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Serum and/or salivary Uric Acid as a Potential Biomarker in oral Squamous Cell Carcinoma: A Systematic Review and Meta-analysis

Shreya A Dalvi [1], Kamlesh Dekate*, Jigna R Pathak [1], Shilpa Patel [1], Anupama K Warrier [1], Neelam Rajpal [1]

[1] Department of Oral and Maxillofacial Pathology and Oral Microbiology, MGM Dental College and Hospital, Junction of NH4 and, Sion - Panvel Hwy, Sector 18, Navi Mumbai, Maharashtra 410209, India

*Corresponding author: Dr. Kamlesh Dekate, Associate Professor in Oral and Maxillofacial Pathology and Oral Microbiology, MGM Dental College and Hospital, Junction of NH4 and, Sion - Panvel Hwy, Sector 18, Navi Mumbai, Maharashtra 410209, India.

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KEYWORDS

Squamous Cell Carcinoma of Head and Neck, uric acid, OSCC, HNSCC

ABSTRACT:

Introduction: Head and neck squamous cell carcinoma (HNSCC) poses a significant global health burden, highlighting the urgent need for improved diagnostic and prognostic biomarkers. Uric acid, commonly measured in routine diagnostic tests, offers potential as a cost-effective and reliable marker for HNSCC screening. Numerous studies have investigated the viability of uric acid as a biomarker for HNSCC.

Objectives: This study aim to evaluate whether serum and/or salivary uric acid can serve as a dependable biomarker for diagnosing HNSCC.

Methods: Search was conducted across major scientific databases using combinations of MeSH terms and keywords to identify relevant studies. The quality assessment and data extraction followed PRISMA guidelines. A total of 265 records were identified through database searches.

Results: From 265 records 11 studies were selected, focusing on both serum and salivary uric acid levels in HNSCC patients. The quality of the studies was assessed using the Newcastle-Ottawa Scale. The meta-analysis included eight studies and found no statistically significant differences in salivary or serum uric acid levels between patients with oral squamous cell carcinoma (OSCC) and healthy controls. A significant limitation encountered was the lack of specific data, such as means and standard deviations of uric acid levels, in many studies. This absence of crucial information necessitated the exclusion of several potentially relevant studies from the meta-analysis.

Conclusions: Serum uric acid levels do not significantly differ between OSCC patients and healthy individuals; salivary uric acid may still hold potential as a diagnostic marker. Further need of confirmation on larger sample size.

1. Introduction

The term "head and neck squamous cell carcinoma" (HNSCC) describes a class of cancers that originate from the squamous cells lining the tissues in the head and neck area.[1] HNSCC estimates the seventh most prevalent cancer in the world, accounting of 890,000 emergence of new cases and 450,000 deaths each year.[2] Males are more commonly affected than females with a ratio of 2:1. [2] India accounts for highest incidence rate of HNSCC, where up to 80% of cases are related to tobacco use.[1] Epidemiological study data has demonstrated a correlation between a higher risk of cancer and low blood levels of key antioxidants (Superoxide Dismutase, Glutathione and uric acid). Their presence act as a defence mechanism and are known to be anti-carcinogenic agent and could possibly increase life expectancy in cancer. [3]

According to recent researches, it might be beneficial to look at some malignancies and their uric acid levels. In humans, uric acid has been shown to be a potent antioxidant and free radical scavenger.[3] Multiple studies have reported a link between elevated Serum uric acid (SUA) levels and inflammation, obesity, diabetes and metabolic syndrome. This suggests that SUA may function as a metabolic regulator and be involved in the etiology of a number of disorders, including cancer. [4]

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2. Objectives

The use of biochemical markers is a viable and affordable method for early cancer detection, and its benefits have been extensively proven in the literature. Studies using blood and/or salivary uric acid as a biochemical marker in diagnosis show that there is an increase in uric acid levels whereas other studies show a decrease in uric acid levels in individuals with head and neck squamous cell carcinomas. There is, however, limited evidence that it can be used effectively for early cancer detection. Determining whether serum and/or salivary uric acid can be employed as an efficient biochemical marker in head and neck squamous cell carcinoma is therefore crucial. This systematic review and meta-analysis aim to determine if serum and/or salivary uric acid can serve as a reliable biomarker for head and neck squamous cell cancer.

3. Methods

Research protocol

This systematic review was carried out based on the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA statement).

Statistical population

The research population includes case-control, cohort, cross-sectional, pilot studies. from 1st January 2000 until to 31st December 2023 which were selected and reviewed by two researchers.

Search strategy

Studies were selected based on the PICOS inclusion criteria in the review protocol. Two reviewers assessed titles and abstracts to identify potentially eligible studies. Any queries were discussed with a third reviewer. Electronic search of PubMed (including MEDLINE), Cochrane Central database & Ebsco was conducted. The terms mentioned in the concept table were used to formulate a search strategy. The terms were combined using suitable Boolean operators (AND, OR, NOT). A similar search strategy was applied in all the three electronic searches. A partial gray literature was assessed by screening the abstracts of first 150 results filtered by relevance. The English language and the time limit filters were used at the end as search limits.

Inclusion and exclusion criteria

Inclusion criteria:

•Studies published between 1/01/2000 till 31/12/2023
•Studies published in any language where english translation is possible.
•Studies with full-text articles only will be included.
•Studies assessing any association between serum and/or salivary uric acid levels with clinicopathologic parameters in patients with head and neck squamous cell carcinoma

Exclusion criteria:

•Studies not fully available in the database.
•In-vitro and animal studies
•Gene expression, cell line, cell culture studies.
•Studies including patients with any systemic diseases affecting uric acid levels.
•Single group studies without the control group were excluded.
•Review reports, case series, in-vitro and animal studies were excluded.
•Studies providing only abstract and not full text.
•Studies not mentioning required outcomes will be excluded

Qualitative assessment of the articles

The quality of the selected articles was measured by the Newcastle-Ottawa Scale. [5] According to this protocol, a score of 0 to 9 was assigned based on having the above items recorded in the tables for each study. Two researchers scored each study, and if the study score did not match, the third researcher took it. Finally, the scores of the articles were collected: according to their final scores. They were classified as high-quality (score 6–9), medium-quality (score 3–5), and low-quality (score 0–2) articles. Then, the articles were reviewed for collecting the relevant data and analyzed based on their significance and quality degrees. The researchers generally assessed the quality of the selected articles using the standard PRISMA checklist, [6] consisting of 27 sections and evaluating various aspects of the methodology.(Table - 1)

Data collection

The data was subsequently extracted from the 11 included studies and will be recorded and analyzed in respective excel data extraction sheets. The data extracted was entered under the following headers: 1. Author 2. Year 3. Title 4. country/ study setting 5. Age

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range/mean of patients included in the study 6. gender 7. study design 8. Sample size 9. grade (clinical/ histological) 10. Site 11. fluid source 12. salivary mean uric acid 13. serum mean uric acid 14. SD 15. Author conclusions (Table-1)

Statistical analysis

Review Manager (RevMan) 5.4 was used for statistical analysis. The combined results were expressed as standardize mean and standard deviation for the continuous data at 95% confidence intervals (CIs) and P50% and P≤0.10. For I2>50%, the random-effects model was applied. Also, the statistical significance was set at p-value (two-tailed) <0.05.

4. Results

Selection of articles

The initial electronic database search on PubMed/MEDLINE, Cochrane library and Ebsco resulted in 265 titles. Five articles were cited as duplicates. After screening the abstracts, 260 relevant titles were selected by two independent reviewers were sought for retrieval and 3 were excluded for not being retrievable. Following examination and discussion by the reviewers, 29 articles were selected for full-text evaluation. Hand searching of the reference lists of the selected studies did not deliver additional papers. After pre-screening, application of the inclusion and exclusion criteria and handling of the PICO questions, 11 studies remained. 11 studies were included in the qualitative synthesis which were subjected for data extraction and 8 were included for meta-analysis . **(Figure 1)** [7]

Characteristics of the selected articles

In the present study, systematic review was conducted of 11 studies, (Table1) with a total sample size of 2470 participants. The study group comprised 1246 patients, while the control group included 1224 patients. Certainly! In the systematic review, various methods were employed for estimating uric acid levels in both blood and serum samples. These methods included by using:

- In Saliva: Enzymatic Colorimetric Assay
- In Blood Serum:1. Enzymatic Colorimetric Assay, 2. Uricase-Trinder Endpoint Method, 3. Automated Methods

Enzymatic colorimetric assays are the most often used methods for determining uric acid levels in saliva and blood serum utilized by Soheila Manifar et.al, Giovanni Almadori et.al, Gideon Bahar et.al, Chi-Yao Hsueh et.al, J. Giebułtowicz et.al. These assays rely on uricase to convert uric acid, which is then colorimetrically reacted with various substrates and reagents. Spectrophotometry is commonly used to measure the absorbance of colored products at specific wavelengths deployed by Hanspal Singh et.al. Uricase-Trinder Endpoint Method was used by Anitha G et.al, enzymatic method was used by Karthik D et.al, Semiauto analyzer was utilized by Syeda Arshiya Ara et.al. Automated systems with specific analyzers and reagents improve efficiency and accuracy when monitoring uric acid levels in clinical settings. These methods give reliable and accurate ways to measure uric acid levels, which aids in the diagnosis and treatment of a variety of medical disorders and was utilized by Karolina Babiuch et.al.

Age is a significant factor influencing physiological changes in body fluids, which can affect various biomarkers. [18] In our study, 2470 patients were included with the mean age of 58 years. This is comparable to the mean age specified by Soheila Manifar et.al, Giovanni Almadori et.al, H. singh et.al, S Ara et.al Thus, most of our patients were in the fifth sixth decades of life. This is agreement with Ara, et al where they found majority of their in age range of 41–50 years ie fourth and fifth decades of life. Moreover, according to Manifer et, al., there was a significant direct correlation between serum uric acid level and age in OSCC patients (r = 0:714, P < 0:0001). Karolina Babiuch et.al found out positive correlation between UA and age of participants observed in their study which could be from reduced salivary flow in elderly and, as a consequence, increased concentration of salivary markers. Although inconsistent, age-related distributions of SUA levels in different population-based samples seem to be due to the fact that SUA levels in individuals are affected by genetic, biological, and environmental factors.[19]

In our research, we revealed male dominance with 2142 patients and 254 were females patients in agreement to Ana Caruntu et.al, Karthik D et.al, Syeda Arshiya Ara et.al. Whereas, Giovanni Almadori et.al stated that hyperuricemia is strongly associated with male gender. Men have higher rates than women, as estrogen is

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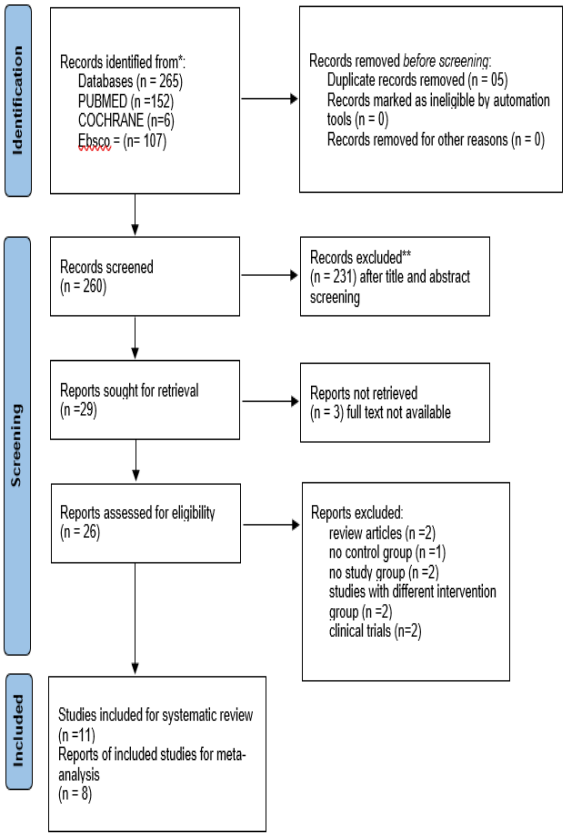
protective against hyperuricemia, and women can develop hyperuricemia after menopause.[20] Similarly Karolina Babiuch et.al found out that female participants had lowered TAC and UA which was explained by lower unstimulated salivary flow in females owing to the smaller size of their salivary glands based on their smaller body size.

Sr. No.	Author	Country	Sample size	Gender	Salivary mean uric acid ± SD (mg/dl)	Serum mean uric acid ± SD	RISK OF BIAS ASSESSMENT Newcastle-Ottawa Scale (NOS)
1	Anitha G et.al 20228	India	Study-18 Control-18	Males-16 Females-2	Study-5.88±2.75 Control-4.73±1.48	Study - 6.92±3.02 , Control - 5.06±1.33	7
2	A.Caruntu et.al 20229	Romania	Study-145 Control-80	Males -114 Females - 31	NA	Study - 5.267±1.36 Control - 5.338±1.19	7
3	Soheila Manifar et.al 2020[18]	Iran	Study- 40 Control-40	Males- 40 Females-40	NA	Study - 4.2 ± 1.5, Control - 4.38 ±1.22	8
4	Karthik D et.al 2020[11]	India	Study-33 Control-30	Male-24 Females-9	NA	Study-4.19±1.66, Control - 5.16 ±0.37	7
5	Karolina Babiuch et.al 2019[12]	Poland	Study-20 Control-20	Males-12 Females-8	Study-4.85±6.43 Control-2.9±2.09	NA	7
6	Chi-Yao Hsueh et.al 2019[13]	China	LSCC- 814, Control-814	Males-814	NA	NA	6
7	Syeda Arshiya 20163	India	Study-41 Control-40	Males-24 Females-17	NA	Study-3.80±2.26, Control-5.66±1.82	5
8	H. Singh et.al 2014[14]	NA	Study-50 Control-50	Males-36 Females-14	Study - 2.0936±0.93535 Control - 5.9675±1.07319	NA	6
9	Joanna Giebułtowicz et.al 2011[15]	Poland	Study-10 control-30	Males-6 Females-4	Study-4.5±4.86 Control - 8.64±3.18	NA	6
10	G.Bahar et.al 2007[16]	Israel	Study-25 control-25	Males-12 Females-13	Study-1.30 Control-4.12	NA	6
11	G. Almadori et.al 2007[17]	Italy	Oral and pharyngeal cancers - LSCC- 31 Control 77	Males-99 Females-98	NA	NA	7

Table-1: The details of the extracted data & Risk of bias assessment

Figure1: Prisma Flow Chart 2020



Results of a meta-analysis of changes in salivary LDH levels in OSCC patients

A total of 8 studies [3,8,9,10,11,12,14,15] fulfilled the inclusion criteria for quantitative analysis. Subsequently, three meta-analyses, including one subgroup analysis were performed to assess the salivary and serum uric acid levels among the OSCC patients as compared to healthy individuals.

1. OSCC versus healthy individuals for Mean Salivary Uric acid levels.

The meta-analysis of four studies [8,12,154,15] (Figure 2) assessing the standardized mean difference for salivary uric acid levels between OSCC and healthy individuals was carried out using random effect model. The pooled standardised mean difference of salivary uric acid levels expressed as mg/dl for a total sample size of 98 OSCC cases and 118 healthy individuals did not show a statistically significant difference (SMD, -0.83, 95% CI = -2.81 - 1.16, p - 0.41, I2 - 97%).

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OSCC versus healthy individuals for Mean Salivary Uric acid levels

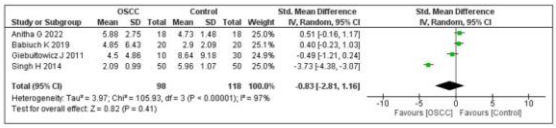

Figure 2 shows the comparison of mean salivary uric acid levels between OSCC (Oral Squamous Cell Carcinoma) patients and healthy individuals. Rectangles represent individual study estimates, and diamonds show the pooled estimate using a random-effects model.

2. OSCC versus healthy individuals for Mean Serum Uric acid levels

The meta-analysis of five studies [8,3,9,10,11] (Figure 3) assessing the standardized mean difference for serum uric acid levels between OSCC and healthy individuals was carried out using random effect model. The pooled standardised mean difference of serum uric acid levels expressed as mg/dl for a total sample size of 227 OSCC cases and 208 healthy individuals did not show a statistically significant difference (SMD, -0.23, 95% CI = -0.69 - 0.24, p - 0.34, I2 - 82%).

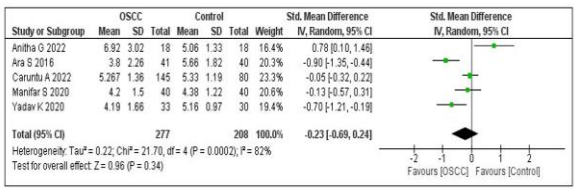

Figure 3 compares mean serum uric acid levels among OSCC patients and healthy individuals. The plot uses rectangles for study-specific data and diamonds for the pooled estimate generated through a random-effects meta-analysis.

3. OSCC versus healthy individuals for Salivary Uric acid levels based on the TNM classification system

The meta-analysis of two studies [12,14] (Figure 4) assessing the standardized mean difference for salivary uric acid levels between OSCC and healthy individuals was carried out using random effect model based on the TNM classification system. For TNM stage 1, standardised mean difference of salivary uric acid levels expressed as mg/dl did not show a statistically significant difference (SMD, -1.36, 95% CI = -5.44 - 2.73, p - 0.52, I2 - 97%). For TNM stage 2, standardised mean difference of salivary uric acid levels expressed as mg/dl did not show a statistically significant difference (SMD, -1.37, 95% CI = -4.34 - 1.59, p - 0.36, I 2 - 93%). Similarly, for TNM stage 3 and stage 4, standardised mean difference of salivary uric acid levels expressed as mg/dl did not show a statistically significant difference (SMD, -2.01, 95% CI = -5.24 - 1.22, p - 0.22, I2 - 95%) and (SMD, -1.67, 95% CI = -5.98 - 2.65, p - 0.45, I2 - 96%) respectively. When the total analysis using random effect model irrespective to the TNM classification system was considered for a total sample size of 70 and 280 samples for OSCC and healthy individual groups respectively, standardised mean difference of salivary uric acid levels expressed as mg/dl between both the groups show a statistically significant difference with higher salivary uric acid levels in the healthy individuals as compared to OSCC patients (SMD, -1.61, 95% CI = -3.08 - -0.13, p - 0.03, I2 - 94%).

Figure4: OSCC versus healthy individuals for Salivary Uric acid levels based on the TNM classification system

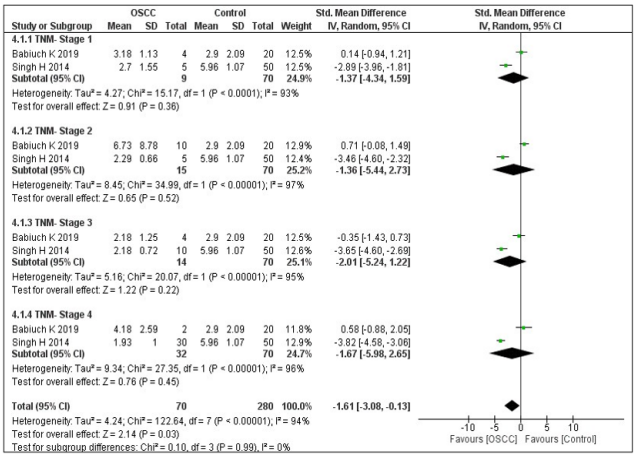

Figure 4 displays salivary uric acid levels in OSCC patients categorized according to the TNM classification system. The forest plot represents stage-wise estimates with the overall pooled estimate indicating the relationship between tumor stage and uric acid levels.

5. Discussion

Uric acid (UA) is the final byproduct of human purine metabolism. It is an oxidizable substrate for haem protein/H2O2 systems, and it can protect against

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oxidative damage by functioning as an electron donor. According to the literature, significant UA levels may lengthen human life expectancy by guarding against cancer and aging brought on by oxidative stress. Apart from its role as a radical scavenger, UA may also prevent lipid peroxidation and chelate metal ions transforming them to less reactive forms incapable of catalyzing free-radical processes.[21]

The levels of UA found in the saliva of healthy individuals are 199 ± 27 μmol/L, which is similar to that seen in blood serum (120–400 μmol/L).[22] Diet can influence serum uric acid levels, the foods such as meats, sausages, mussels, and sardines contain a high concentration of purines, which contribute to uric acid generation. In cancer patients, low blood uric acid levels may be attributed to nutritional deficiencies as well as raised TNF and Interleukin 6 production.[4]

Cancer development is a complex process, which is due to the level of DNA damage in proportion to oxidative and nitrative stress generation.[4] Rather than being a separate risk factor for the development of cancer, cancer itself may cause hyperuricemia through cancer related cell death. However, data from prospective studies do point to serum uric acid as a potential predictor of cancer development.[23]

In the present study, we conducted a systematic review of 11 studies and the results of this study are in agreement with a subset of studies by Soheila Manifar et.al, Giovanni Almadori et.al, Ana Caruntu et.al and Karolina Babiuch et.al.

S Manifar et.al findings indicated that there was no significant difference in the mean serum uric acid level between OSCC patients and healthy controls. Similar results were obtained from the studies conducted by G Almadori et.al, Ana Caruntu et.al, Karolina Babiuch et.al. While some studies by Gideon Bahar et.al, Hanspal Singh et.al, Chao-Hung Wang et.al, Karthik D et.al, Syeda Arshiya Ara et.al, Joanna Giebułtowicz et.al, Anitha G et.al. showed contradictory results which reported statistically significant findings.

G Bahar et.al showed that uric acid levels were statistically significant in oral squamous cell carcinoma (OSCC) patients, uric acid levels were reduced by 69% compared to healthy controls ($P < 0.01$). Their findings suggest that oxidative stress in saliva may contribute to OSCC development. Singh et.al discovered that the average salivary levels of uric acid was significantly lower than those in healthy controls. Chi-Yao Hsueh et.al conducted a study which revealed significantly higher serum UA levels and UA/creatinine (Cr) ratios in the control group compared to the LSCC group ($P < 0.001$). Additionally, logistic regression analysis indicated that elevated UA levels ($P = 0.002$) and UA/Cr ratios ($P < 0.001$) were independent protective factors against the development of LSCC. Furthermore, receiver operating characteristic (ROC) analysis demonstrated moderate discriminative ability for UA ($P < 0.0001$) and UA/Cr ratios ($P < 0.0001$) in distinguishing LSCC patients from controls. S Ara et.al stated that the mean serum uric acid in the study group was very low when compared to the control group. Statistically it showed very high significance ($p= <0.001$), the study also highlighted a significant association between low serum uric acid levels and increased OSCC risk, particularly in individuals with a history of tobacco use. Joanna Giebułtowicz et.al showed that patients with oral cavity cancer (OCC) and those with odontogenic cysts had significantly lower concentrations of uric acid (UA) in their saliva compared to healthy subjects. This decrease in UA concentration suggests a compromised antioxidant defense system in these patients, potentially increasing their risk of oxidative stress and related DNA damage, which could contribute to the development or progression of cancer.

Despite variations in study designs and methodologies, there is consistency in the findings regarding the lack of significant differences in UA levels between OSCC patients and healthy controls across these studies. This convergence of results supports persistent dilemma that uric acid may or may not serve as a robust biomarker for distinguishing OSCC patients from healthy individuals. However, when considering the overall analysis irrespective of TNM classification, a significant difference was observed, with healthy individuals exhibiting higher salivary uric acid levels compared to OSCC patients. This finding suggests that while salivary uric acid may not be informative for disease staging, it may still have diagnostic utility in distinguishing OSCC patients from healthy individuals. It is important to interpret these findings in the context of several limitations. First, the included studies varied in terms of patient characteristics, study designs, and measurement methods, which may have contributed to heterogeneity and biased the results. Additionally, the potential

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influence of confounding variables such as diet, medication, and co-morbidities, all these factors with uric acid levels was not adequately addressed in the primary studies.

Conclusion

The findings of this meta-analysis suggest that serum uric acid levels may not differ significantly between OSCC patients and healthy individuals, while salivary uric acid may still hold diagnostic potential for distinguishing OSCC patients from controls. The complex interplay of age, gender, site of cancer, histological grading, and clinical staging highlights the nuanced role of uric acid in OSCC. Further research with standardized methodologies and larger sample sizes is necessary to better understand UA's diagnostic and prognostic value in OSCC. Moreover, in the literature it is observed a statistically significant strong positive correlation between serum uric acid and salivary uric acid levels, thus monitoring salivary uric acid levels could potentially serve as a reliable non-invasive biomarker in OSCC patients. However, further research is needed to validate these findings and elucidate the underlying mechanisms causing alterations in uric acid levels in OSCC.

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