REVIEW

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Salivary Sialic Acid Levels as a Biomarker for Early Detection of Oral Precancer and Oral Cancer: Systematic Review and Meta-Analysis

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Abstract

Objective: Salivary sialic acid (SSA) has been detected as biomarker in several cancers and the level of salivary sialic acids has been proven to have a potential diagnostic value in early detection of cancer. This systematic review aims to assess Salivary Sialic Acid (SSA) levels as a biomarker for early detection of oral precancer and oral cancer. **Data Sources:** A comprehensive Literature search was conducted in various databases such as PubMed, Scopus, Google scholar and ProQuest. Quality assessment of articles was done by Newcastle Ottawa Quality Assessment Scale. **Results:** A total of 22 studies were included in the systematic review and 14 articles were included for meta-analysis. Studies showed an increase in SSA levels in both oral precancer (SMD 1.79; 95% CI 0.41-3.18), and oral cancer (SMD 11.30; 95% CI -17.04 – 39.64). Total free and protein-bound sialic acid levels were increased in oral cancer group as compared to the healthy controls. The overall standard mean difference of FSA, PBSA, TSA among oral cancer and HC (SMD 23.83; 95% CI 9.22-38.44; p=0.02) and the data revealed statistically significant differences. The results of Meta-analysis revealed statistically significant differences between SSA levels of oral cancer and healthy group. **Conclusion:** Salivary sialic acid levels were observed to be consistently higher in oral cancer group compared to oral precancer and healthy group. However, a cut-off value of SSA levels for the early detection of oral cancer and precancer could not be established because of the limited and heterogeneous data. In order to translate the use of SSA levels into clinical practice, to utilize it as a sensitive and reliable biomarker, more standardized method of saliva processing and biochemical analysis are required with studies conducted on larger populations.

Keywords: Salivary sialic acids- oral precancer- oral cancer- biomarker- early detection

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Introduction

Oral squamous cell carcinoma (OSCC) is considered as the 15th most frequently occurring cancer across the world [1] with its incidence reported to have increased by 36.5% in the past decade [2, 3]. OSCCs are usually preceded by Oral potentially malignant disorders (OPMD's) with a malignant transformation rate ranging from 0.6% to 36%.1,2 About 2.5% of the population harbors precancerous lesions in the oral cavity, [4, 5] out of which 15%–48% of the precancerous lesions and conditions transform into OSCC [6-8].

The five-year survival rate of OSCC is approximately 53-56% and has not greatly increased over the previous decades despite advancements in its management.[3] Early detection of oral cancer is essential for improving the patient's quality of life and increasing their chances of survival. One of the methods for early detection is through identification of sensitive and precise diagnostic cancer biomarkers. [7, 8] which can be obtained from biological fluids such as blood, urine, and saliva [9].

Among these fluids, saliva due to its close contact with the oral cancerous lesions is considered as a reliable tool for early diagnosis of cancer. Additionally, it is non-invasive and allows easier sample collection. Various studies have highlighted the use of salivary biomarkers for the detection of oral cancer [10-12]. More than 100 salivary biomarkers have been identified in oral cancer such as DNA, RNA, protein and various metabolomic indicators etc., which serve as a stratification tool for accurate diagnosis and prediction of the prognosis [11, 12].

One of the metabolic indicators i.e Sialic acid (SA), is a glycoconjugate and glycosylation related molecule found within the glycoprotein and glycolipid components of the cell membrane [13]. The most prevalent type of SA in bodily fluids is N-acetyl neuraminic acid, often known as Neu5AC. It is a carbohydrate epitope moiety that plays an essential role in cellular adhesion, cell – cell interactions,

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regulation of innate immunity, restricts injury, promotes recovery and acts as a crucial signal in GCF to determine the host immunological response [14-16].

Aberrant glycosylation is one of the universal features of oral cancer [15]. Sialic acid glycol-conjugates acts as tumor markers and have significant role in malignant transformation process [16, 17]. On their cell surface, malignant cells frequently exhibit a relatively high density of SA, and this change appears to be a precursor to carcinogenesis. Malignant cells secrete SA, which is then circulated and results in higher concentrations of it in bodily fluids like blood [16-18]. They are present on receptors of cell membrane and are capable of masking cancer cells from getting recognized by the immune system pathways. [15] Therefore, SA forms a major constituent, in modifying the characteristics of transformed cells as they initiate the changes in glycoproteins at an early stage of tumorigenesis [14].

In the presence of cancer, it has been established that the levels of SA in the serum, saliva and other bodily fluids are increased [19, 20]. Salivary sialic acid (SSA) has been detected in several cancers such as lung, ovarian, uterine, and Breast cancer and the level of salivary sialic acids has been proven to have a potential diagnostic value [21, 22].

However, studies on the levels of SSA in oral precancer and oral cancer have consistently found higher levels when compared to healthy groups [19]. Studies have also found higher levels of SSA in oral cancer when compared to oral precancer [23-27]. Its potential as a biomarker for the early identification of oral cancer and precancer has not yet been determined due to limited studies with varied results, hence a definitive cut-off value has not been achieved. The present systematic review aims to assess all the data available to determine whether SSA levels can be used as a biomarker for the early detection of oral precancer and oral cancer.

Materials and Methods

Protocol and Registration

This systematic review was prepared by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). It has been registered and published at the International prospective register of systematic reviews (PROSPERO) - CRD42022338354. Two independent authors (PJ and MM) performed the data search, screening and extraction of the data.

Search strategy and eligibility criteria

Literature search was performed in various databases including PubMed, SCOPUS, Google scholar and ProQuest for articles published between the year 2011 to 2021. The search was restricted to articles published in English language only.

The following keywords were used for data search - "Salivary sialic acid" OR "N-acetylneuraminic" AND "Oral precancer" OR "oral premalignant lesions" OR "Oral potentially malignant lesions" AND "Oral squamous cell carcinoma" OR "mouth neoplasm" OR cancer of mouth" OR "oral neoplasm". Search strategies were performed with different permutation and combination of these above key words. Title and abstract screening, followed by full-text links were performed and the duplicates were checked and excluded by the two reviewers (PJ and MM).

Eligibility criteria:

Original studies on the estimation of SA levels in salivary secretions for oral pre-cancer & oral cancer along with healthy controls were included descriptive studies conducted in humans and published in English till 2022 were included. Studies which do not have healthy group comparison, conducted on animals, case reports & series, reviews articles, conference abstracts, editorials and commentaries were excluded.

Study selection and data extraction process

Data extraction

A standardized data extraction format was prepared and data items such as - Author's name, year of publication, title, ethnicity of the population studied, aim and objectives, study design, age group, sample size, patients diagnosed clinically and/or histo-pathologically with oral precancer and oral cancer, healthy comparison group, methodology for estimation of sialic acid, SSA levels amongst healthy, pre-cancer and oral cancer group and outcome of the study were included. The data entries were made in the Excel sheet and was reviewed by two authors (PJ and MM). Any disagreement between the authors was resolved by discussion with the third author. (PVA)

Risk of bias and Quality assessment of individual studies

The Quality of all the included Cross-Sectional Studies was done using Newcastle Ottawa Quality Assessment Scale [28].

Statistical Analysis

Data synthesis & Meta-analysis

Study characteristics were tabulated in the excel sheet that aided in the assessment and comparison of PICO elements across the included studies, also facilitated the synthesis of these data for grouping of studies for statistical analysis. Meta-analysis was performed for 13 articles which provided the standard mean difference of various groups.

For meta-analysis, STATA software was employed. Fixed effects model with a confidence interval of 95% were used to assess the mean differences. $p < 0.05$, was considered as significant. Forest plot analysis was performed to assess the data and quantify the heterogeneity among the included studies based on the I^2 values.

Results

Literature search and study selection

In the present systematic review, study selection was initiated by stepwise screening of each article. PubMed revealed 18 records, Google scholar retrieved 832 articles and 20 articles were identified in ProQuest and 1 article from SCOPUS. Thus, a total of 871 articles were retrieved. Flow diagram depicting the process of selection and exclusion of articles at each step is shown in (Figure 1).

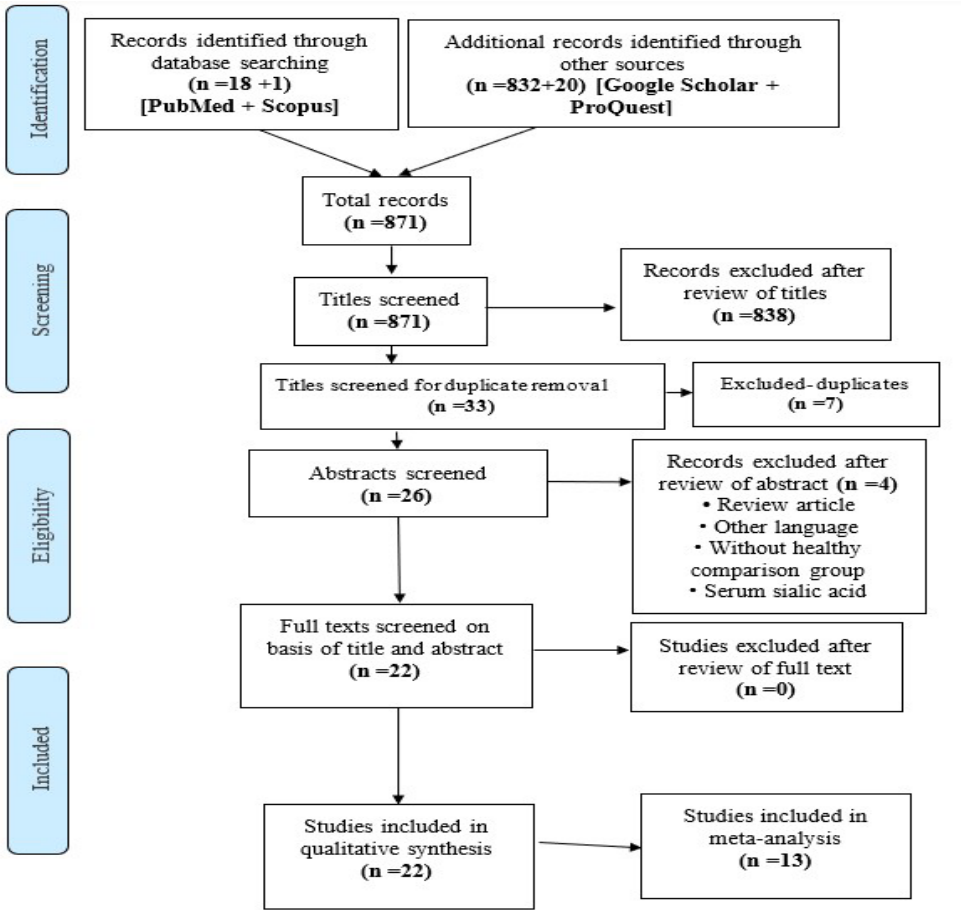

Figure 1. Flow Diagram Depicting the Process of Selection and Exclusion of Articles at each Step

Finally, the present systematic review included 22 articles which revealed the following evidence (Supplementary Table 1).

General characteristics of the included studies

Most of the studies were conducted in Indian population except one study was done in Nepal population [29]. The age range in all the studies were 20-70 years. In all the studies included, we found that male participants were more than females, except one study showed female predominance [30]. All the studies included were cross-sectional studies. The sample size for healthy individuals, oral precancer, and oral cancer were not distributed equally in the included studies.

All the included studies have used 2-5ml of unstimulated whole saliva sample to determine the sialic acid levels. Most of them collected saliva samples in the morning between 10am to 12pm, after 2 hours of refraining from consumption of food and in most of the studies the individuals were informed to rinse their oral cavity with distilled water for removal of any food debris prior to saliva sample collection.

After saliva sample collection, it was subjected for centrifugation at 2500 - 3000 rpm for 15-20 mins in most of the studies except one study which did not mention about the centrifugation rate and processing of saliva sample [31]. In most of the studies, detection of SSA was done through biochemical analysis where different reagents were used such as acid ninhydrin reagent / diphenylamine by Yao et al. [20, 27-29], Skoza and Mohos [30, 32, 33] method using thiobarbituric acid and one study estimated SSA levels through Ehrlich's reagent and all studies analyzed SSA through UV Spectrophotometer [25, 34, 35-37]. However, Rasool et al. [37] did not mention about the biochemical analysis method performed .

Main outcomes

The characteristics of each study and the levels of SSA in each group is mentioned in (Supplementary Table 1). Since most of the studies showed variation in the units of SSA levels, for the convenience of performing meta-analysis, units of SSA levels were converted to milligrams per deciliter of saliva (mg/dL). Only 12 articles out of 22 mentioned Total sialic acid (TSA) levels in healthy individuals, which ranged from 0.16 + 0.08 to 42.75 + 3.41mg/dL. Free sialic acid (FSA) levels in healthy individuals were seen in varied range from lowest being 0.401 + 0.138 mg/dL to the highest being 21.62 + 8.86 mg/dL in the included studies. Protein bound sialic acid (PBSA) in healthy individuals ranged from 0.092 + 0.038 to 22.73 + 3.01 mg/dL. Only 9 articles out of 22 mentioned the levels of TSA in oral precancer which ranged from 0.0126 + 0.001 to 169.80 + 66.43 mg/dL [19, 33]. Only 4 articles mentioned the level of FSA in oral precancer patients which ranged from 3.559 + 0.554 to 6.73 + 0.71 mg/ dL [27, 37]. PBSA was mentioned in the range of 2.60 + 0.34 to 5.20 mg/dL [26, 31].

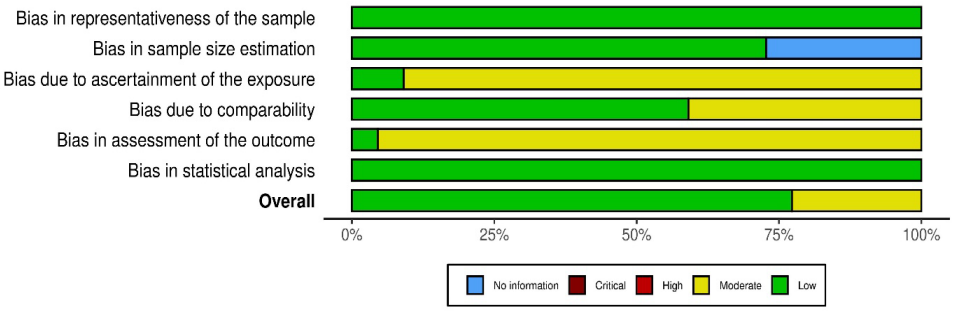

Figure 2. Summary Plot of Newcastle Ottawa Scale Tool Used for Assessment of Risk of Bias of All Included Studies

Around 13 articles out of 22 have mentioned the levels of TSA in oral cancer in the range of 1.88 + 0.73 to 545.45 + 100.04 mg/dL [25, 37]. Only 6 articles have mentioned the levels of FSA in oral cancer patients which ranged from 0.936 + 0.391 to 63.45 + 9.8 mg/dL [29, 38]. PBSA was mentioned in around 8 articles within the range of 0.494 + 0.419 to 31.17 + 7.6 mg/dL [29, 39]. The findings of every study pointed to the possible utility of SSA as a sensitive/potential biomarker for the early diagnosis of oral precancer and cancer.

Quality Assessment

All 22 articles were assessed for quality assessment using the Newcastle Ottawa Scale Risk Bias tool for Cross-sectional studies. Out of 22 studies, 17 were of low risk and 5 were of moderate risk. A low ROB was found among the "sample representativeness" (100%), "sample size estimation" (75%), and in "statistical analysis" (62.5%). Moderate risk was seen in "ascertainment of exposure "(85%), "comparability" (62.5%) and "outcome "(90%) [40] (Figure 2).

Meta-Analysis

The meta-analysis was planned based on the overall evaluation of the studies that showed mean + SD of SSA (TSA, FSA & PBSA) in healthy controls, oral pre-cancer and oral cancer. Therefore, 13 articles were included in the meta-analysis which had provided the data in the form of mean with standard deviation were considered (Table 1).

Forest plot analysis of Oral pre-cancer and healthy group showed that FSA were higher in oral precancer group than in healthy control (HC) (SMD 1.79; 95% CI 0.41-3.18), PBSA levels were higher in oral precancer group than in HC (SMD 1.25; 95% CI -0.21-2.72). When oral pre-cancer group and HC were compared, the meta-analysis showed greater TSA levels in oral pre-cancer than in HC (SMD 14.77; 95% CI -1.89 – 31.42). The overall standard mean difference of FSA, PBSA, TSA among oral precancer and HC (SMD 8.10; 95% CI -0.97 – 17.16; p=0.26) but the data didn't reveal any statistically significant differences. Heterogeneity in the studies included in the different analyses were high as the mean values among the studies included were not uniform. (I^2 = 99.99%) (Figure 3).

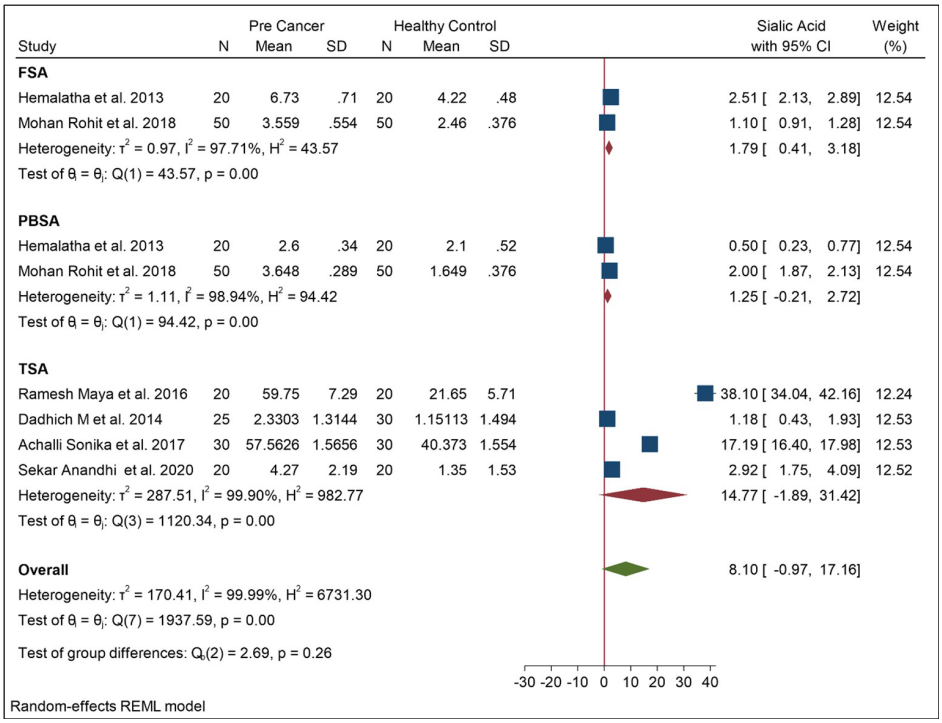

Figure 3. Graph Showing Forest Plot Analyses of Studies Compared for Free Sialic acid, Protein Bound Sialic Acid and Total Sialic Acid Levels in Oral Precancer and Healthy Individuals.

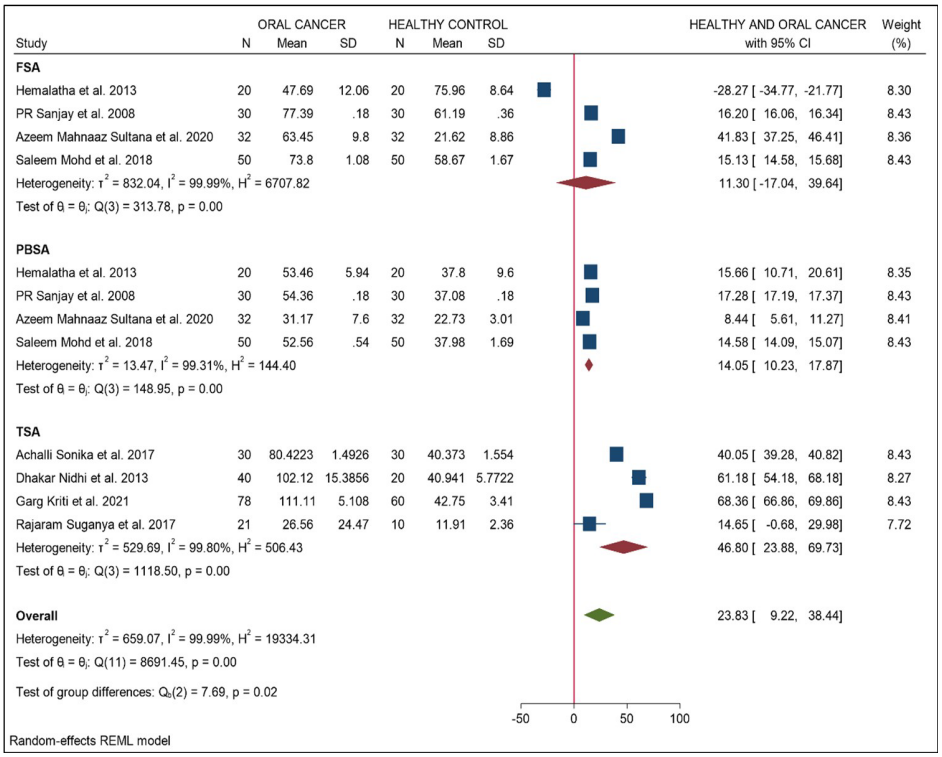

Figure 4. Graph Showing Forest Plot Analyses of Studies Compared for Free Sialic Acid Levels, Protein Bound Sialic Acid and Total Sialic Acid Levels in Oral Cancer and Healthy Individuals

Table 1. Articles Included in Metanalysis

S.No	Author	Year
1	Hemalatha et al. [26]	2013
2	Mohan Rohit et al. [35]	2018
3	Ramesh Maya et al. [27]	2016
4	Dadhich M et al. [20]	2014
5	Achalli Sonika et al. [34]	2017
6	Sekar Anandhi et al. [44]	2020
7	Sanjay et al. [27]	2008
8	Azeem et al. [39]	2020
9	Saleem et al. [24]	2018
10	Dhakar Nidhi et al. [30]	2013
11	Garg Kriti et al. [33]	2021
12	Rajaram Suganya et al. [36]	2017
13	Daniel D et al. [25]	2021

When oral cancer (OC) group was compared with HC, the meta-analysis showed a greater FSA level than HC (SMD 11.30; 95% CI -17.04 – 39.64) except a study by Hemalatha et al showed higher FSA levels in healthy group [26]. PBSA levels were higher in OC group than in HC (SMD 14.05; 95% CI 10.23-17.27). When OC group and HC were compared, the meta-analysis showed greater TSA levels in OC than in HC (SMD 46.80; 95% CI -23.88 – 69.73). The overall standard mean difference of FSA, PBSA, TSA among oral cancer and HC (SMD 23.83; 95% CI 9.22-38.44; p=0.02) and the data revealed statistically significant differences. Heterogeneity in the studies included in the different analyses was high (I^2 = 99.9%) (Figure 4).

When Oral pre-cancer patients were compared with OC, the results of the meta-analysis showed that TSA levels were higher in OC group than in HC (SMD 108.70; 95% CI -29.45-246.85 p=0.12) though the data didn't reveal

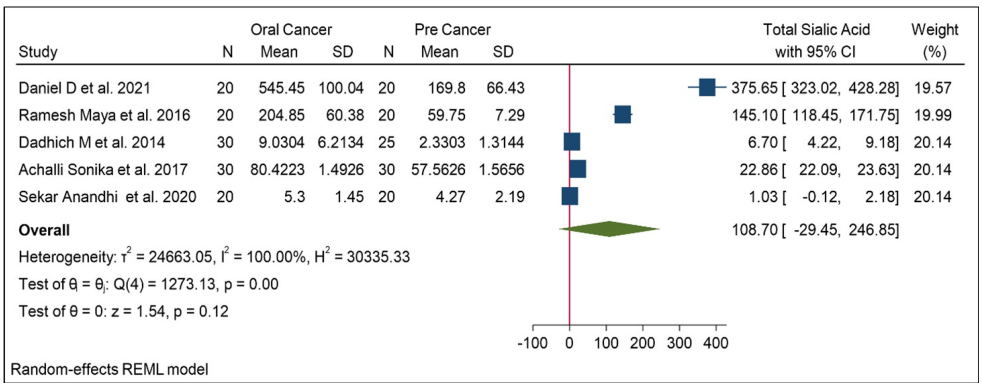

Figure 5. Graph Showing Forest Plot Analyses of Studies Compared for Total Sialic Acid Levels in Oral Cancer and Oral Precancer

any statistically significant differences. Heterogeneity in the studies included in the different analyses was high (I^2 = 100%) (Figure 5). The reason could be difference in the mean values as they were widely distributed and thus, the overall standard mean difference did not reveal any statistically significant differences. This contributed to the high heterogeneity among all the studies in this review

Discussion

One of the most prevalent cancers, OSCC is widely distributed and has a substantial variation in both incidence and prevalence across the globe [24]. It is crucial to use sensitive and specific diagnostic biomarkers to detect oral cancer early in order to lower the death rate and improve patients' quality of life [6].

Several studies in the literature have shown increased serum and SSA levels in various cancers and also in premalignant conditions [18, 19, 41]. José de Jesús Zermeño-Nava et al. [41] showed increased SSA secretions in ovarian cancer patients with sensitivity/specificity of 80%/100% respectively with a cutoff value of 15.5 mg/dL to differentiate benign and malignant cases and suggested that SA could be a useful biomarker for the detection of ovarian cancer [41].

Higher TSA and lipid bound sialic acid levels (LBSA) were reported to be helpful for identifying the early stages of the disease and there is a gradual increase in the levels of serum TSA from normal to nondysplastic to dysplastic cases in leukoplakia, suggesting its association with malignant transformation [23].

In the studies analyzed in this review, most of the studies have shown that aberrant glycosylation is the major causative factor in the disease process, suggesting that SA may be considered as a sensitive biomarker in predicting the rate of malignant transformation, either de novo or from a pre-existing precancerous condition [42].

Studies on the levels of SSA in oral pre-cancer & oral cancer has shown consistently increased levels compared to healthy groups, studies have also shown increased SSA levels in oral cancer compared to oral pre-cancer. The SSA levels have not been signified which on routine diagnostic procedure can aid as a reference level to check for increased risk in individuals harboring pre malignancy and oral cancer.

Among all the included studies SSA levels showed wide variation in healthy individuals is due to heterogeneity in the sample size and methodological disparities noted in included articles of the review. Till date there is no literature regarding the cut-off values for SSA levels in healthy individuals which needs to be established.

In relation to oral pre-cancer, results of this review revealed a higher concentration of SSA levels in oral precancer when compared to healthy individuals. Increased sialylation is seen in a transformed epithelial cell owing to its elevated levels in the body fluids such as saliva. This explains elevated levels in oral precancer compared to healthy individuals.

SA levels are increased when the cell transforms during early tumorigenesis due to alterations of glycoproteins with increased activity of glucosyltransferases causing over expression of terminal glycans involving SA. Increased sialylation and sialyl transferase activity are related to invasiveness of tumor cells and involved in tumor cell metastasis, as the tumor cells have a heavily sialylated surface. This process causes evasion of immune response system and facilitates the metastatic spread of the tumor and further contributes to the formation of larger tumor emboli due to the increase in cell adhesiveness [32].

Sayeeda et al has suggested a cutoff value of SSA to differentiate oral cancer from healthy control - 5.4mg/dL with a sensitivity and specificity of around 95.24% & 100% respectively [43].

We found that the overall standard mean difference of FSA, PBSA, TSA among oral cancer and HC revealed statistically significant differences with a p value < 0.05. These observations show that high SSA levels are associated with oral cancer when compared to oral precancer and healthy individuals.

Limitations

This review has few limitations such as lot of heterogeneity in terms of mentioned age and gender groups, unequal sample size distribution, wide mean values of SSA, variations in saliva processing methods, reagents used and identification protocols and also histopathological grades of oral cancer. Meta-analysis did not reveal any statistically significant differences due to high heterogeneity in the studies included in the different analysis ranging up to 100 %.

Future recommendations

Despite few limitations in this review, there is evidence showing that measuring SSA levels could be implicated as a potential and sensitive screening tool which can be used as an adjunct for early diagnosis of oral precancer and oral cancer. Hence, we recommend further robust studies should be carried out to analyse with a larger sample size and among different ethnic groups globally, also develop validated standardized methods of saliva collection, processing and biochemical analysis in order to establish a precise and standard cut-off value for measuring SSA levels to distinguish between healthy individuals, oral precancer and oral cancer groups.

In conclusion, this systematic review and meta-analysis analysed all the evidences available to determine whether SSA levels could be used as a biomarker for early detection of oral precancer and oral cancer. Therefore, we recommend that more thorough research has to be done worldwide to examine these SSA levels using larger samples and across different ethnic groups. However, established methods for biochemical analysis, standardization of saliva collection, and processing must be developed. This will assist in establishing accurate and consistent cut-off values for SSA level measurements in order to differentiate between groups with oral cancer, oral potentially malignant disorders, and healthy persons.

Author Contribution Statement

The conceptualization, investigation, validation, analysis, writing and review, supervision and project

administration was done by Dr. Manjula M Awatiger and Dr Punnya Angadi. The methodology, validation, investigation, analysis, collection of resources, draft was done by Dr. Pavithra Jayshankar

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If any scientific Body approved it/ if it is part of an approved student thesis

This review is approved by Institutional Systematic review committee of KLE VK Institute Of Dental Sciences Belagavi , Karnataka, India.

Availability of data (if applicable to your research)

The raw data related to systematic review and meta-analysis is with first author.

Was the study registered in any registration dataset (for clinical trials, guidelines, meta-analysis)

It has been registered and published at the International prospective register of systematic reviews (PROSPERO) - CRD42022338354.

Any conflict of interest

None.

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