ORIGINAL RESEARCH

Validating Saliva's Utility in Assessing Predictive Metrics for Treatment Outcomes in Oral Squamous Cell Carcinoma (OSCC) Patients: An Extensive Investigation in the Chennai Population

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Abstract

Introduction: Saliva is a convenient and non-invasive source for exploring biomarkers in postoperative oral squamous cell carcinoma (OSCC) patients. Salivary proteomics is a promising technique for discovering potential disease progression and treatment response biomarkers, especially within extracellular vesicles (EVs). However, the impact of salivary flow and consistency on postoperative OSCC monitoring is not fully understood. This study aims to fill this gap by examining the effect of chemotherapy and radiotherapy on salivary parameters, which can significantly impact the well-being and survival of OSCC patients.

Materials and Methods: This study analyzed the medical records of 155 postoperative oral squamous cell carcinoma (OSCC) patients over one year. The data collected included demographics, treatment modalities, and salivary parameters. To investigate the correlations between these factors, statistical analyses were carried out. The study received institutional approval and adhered to ethical guidelines.

Results: The study cohort had a larger sample size (n=150) with diverse demographic and clinical variables. While correlations between salivary parameters and demographic or clinical variables were observed, the lack of statistical significance in some associations raised questions about the strength of the relationships. Additional analyses were conducted to explore potential confounding variables and improve methodological clarity. The salivary flow rate and viscosity showed variation within the group. However, salivary characteristics, comorbidities, age, site, or treatment did not show significant interactions ($p > 0.05$). Salivary flow and consistency were satisfactory for predictive and survival analysis after the surgery.

Conclusion: This research provides essential information on monitoring oral squamous cell carcinoma (OSCC) after surgery, emphasizing the necessity of detailed assessments beyond initial improvements in salivary indicators. Additional investigation is needed to comprehensively understand the complex relationship between salivary biomarkers, treatment outcomes, and patient well-being in OSCC survivors.

Keywords: OSCC, salivary biomarkers, postoperative monitoring, chemotherapy, radiotherapy, salivary flow, salivary consistency.

Introduction

Oral Squamous Cell Carcinoma (OSCC) is a significant global health concern, with its incidence rising, especially in areas such as Chennai, India. Managing OSCC presents several challenges, from timely diagnosis to effective treatment and postoperative care. Accurately assessing treatment response and predicting prognosis is crucial for enhancing patient outcomes. Recently, saliva has emerged as a promising source for exploring predictive metrics that could potentially transform the monitoring and management of OSCC post-operative patients due to its non-invasiveness, ready availability, and proximity to the tumor site[1]. Proteomic strategies have been developed to identify proteins and phosphoproteins within salivary extracellular vesicles (EVs), aiming to discern molecular distinctions between OSCC patients and healthy individuals, providing a deeper understanding of the disease progression and treatment response[2]. Salivary proteomics has unveiled a spectrum of

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putative biomarkers for OSCC, including cytokines, matrix metalloproteinases, and acute-phase response proteins[3].

In the postoperative phase following treatment for Oral Squamous Cell Carcinoma (OSCC), the assessment of salivary flow rate and consistency becomes particularly crucial. Salivary gland function commonly undergoes substantial alterations due to surgical intervention, chemotherapy, and radiotherapy, which can significantly impact both the quantity and quality of saliva produced. Postoperative OSCC patients frequently experience dry mouth as a result of reduced salivary flow rates and changes in saliva consistency. These changes not only affect oral comfort but also present challenges in swallowing, speaking, and maintaining oral hygiene[2]. Moreover, compromised salivary function can worsen oral complications such as mucositis, dental caries, and oral infections, further impacting the quality of life of OSCC survivors. Therefore, in the context of postoperative OSCC care, the assessment of salivary flow rate and consistency plays a vital role in evaluating oral health status, identifying potential complications, and implementing targeted interventions to mitigate adverse effects and improve patient well-being[3].

Salivary biomarkers represent a paradigm shift in oncological monitoring, with the potential for early OSCC diagnosis and assessment of overall health status[4]. Microfluidic technologies have been used for isolating and detecting specific subpopulations of EVs in saliva, showcasing a real-time monitoring capability for tracking OSCC progression[5]. There is a notable gap in the existing literature regarding the particular role of salivary flow and consistency in monitoring OSCC patients after surgery. This is crucial for comprehensively understanding the dynamic interplay between salivary biomarkers and the postoperative landscape in OSCC patients.

Chemotherapy and radiotherapy are crucial oral squamous cell carcinoma (OSCC) treatments[6]. They significantly impactsaliva's flow rate and consistency, which requires careful monitoring[7]. Chemotherapy can have systemic effects that extend to salivary glands, potentially causing mucositis and compromising saliva's protective functions[8]. Radiotherapy, on the other hand, is essential for tumor control but can damage salivary glands, leading to a reduction in salivary flow, also known as xerostomia[9]. When both treatments are used together, they can exacerbate oral dryness and alter saliva composition[8]. These changes can affect patient's immediate well-being, including their oral comfort, speech, and dietary habits, and have long-term implications for survivorship[10]. This study aims to provide valuable insights into personalized patient care by investigating interventions to mitigate salivary gland damage and enhance postoperative quality of life. By integrating salivary assessments with imaging studies, the study will provide a comprehensive understanding of functional changes, thus informing therapeutic strategies for optimizing oral health outcomes in OSCC survivors.

In light of these considerations, this study aims to validate saliva's utility in assessing predictive metrics for treatment outcomes in OSCC patients, focusing on the Chennai population. Through an extensive investigation integrating proteomic analyses, clinical assessments, and patient outcomes, this research seeks to contribute valuable insights to the evolving field of saliva-based diagnostics in oncology, ultimately enhancing personalized patient care and improving survival rates for OSCC patients in Chennai and beyond.

The main objective of this study is to address this knowledge gap by investigating the combined relationship between salivary flow, consistency, and the postoperative monitoring of OSCC patients. This will contribute valuable insights to the evolving saliva-based oncology diagnostics field.

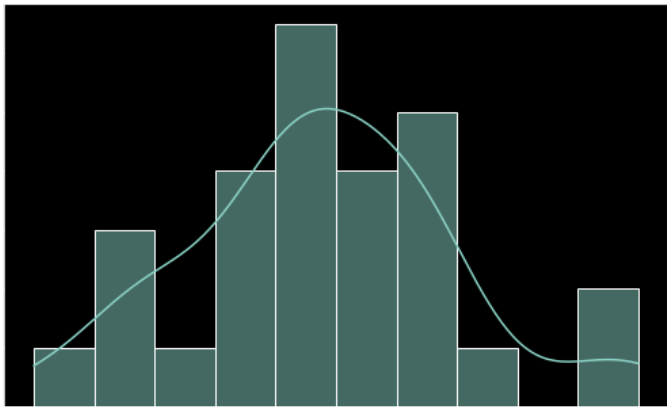

Fig.1: Age distribution of postoperative patients

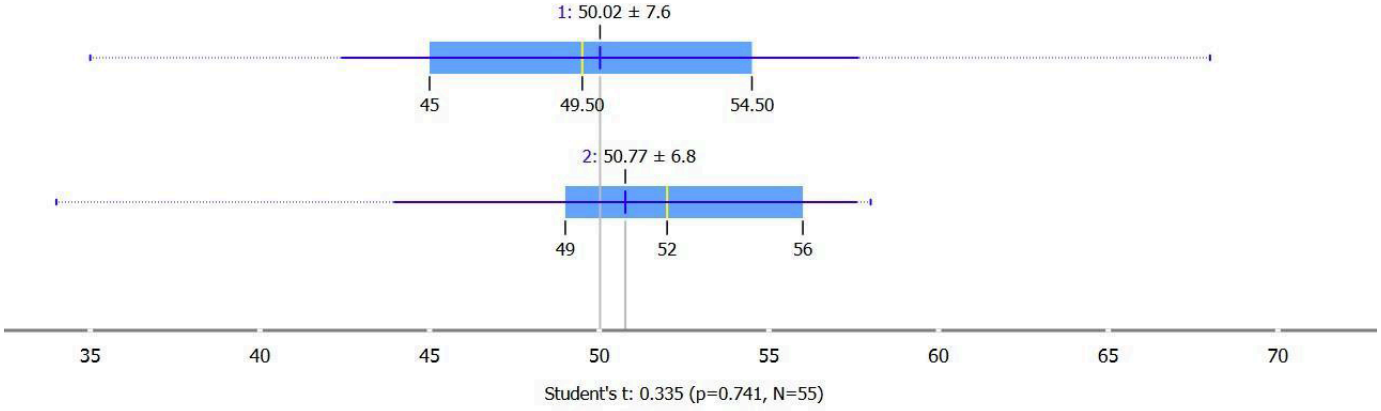

Fig. 2: Age and saliva flow rate of post-operative OSCC patients

Materials and Methods

Saliva collection protocol:

The study employed a retrospective examination of medical records from the past year to gather data on specific salivary parameters, with a focus on salivary flow rate, pH, and consistency. Salivary pH levels were consistently measured using the Eutech pH meter, PC 2700, equipped with ion-sensitive probes (Thermo Fisher Scientific, Waltham, Massachusetts, USA), offering detailed information on pH balance maintenance. The salivary flow rate was recorded through standardized sialometry methods, noting the saliva volume produced over a designated period under unstimulated conditions. Salivary consistency was qualitatively assessed, documenting any deviations from normal viscosity, such as increased thickness or dryness.

Participants were directed to use a designated device twice daily (morning and evening) for 10 minutes at a frequency of 80 Hz. Saliva samples were collected before and after the intervention using the "spit method" between 9 a.m. and 11 a.m. to account for circadian rhythm variations in salivary parameters. Participants were instructed to sit upright and spit saliva into a tube for 10 minutes to ensure uniformity. They were also advised to abstain from chewing gum, eating, drinking any liquids or alcohol, and smoking for at least one hour before sample collection[4,5]. Although the 10-minute collection period was mainly for assessing salivary flow rate, participants continued spitting until a minimum of 5 ml of saliva was obtained. For subsequent analysis, the collected saliva samples were stored in a deep freezer at -80°C. This comprehensive methodology provided an in-depth understanding of salivary

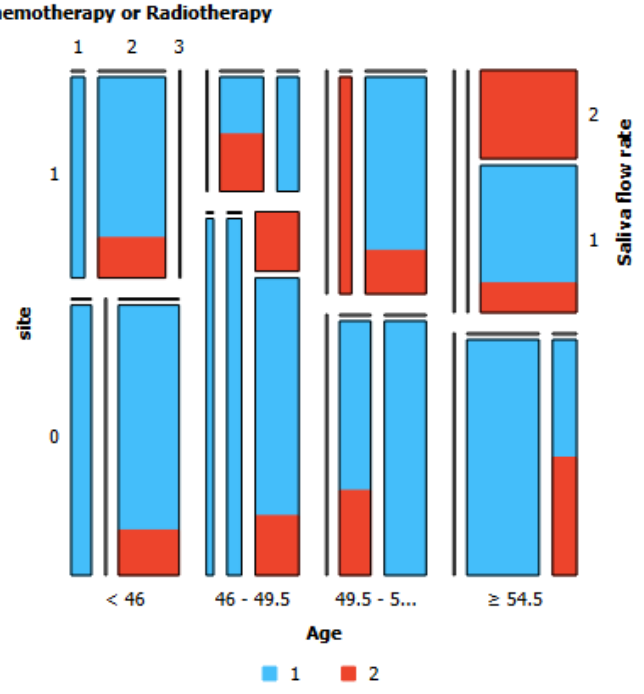

Fig. 3: Mosaic graph showing the relationship between age, site, treatment (chemotherapy /radiotherapy), salivary flow rate, and consistency.

characteristics and their impact on oral health.

Data extraction:

Data was collected from medical records retrospectively for the past 1 year. The study population included individuals aged 35 to 68 years with diverse demographic and clinical variables.

Categorization of data:

Gender was classified as 'Female' (coded as 0) or 'Male' (coded as 1). The tumor site was categorized as 'Unilateral' (coded as 0) or 'Bilateral' (coded as 1), while comorbidities were documented as 'no comorbidities' (coded as 0) or 'Comorbidities' (coded as 1). Treatment modalities, including 'Chemotherapy' (coded as 1), 'Radiotherapy' (coded as 2), or 'Chemotherapy+Radiotherapy' (coded as 3), were retrospectively analyzed. Additionally, salivary parameters were assessed, such as flow rate ('Normal' coded as 1 or 'Less' coded as 2) and consistency ('Normal' coded as 1 or 'Viscous' coded as 2).

Statistical analysis:

After extracting the data, descriptive statistics were computed for categorical variables, including frequencies and percentages, to provide an overview of the study cohort's demographic and clinical characteristics. Subsequently, appropriate statistical tests were employed to explore the associations between these variables. Specifically, Pearson correlation analysis was utilized to examine the relationships between salivary parameters (flow rate and viscosity) and demographic or clinical variables such as age, gender, tumor site, and treatment modalities. This analysis aimed to elucidate potential correlations and identify factors influencing salivary biomarkers in postoperative OSCC patients. Additionally, the statistical tests adhered to established assumptions, ensuring the validity and reliability of the findings. Furthermore, potential sources of bias or confounding variables were considered during the analysis to enhance the robustness of the statistical conclusions. This comprehensive statistical approach enhances methodological transparency and strengthens the validity of the study's findings, contributing to the overall rigor of the research in salivary diagnostics in OSCC monitoring.

Ethical considerations were given utmost importance, and approval was obtained from the Institutional Review Board (IRB) to adhere to ethical guidelines and maintain patient confidentiality throughout the retrospective analysis. This methodology provides a robust framework for investigating the relationships between demographic factors, treatment modalities, and salivary parameters in a retrospective context, shedding light on the retrospective dynamics of OSCC patient profiles.

Results

Demographic data:

The study cohort consisted of 155 post-operative OSCC individuals evaluated based on their demographic data, including age, gender, site of the condition, cancer stage, presence of hypertension or diabetes, and the type of treatment (Chemotherapy or Radiotherapy). The participants in this study ranged in age from 34 to 68 years, with a standard deviation of 7.50 and a mean age of approximately 55 years. The

gender distribution of the sample was almost balanced, with 55% female and 45% male. The site of the condition appeared to be predominantly unilateral. A significant proportion of the participants had comorbid conditions as indicated by the presence of hypertension or diabetes. Most individuals underwent either Chemotherapy or Radiotherapy as treatment modalities, with a smaller subset receiving a combination of both. Critical parameters of the study included saliva flow rate and consistency, which exhibited variation within the sample. Different individuals showcased average and reduced flow rates and viscous consistencies. Overall, this demographic profile reflected a heterogeneous cohort and emphasized the need for a comprehensive understanding of various factors in the context of oral health and cancer treatment outcomes.

Statistical analysis:

The patterns observed in the correlation analysis between salivary flow rate, salivary viscosity, and various criteria are intriguing. It is worth noting that while correlations were observed, the lack of statistical significance in some associations raises questions about the strength of the relationships. Additional analyses were conducted to explore potential confounding variables and improve methodological clarity. Despite positive trends in the correlation coefficients, the associations between salivary flow rate, viscosity, and the considered criteria, such as age, site, treatment, and comorbidities, were not statistically significant.

The patterns observed in the correlation analysis between salivary flow rate, salivary viscosity, and various criteria are intriguing. It is worth noting that the correlation between salivary flow rate and age was positive (r = 0.190), which indicates a potential association. However, the p-value (p = 0.164) was above the conventional significance threshold, making the correlation statistically insignificant. Similarly, the salivary flow rate demonstrated positive correlations with the site (r = 0.188) and treatment (r = 0.219), but once again, the corresponding p-values (p = 0.168 and p = 0.109, respectively) exceeded the significance level. The correlation between salivary flow rate and comorbidities was positive but not statistically significant (r = 0.109, p = 0.172). Interestingly, the salivary viscosity did not correlate significantly with the criteria. These results suggest that despite positive trends in the correlation coefficients, the associations between salivary flow rate, viscosity, and the considered criteria, such as age, site, treatment, and comorbidities, were not statistically significant. It is worth noting that the salivary flow and consistency improved in postoperative patients, although the overall results were considered insignificant.

Discussion

Saliva is vital in aiding postoperative patients in swallowing food and fluids and articulating speech[1]. Adequate saliva production ensures lubrication of the oral cavity, facilitating the movement of ingested substances and promoting oral comfort[11]. However, compromised saliva production in postoperative patients can hinder these essential functions, resulting in difficulties in swallowing and speech articulation[3]. Saliva contains various biomarkers indicating a patient's health status, including inflammation, stress, and disease progression[12]. Therefore, postoperative monitoring of saliva biomarkers offers a non-invasive approach to assessing the patient's recovery progress and overall well-being[10]. Healthcare providers can gain valuable insights into a patient's physiological responses to surgery and subsequent recovery by analyzing changes in saliva biomarkers, enabling timely interventions and personalized patient care[12].

Researchers are investigating the potential of using saliva to monitor oral squamous cell carcinoma (OSCC) patients after surgery[11,12]. They utilize proteomic techniques to differentiate the molecular changes in OSCC patients from healthy individuals[11]. Microfluidics technology allows for the real-time tracking of OSCC progression by isolating specific extracellular vesicles in saliva[12]. However, there is still a gap in our understanding of the relationship between salivary flow and consistency and the efficacy of postoperative OSCC monitoring. This study aims to address this issue by exploring interventions that can improve the quality of life for OSCC survivors. The study will integrate salivary assessments with imaging studies to better understand the disease and its progression.

The relatively modest sample size may restrict the generalizability of findings, particularly in accounting for

Table 1: Demographic data of postoperative OSCC patients

		Demographic data							
		Age	Gender	Site	Stage	Hypertensive/ diabetes	Chemotherapy or Radiotherapy	Saliva flow rate	Saliva Consistency
N	Valid	155	155	155	155	155	155	155	155
	Missing	0	0	0	0	0	0	0	0
Std. Error of Mean		1.0115	.0391	.0671		.0606	.0856	.0353	.0578
Std. Deviation		7.5016	.2901	.4978		.4495	.6346	.2621	.4288
Variance		56.274	.084	.248		.202	.403	.069	.184
Range		34.0	1.0	1.0		1.0	2.0	1.0	1.0
Minimum		34.0	1.0	.0		.0	1.0	1.0	1.0
Maximum		68.0	2.0	1.0		1.0	3.0	2.0	2.0

variations across different demographic groups, tumor stages, and treatment modalities. As diverse clinical presentations and treatment responses characterize OSCC, a more extensive and varied sample would better reflect the complexity of the patient population and allow for more robust statistical analyses. Acknowledging the potential implications of sample size constraints fosters transparency in research interpretation and underscores the need for cautious extrapolation of findings to broader clinical contexts. Despite these limitations, the insights gained from the study offer valuable preliminary evidence and provide a foundation for future research endeavors with larger cohorts to validate and extend the findings.

The study cohort showed diverse demographics, including age, gender, tumor stage, and comorbidities. However, delving deeper into these characteristics and their impact on salivary parameters would enrich the analysis. Exploring age-related trends in salivary flow rate and viscosity could inform age-specific interventions, while investigating gender disparities may reveal sex-specific patterns in disease progression. Additionally, stratifying by tumor stage and comorbidity profiles could unveil nuanced associations, guiding personalized care strategies for OSCC survivors. This comprehensive approach could lead to more effective postoperative care protocols. No statistical significance was found, although correlations were observed in salivary parameters after surgery. To understand the influence of age, treatment modalities, and comorbidities on salivary health in these patients, it's essential to consider them comprehensively. There is no correlation between age and salivary flow rate in contrast to the study by Yehuda et al., which highlights age-related variations, with a decline in flow rate and viscosity in the 31-65 age group compared to the 18-30 age group[13].

Even though statistical significance wasn't achieved, the observed trends could still have clinical implications that merit exploration in subsequent research endeavors. The clinical implications suggest a presence of salivary flow with regular consistency, which could be used to assess treatment outcomes, prognosis, and survival analysis, unlike previous studies suggesting reduced salivary flow after surgery[14,15]. Additionally, the absence of statistical significance in a larger sample indicates that the relationship between salivary flow rate, viscosity, and postoperative outcomes for oral squamous cell carcinoma patients may not be as substantial as initially suggested.

Table 2: Pearson correlation of age, site, treatment(chemotherapy /radiotherapy), salivary flow rate, and consistency.

Criteria	Pearson Correlation	
	Salivary flow rate	Salivary viscosity
Age	0.190 (p = 0.164)	0.043 (p = 0.757)
Site	0.188 (p = 0.168)	0.222 (p = 0.103)
Treatment (chemotherapy/ Radiotherapy)	0.219 (p = 0.109)	0.162 (p = 0.237)
Co-morbidities	0.109 (p = 0.172)	0.182 (p = 0.243)

Diabetes and hypertension are both known to be significant risk factors for various health conditions, including postoperative complications. These conditions can impact postoperative salivary flow rate and viscosity in the context of oral and maxillofacial surgery patients. However, in contrast to previous studies[16,17], our study has not shown any significant correlation.

The study on patients undergoing chemotherapy for solid tumors adds complexity to our exploration of treatment effects on salivary flow. The finding that the first cycle of chemotherapy did not induce significant changes in the stimulated salivary flow rate aligns with our broader investigation into chemotherapy's impact on salivary glands, emphasizing the adaptability and resilience of salivary function under specific treatment conditions[18,19]. Mayara et al. investigated the effect of cytotoxic chemotherapies on salivary flow velocity in cancer patients and explored potential factors influencing the observed outcomes[19]. Despite administering various cytotoxic drugs, including cyclophosphamide and cisplatin, the study found no significant reduction in salivary flow rate after the first cycle of chemotherapy[20].

In summary, the collaborative approach of incorporating recent insights from various studies enriches the ongoing discourse on salivary diagnostics. Although the specific correlations in our study did not reach statistical significance, the collective evidence underscores the potential diagnostic relevance of salivary parameters and the nuanced responses of salivary flow to specific conditions. These findings provide a robust foundation for continued research and clinical applications in the dynamic field of salivary diagnostics.

Conclusion

In conclusion, the present study provides a comprehensive insight into the clinical and demographic profiles of postoperative Oral Squamous Cell Carcinoma (OSCC) patients. The results of this study highlight the need for personalized treatment plans and comorbidity management for OSCC patients. Despite the absence of statistical significance in particular associations, the nuanced findings of this study are of significant value to the evolving landscape of salivary diagnostics. In this regard, future studies are warranted to validate these insights and explore additional factors that may impact OSCC treatment outcomes. Some limitations should be addressed in future research. Future studies can build upon these findings by expanding sample sizes, considering additional confounding variables, enhancing methodological clarity, and contributing to advancing salivary diagnostics in oncology. Such studies will foster the development of non-invasive diagnostic tools for monitoring disease progression and treatment efficacy, further advancing the field of salivary diagnostics and improving OSCC treatment outcomes.

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