serious	Undetected	MODERATE	Very large effect size (SMD = 2.78) upgraded certainty
Leukoplakia vs. OSCC	4	Observational	Not serious	Serious ( $I^2 = 81\%$ )	Not serious	Serious (CI crosses null)	Undetected	LOW	No statistically significant difference
OSMF vs. OSCC	4	Observational	Not serious	Moderate ( $I^2 = 65\%$ )	Not serious	Serious (CI crosses null)	Undetected	LOW	Overlapping SCP levels reduce discrimination ability

**Leukoplakia vs. OSCC:** Four studies found a slight, nonsignificant trend toward higher SCP in OSCC than in leukoplakia (pooled SMD=0.46, 95% CI: -0.09 to 1.00;  $I^2=81%$ ,  $P=0.10$ ), with high heterogeneity and inconsistent results across studies.

- **OSMF vs. OSCC:** Comparing OSMF and OSCC, the pooled SMD was 0.16 (95% CI: -0.23 to 0.56;  $I^2=65%$ ,  $P=0.42$ ), indicating no significant difference in SCP levels between these groups and only moderate heterogeneity.

The findings of the study revealed a clear and consistent trend in SCP levels across the three groups. It was observed that SCP levels increased progressively from healthy individuals to those with OPMDs and further escalated in patients with OSCC. Specifically, individuals with OPMDs exhibited significantly higher SCP levels compared to healthy individuals, suggesting that increased CP levels could be associated with the early stages of disease progression. Furthermore, patients diagnosed with OSCC showed an even more pronounced elevation in SCP levels, indicating a potential link between ceruloplasmin and the severity of malignancy. No significant differences were found between OPMD and OSCC groups, indicating limited diagnostic discrimination at advanced disease stages.

The risk of bias was low in all included studies (score=8), suggesting high methodological quality. These results underscore CP's potential in early detection and monitoring of OPMDs and OSCC conditions but also stress the requirement for further investigation before clinical implementation.

Based on the GRADE assessment, the overall certainty of evidence was considered moderate for comparisons between normal oral mucosa and OPMDs or OSCC, suggesting that serum ceruloplasmin may serve as a promising biomarker for disease progression. In contrast, the certainty of evidence was low for comparisons between OPMDs and OSCC, indicating limited diagnostic discrimination between advanced precancerous lesions and established malignancy. The evidence was downgraded primarily due to substantial heterogeneity among the included studies and variations in assay methodologies (Table VIII).

## Discussion

To improve treatment results and lower disease morbidity, early diagnosis of OPMDs and OSCC is needed. A possible biomarker for oral carcinogenesis is SCP, an acute-phase copper-binding glycoprotein involved in immune responses and oxidative stress regulation [7,18,19].

This systematic review and meta-analysis's main goal was to ascertain if SCP can accurately differentiate between OSCC, OPMDs, and healthy oral mucosa. The results show that SCP levels gradually rise from healthy controls to leukoplakia, OSMF, and OSCC. However, OPMDs' efficacy as a stand-alone diagnostic marker for malignant transformation is limited by the significant overlap in values between OSCC and OPMDs.

SCP may represent early pathophysiological changes, such as chronic inflammation, oxidative imbalance, copper dysregulation, and tumor-associated metabolic abnormalities, as indicated by consistently higher SCP levels in OPMDs and OSCC compared to healthy individuals [18,20-26]. The biological plausibility of SCP as a disease-associated biomarker is further strengthened by the substantial pooled effect sizes in the comparisons between Normal and OPMD and Normal and OSCC. However, the lack of statistically significant differences between OSCC and OPMDs suggests that oxidative stress levels in severe OPMDs are similar to those in early cancer or that SCP increase may plateau during advanced dysplasia.

## Biological mechanisms supporting SCP elevation

The gradual rise in serum copper protein (SCP) levels is consistent with known carcinogenic processes. This increase can be attributed to multiple interrelated biological mechanisms. Oxidative stress plays a significant role, as elevated levels of reactive oxygen species in OPMDs trigger an antioxidant response, leading to the upregulation of SCP. Chronic inflammation is another important factor, as persistent mucosal inflammation in conditions such as leukoplakia and oral submucous fibrosis stimulates the production of acute-phase proteins, including SCP. Furthermore, tumors exhibit a dependence on copper for angiogenesis and cellular proliferation, resulting in altered copper homeostasis during malignant transformation. In addition, remodeling of the tumor microenvironment, particularly through hypoxia-driven angiogenic signaling pathways, further enhances SCP production. Taken together, these mechanisms support the role of SCP as a biologically significant indicator of early carcinogenic alterations [18,19,26].

## Comparison with previous evidence

The present findings corroborate other studies that found elevated SCP levels in leukoplakia, OSMF, and OSCC [6,9,16,17]. SCP increase appears to begin early in carcinogenesis, although it becomes less helpful in differentiating OPMDs from OSCC, possibly due to biological saturation of oxidative stress pathways. Study-to-study variability brought on by differences in assay kits, laboratory procedures, sampling strategies, and analytical techniques has made it difficult to determine reliable diagnostic cut-off values. Furthermore, malignant and systemic inflammatory disorders are known to cause SCP increase [5,18,19], indicating that it lacks disease specificity and should not be interpreted in isolation.

## Clinical relevance and diagnostic utility

Although SCP shows a substantial correlation with the presence of disease, its clinical value necessitates careful interpretation. In high-risk populations, especially in areas where tobacco or areca nut usage is common, SCP may be used as an additional screening technique. SCP should not be

utilized as a stand-alone diagnostic test but rather in conjunction with clinical and histological evaluation. Increasing SCP levels may be a sign of increased lesion severity, but they cannot be used to establish malignant transformation because OPMDs and OSCC have overlapping values. Also, in situations with limited resources, SCP might help with initial evaluation, but histopathology is still essential. Overall, rather than being a conclusive biomarker, SCP is best viewed as a supporting tool within a multimodal diagnostic framework.

## Strengths and limitations

### Strengths

- The first thorough systematic review and meta-analysis that summarized SCP levels in groups with OSCC, OPMD, and health.
- Methodological rigor was improved by duplicate screening, PROSPERO registration, and strict PRISMA methodology.
- All of the included high-quality studies received an 8 on the Newcastle–Ottawa Scale, indicating a low risk of bias.
- Accurate cross-study comparison was made possible by standardizing SCP values to mg/L.

### Limitations

- Extremely high heterogeneity in the majority of comparisons ( $I^2 = 65–96\%$ ), mostly because to variations of test kits, laboratory procedures, sample handling, demographic characteristics, and measurement units.
- In a number of investigations, statistical precision was diminished by small sample sizes. Small-study effects and the scarcity of negative/null research raise the possibility of publication bias.
- The inability to establish diagnostic thresholds due to the absence of conventional SCP cut-off values.
- According to the GRADE framework, the included studies' (all observational) design naturally reduces the certainty of the evidence.
- The evaluation of SCP as a stand-alone diagnostic tool was limited by the lack of diagnostic accuracy metrics (sensitivity, specificity, and AUC).

## Conclusion

Serum ceruloplasmin levels gradually rise from healthy controls to leukoplakia, OSMF, and OSCC, according to this comprehensive review and meta-analysis. Due to substantial heterogeneity, poor overall certainty of evidence, and a lack of discriminatory power between OPMDs and OSCC, SCP's diagnostic utility is still restricted, despite its potential as a supporting biomarker indicating disease severity and underlying oxidative alterations. Before SCP is suggested for routine clinical use, further well-planned, multicentric trials employing standardized assays and reporting diagnostic accuracy metrics are required.

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No grants or any other support funding was received for conducting this systematic review.

## Conflicts of interest

The authors declare that they have no conflict of interest.

## Data availability statement

All data are available from the corresponding author upon reasonable request.

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