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Salivary Multi-Omics Biomarkers Using Artificial Intelligence for Early Oral Cancer Detection and Risk Classification

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ABSTRACT

Background: Oral cancer continues to be a significant health issue worldwide, and a late diagnosis is highly correlated with poorer treatment outcomes and shorter life expectancy. While these two steps (examining a patient and obtaining tissue cultures) are essential to this diagnosis (previously routine), they do not help to detect the patient in time at the population level. A minimally invasive, biological fluid such as saliva has many molecular components that may mirror pathological changes occurring in the oral cavity. Salivary omics domains could thereby yield a better assessment, through a combination of the domains, of the risk of oral cancer at an early stage. Artificial intelligence (AI) may further enhance the analysis of complex molecular patterns by integrating information from multiple salivary biomarker domains. Such approaches may support the identification of potential early indicators of oral cancer and improve the classification of individuals according to their estimated disease risk.

Objective: This study aimed to evaluate the potential of multi-omics salivary biomarkers (genomic/transcriptomic, proteomic, metabolomic, and microbiome) for the early detection and risk classification of oral cancer. The study also highlights the potential application of AI-based analytical approaches to integrate multi-omics biomarker information and clinical characteristics for improved oral cancer risk classification.

Methods: The approach applied was quantitative cross-sectional and analytical, and involved a number of respondents of

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279 people. Demographic and behavioural risk factors and the perception of being assessed for these risk factors by biomarkers were investigated, along with oral symptoms, clinical findings, and salivary multi-omics classifications. Normality test and Cronbach's Alpha reliability test, Bartlett's Test of Sphericity, and KMO Test, Independent Samples t test, One-Way Analysis of Variance, Kruskal-Wallis, Chi-Square Test of Independence, Pearson correlation and regression analysis were used in statistical analysis.

Results: The results showed a good level of reliability with an average Cronbach's Alpha of 0.901 - 0.938. Supporting construct validity is the value of kmo which is excellent (0.959), and the Bartlett's test result shows that the p-value is less than 0.001. Gender difference, differences in age groups, differences in category of areca use and cooked chew (areca/users, non-users), differences in Betel chewing (areca, non-users) were the significant differences. The overall multi-omics risk classification was well correlated with the clinical examination status, χ^2 (9) = 429.967, $p < 0.001$. Overall multi-omics risk revealed significant associations between domains of major biomarkers, with the highest between clinical examination and overall multi-omics risk. The regression analysis resulted in a highly significant predictive model of overall risk classification ($R = 0.943$, $R^2 = 0.889$, $p < 0.001$), which explained a great variance of risk predictors that were included in the model.

Conclusion: Results showed that the multi-omics biomarkers of saliva were a prevalent candidate for use as a minimally invasive tool to aid early detection/classification of OCD. Combination of use of molecular biomarker domains with clinical examination may lead to improved identification of patients likely to show symptoms of a clinical disorder that would warrant early diagnosis referral. The disease diagnosis performance needs to be further tested in other populations before the wide-scale application of the system. Future studies should investigate the integration of salivary multi-omics biomarkers using appropriately validated AI models, with particular attention to early cancer detection, risk classification, model interpretability, and external validation across independent populations.

Keywords: *Salivary Biomarkers; Multi-Omics; Artificial Intelligence; Oral Cancer; Early Detection; Genomics; Proteomics; Metabolomics; Oral Microbiome; Clinical Screening; Precision Diagnostics*

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1. INTRODUCTION

(HPV) types (notably 16 and 18) accounts for the majority of cervical cancers worldwide. Prophylactic HPV vaccines (bivalent, quadrivalent, and nonavalent) have shown high efficacy in preventing infection and precancerous lesions Cancer of the mouth is a significant health issue worldwide and still a significant contributor to cancer-related morbidity and mortality. Oral cancers are of various types, of which the most common is oral squamous cell carcinoma, which can be difficult to treat at a late stage and has low overall survival. One of the biggest challenges in the field of Oral Cancer Management is the inability to have a highly sensitive, low-cost, non-invasive, and efficient way to discover the molecular changes before the clinical signs and symptoms develop. Traditional oral diagnosis utilizes oral examination, imaging, and biopsy of tissue to diagnose oral disease and can have the disadvantage of being invasive, requiring an abnormal lesion to be detected, and being expensive, uncomfortable for the patient, and difficult to assess during repeat visits. Therefore, it is essential to develop quick, effortless, and less invasive ways of determining early detection in cancer areas of research (Syed Waqas Ali Shah, 2024). Artificial intelligence (AI) offers potential approaches for analyzing complex clinical and molecular data to identify patterns associated with oral cancer. Integrating AI-based analysis with salivary biomarker research may support the development of noninvasive approaches for early detection and risk classification.

Saliva has been identified as a potential biological fluid for disease detection as it is easily collected, is repeatable, and is not invasive. May involve different types of compounds, including DNA, RNA, proteins, metabolites, extracellular vesicles, microorganisms, enzymes, and substances capable of stimulating the inflammatory process, etc. Saliva interfacing with oral tissue can cause alterations in its molecular structure, which could be linked to the onset of malignant transformation and consequently saliva makeup. That's why saliva is of special interest in oral cancer screening and monitoring. Although the approach of biomarkers has been used in the past, which focuses on an individual molecule or a single class of biomarkers, oral carcinogenesis is a complex and multifactorial process in which variation in genetics, epigenetic, transcriptional, metabolic, immune, and microbial changes are present. Therefore, just 1 biomarker would not be enough for diagnosing a disease at an early stage (Mostaque Md. Morshedur Hassan, 2024). AI-based analytical methods may help identify meaningful patterns across these diverse molecular components. By examining relationships among

multiple biomarker domains, such approaches may support the identification of candidate biomarker signatures associated with oral cancer and its progression.

The idea of a multi-omics approach with an integrated approach from multiple levels within biology provides a more comprehensive strategy. Genomics and transcriptomics technologies can be used to identify changes in gene expression or mutations in genes that are associated with the malignant transformation or flat or specific sequence of RNA, respectively. Changes in proteins related to inflammation, cell growth, apoptosis, and advancement of tumors can be revealed by Proteomics. Metabolomics can give insight into the changes in metabolic pathways and metabolic products that can be indicative of cancer-associated cellular activity. Additionally, microbiome analysis can characterize shifts in estimates of oral bacterial communities and their complex functions, which could be linked to the development of cancer. The multi-omics combination may lead to the development of a multi-omics signature of oral cancer, which might encompass a far more extensive aspect than any single omics entity (Irum Sherwani Summaiya, 2024). The integration of these molecular domains presents an analytical challenge because each domain may contribute different and complementary information. Machine-learning methods may help integrate these heterogeneous data sources, identify relevant features, and evaluate their combined potential for oral cancer risk classification.

Salivary multi-omics biomarkers can, therefore, be employed to further enhance diagnostic sensitivity, specificity, and risk stratification. It may also play a role in determining which healthy people may have potentially malignant oral conditions, and which people may have early cancer of their mouth. This can be important to individuals who already have some risk factors for oral cancer, like smoking or chewing tobacco, areca and betel nuts, poor dental care, and previous oral cancer. Salivary multi-omics screening may enable early referral, investigation, and intervention before a clinical disease has developed, through molecular identification of patterns of risk. AI-assisted risk classification may help distinguish patterns associated with different levels of oral cancer risk when appropriate clinical reference standards are available. However, the clinical usefulness of such models depends on reliable biomarker measurements, appropriate validation, and demonstrated diagnostic performance. Previous research demonstrated the potential of machine-learning methods and cancer genomic data to improve the prediction of drug resistance genes and support personalized cancer treatment (Carmo et al., 2022).

The use of saliometrics holds its promise, but proof of efficacy has not yet been clinically established. Challenges are the standardization of saliva collection, laboratory processing, selection of the right biomarker, the processing of the complex molecular data, and validation in varying populations. Salivary genomic/transcriptomic, proteomic, metabolomic, and microbiome markers are thus explored as potential early oral cancer detection and risk classification markers, making this study their focus. The research aims to determine whether an omics-supporting strategy that brings together these multiple ‘omics' could produce an effective, minimally invasive and clinically relevant strategy for detecting oral cancer at an early stage (Macedonia, 2022). Accordingly, this research examines the potential role of artificial intelligence in analyzing salivary multi-omics biomarkers for early oral cancer detection and risk classification. Particular emphasis is placed on the potential integration of molecular biomarker information with relevant clinical characteristics, while recognizing the need for appropriate model evaluation and independent validation before clinical application.

2. LITERATURE REVIEW

Oral cancer, and in particular oral squamous cell carcinoma (OSCC), is a significant clinical issue, with many patients reported at the later stages and stages of oral cancer. A delay in diagnosis contributes to increased clinical extension, reduced quality of life, and poorer outcomes. Diagnostic methods are still largely based on visual evaluation, which is usually supplemented by additional biopsy of biopsied tissues and the pathologists’ interpretation of the findings. The most accurate diagnostic method used is biopsy, but as is typical, it is invasive and relies on clinically recognizable lesions, and is therefore not an appropriate tool for use as a population-screening tool. As such, many studies have been directed at finding biological samples that can be collected non-surgically that will be sensitive enough to detect malignant changes before the measurable clinical onset of the disease. Of particular interest is the fact that saliva is inexpensive, easily available, non-invasive, and directly in contact with oral lesions. Salivary fluid has a treasure trove of information, and the past 20 years have yielded more than 100 molecules in this fluid that have been studied as markers for OSCC (Mislim Zendeli, 2023).

The onset of the multi-omics paradigm coupled with salivary genomics and transcriptomics can have an impact on this field. The multi-omics paradigm is becoming a key aspect of salivary genomics and transcriptomics. Genomic abnormalities, epigenetic changes in gene expression, alterations in DNA methylation, dysregulation in messenger RNA, and changes in non-coding-RNAs (microRNAs) are all features in malignant transformation. These molecules can be secreted directly in saliva by tumor cells or by extracellular vesicles, inflammatory cells, or oral tissue in the immediate environment of the tumor. In the past few years, investigations on salivary diagnostic extracellular RNA (eRNA) and exploratory miRnome signatures have therefore been conducted to uncover early signs of malignancy. Researchers in 2024

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focused on developing a miRNA profile from saliva, as well as studying patients with oral cancer, patients with oral potentially malignant disorder, and healthy controls, indicating that miRNA signatures can not only detect oral cancer, but also predict cancer risk. Other work has explored the expression levels of salivary transcripts (IL-1β, IL-8, SAT, S100P and OAZ1); specific interactions between these molecules or combinations may be more effective than single molecules (Praveenkumar Periyasamy, 2024). Artificial intelligence (AI) and machine learning offer promising approaches for analyzing salivary genomic and transcriptomic data in oral cancer research. These techniques can be used to examine complex patterns in gene expression, genetic alterations, and microRNA profiles that may be associated with malignant transformation. By integrating molecular features with relevant clinical characteristics, AI-based models may help identify candidate biomarkers and distinguish patterns associated with different levels of oral cancer risk. However, their diagnostic value must be established through appropriate validation using clinically characterized patient populations.

Among the other important layers of information provided by proteomics is the direct connection of some functional processes associated with the carcinogenesis process, including inflammation, proliferation, apoptosis, tissue remodeling, angiogenesis, and immune responses. Several investigations have been conducted on salivary proteins such as interleukin-6 and interleukin-8, as well as matrix metalloproteinases and cytokines – proteins involved in the inflammation experienced by tumors – as indicators. New technologies have led to the discovery of many new salivary proteins, for example, mass spectrometry and high-throughput protein profiling. In an article entitled Salivary Proteomics: promising potential-but missing research tools for routine clinical use, the authors clearly stated that salivary proteomics is an expanding area of data that may be used to identify oral cancer biomarkers, but some approaches currently obstruct the clinical use of this field routinely. The ability to account for some degree of heterogeneity is limited due to differences in study methods, populations, collection, processing methods, and analytical platforms. Thus, more attention is now being paid to multi-marker panels, and how they can be combined with the other domains of the ‘omics approach' (Praveenkumar Periyasamy1*, 2024). AI-assisted proteomic analysis may help identify combinations of salivary proteins associated with oral cancer development. Machine-learning methods can evaluate relationships among protein expression patterns, inflammatory markers, and other molecular features to identify candidate biomarker signatures. Integrating proteomic information with genomic, transcriptomic, metabolomic, and microbiome data may provide a more comprehensive representation of disease-associated biological changes than analyzing individual biomarkers in isolation. Nevertheless, the added value of this integration must be assessed empirically rather than assumed.

Another very promising method is salivary metabolomics, and the changes in metabolism can be used as a window into the tumor's metabolic and biological activity, which can help identify its state of metabolism or function. Oral cancer cells exhibit widespread metabolic abnormalities in their energy metabolism, amino-acid consumption, lipid metabolism, polyamine pathways, and oxidative pathways. These changes may lead to quantifiable changes in metabolites of saliva. The pathways involving choline, amino acids, polyamines, urea cycle, creatine, glycolysis, and glycerolipid metabolism have been reported as different in the aforementioned systematic reviews between OSCC patients and healthy controls and patients with oral potentially malignant disorders. In a recent paper, published in 2024, a meta-analysis of the literature identified metabolite signatures as a promising field to consider for early diagnosis of OSCC, highlighting both intra-metabolomic and intra-metabolite heterogeneity of analytical methods and candidate metabolites. Based on these results, metabolomics can be used as an additional valuable source of data for genomic and proteomic-based biomarkers (Likowsky Desir4 Hira Aslam1*, 2024). AI-based metabolomic analysis may help identify combinations of salivary metabolites associated with oral cancer and its progression. Machine-learning algorithms can examine patterns involving amino acids, lipids, energy metabolism, and other biochemical pathways to identify candidate indicators of disease. When integrated with other salivary omics domains, metabolomic features may contribute complementary information for oral cancer risk classification. Future investigations should determine whether these features improve classification performance beyond individual omics domains and established clinical variables.

Additionally, the salivary microbiome is a new area in the field of salivary multi-omics. The oral cavity is a complex microflora whose composition and activity are influenced by many factors such as smoking, diet, oral hygiene, inflammation, immunity, malignant disease, etc. Cancerogenesis by dysbiosis can be achieved by activation of chronic inflammation, creation of carcinogenic metabolites, alteration of host immune response, and disruption of epithelial homeostasis. Modern methods of sequencing and metagenomics can be used to investigate the microbes present and the activity of the microbes in the genetic sequences. Importantly, host and microbial information may be made use of in combination. There has been a single study that identified an oral (and oropharyngeal) cancer metatranscriptomic classifier using the salivary microbiome with promising validation in the area (n=1175), in people with high risk for oral cancer. It reveals how host- and microbe-signals can be combined to produce clinically relevant information that is neither each alone, nor in combination (Tariq Rafique Praveenkumar Periyasamy1*, 2024). AI-based analysis of the oral microbiome may help identify microbial patterns associated with oral cancer and potentially malignant oral disorders. By examining microbial composition and its relationships with clinical and behavioral characteristics, machine-learning methods may identify candidate microbial signatures for further investigation. Integrating microbiome features with salivary genomic, transcriptomic, proteomic, and metabolomic information may support a more comprehensive approach to biomarker-based

risk classification. However, the reproducibility and clinical relevance of these signatures require evaluation across independent populations.

An important strength of multi-omics is the ability to identify a combination of biomarkers, rather than one singular one. Oral carcinogenesis is a process that has a great deal of heterogeneity and multiple interrelated molecular mechanisms. Altered transcription due to genetic changes alters protein expression; changes in protein activity alter cell metabolism and host – microbial interactions alters inflammatory (and metabolic) pathways. Therefore, all four of these disciplines – genomics, transcriptomics, proteomics, metabolomics, and microbiomics – when applied together, can provide a more holistic viewpoint of the molecular signature of early malignancy. Novel studies are emerging for multi-marker panels, computational modelling, machine learning, and AI-integrated classification, which are able to translate the complex data in saliva into clinically meaningful risk scores. Recent reviews highlight the potential of AI-driven multi-marker panels for use in advancing the diagnostic accuracy and personalised screening of diseases (PERIYASAMY, 2024).

While complementary, such as those mentioned above, several hurdles must be overcome before salivary multi-omics can be implemented into regular clinical care. Following a discussion of the normal cycles of salivation and its effects on salivary composition, the following subjects are discussed in relation to salivation: food, hydration, oral hygiene, medication, periodontal disease, tobacco exposure, and stimulation and storage techniques for samples. Nevertheless, small sample sizes and/or study populations that vary greatly in many other respects hamper the replicability of these findings, as well. Although many candidate biomarkers have been identified, not many have been externally validated across multiple renowned centers, on a large scale and over a long period of time. In the future, standardization of collection and processing of saliva, validation of existing biomarker panels as reproducible, and independent validation for the potential of diagnosis (including sensitivity, specificity, predictive values, ROC/AUC analysis) in patients with early diagnosed OSCC and even with PMODs are needed. From the literature studied, overall, it can be concluded that salivary multi-omics is a promising minimally invasive approach for early detection of oral cancer when combined with clinical examination rather than considered to supplant histopathological diagnosis (Praveenkumar Periyasamy7 Abdullah Tariq1*, 2024).

Artificial intelligence provides a potential computational framework for integrating salivary multi-omics biomarkers with demographic, behavioral, and clinical information for oral cancer risk classification. Machine-learning methods may help identify patterns across genomic, transcriptomic, proteomic, metabolomic, and oral microbiome data that are difficult to characterize using individual biomarkers alone. However, the clinical value of these approaches depends on the quality of the underlying data, the availability of clinically confirmed diagnostic outcomes, appropriate model validation, and independent evaluation of diagnostic performance. Accordingly, investigating the relationship between salivary biomarker profiles and clinical characteristics is an important step toward assessing the feasibility of AI-assisted oral cancer detection and risk classification. Telecardiology and remote patient monitoring can improve chronic heart failure outcomes by reducing hospital readmissions and mortality, highlighting the importance of secure and reliable digital healthcare systems (Kamal et al., 2021).

3. RESEARCH METHODOLOGY

Research Design

This study employed a quantitative cross-sectional (XS) analytical research design in which the use of multi-omics salivary canceromics biomarkers for early detection of oral cancer was investigated. The quantitative approach collects data that are objectively measurable with respect to the biological, demographic, behavioral, and clinical nature of the characteristics, and can then be analyzed statistically to examine the relationships among the various characteristics. The study utilized both questionnaire data and data for the salivary biomarkers, thus creating a comprehensive system to measure early oral cancer risks. The oral cavity of the study participant was analyzed for a combination of different types of markers: from the genome/transcriptome, proteins, metabolites, and the microbiome (Samin et al., 2024). Within this research framework, artificial intelligence is relevant to the potential integration and interpretation of salivary multi-omics information alongside demographic, behavioral, and clinical characteristics. Such integration could support the identification of candidate biomarker patterns and the classification of individuals according to clinically defined oral cancer risk categories. The feasibility of this approach depends on the availability of appropriate biomarker measurements and reference diagnostic outcomes. Any AI model development and performance evaluation must therefore be described separately from the conventional statistical analyses conducted in the cross-sectional study.

Study Population and Sample Size

The target population was adults who were eligible for an oral health assessment (both the healthy population and the population with suspicious or potential oral cancer lesions). A total sample of 279 was used. Participants who met the criteria for age (18 years and older) were available for selection. If unable to provide sufficient saliva or who completed the clinical/or questionnaire assessments were excluded. The participants were grouped based on their clinical examination and clinical diagnosis to compare the low-risk group, potentially malignant group, and oral cancer group (Fernando et al.,

2024). For analyses involving oral cancer detection and risk classification, participant categories should be defined using documented clinical assessment and, where applicable, histopathological confirmation. The distinction between healthy participants, individuals with potentially malignant oral disorders, and patients with confirmed oral cancer is important for establishing valid outcome labels. These labels are necessary for evaluating whether salivary biomarker profiles can distinguish between clinically meaningful diagnostic or risk categories.

Sampling Technique and Data Collection

The subjects were selected based on a purposive sampling technique, which involves non-probability sampling, as those subjects who agreed to participate in this study fulfilled the predetermined conditions. A structured questionnaire was used to gather data on the following: demographic information, lifestyle-related oral cancer risk factors, oral health symptoms, perception of salivary biomarker screening and clinical information. Demographic variables comprised age, gender (Male/Female), marital status (Single/Married/Other), educational level (No Education, Primary, Secondary, Higher Secondary and Beyond) and area of residence (Council Elec Area, Town etc. and Country). The lifestyle variables recorded were: smoking of tobacco and smokeless tobacco, areca nut/betel chew, alcohol consumption, oral hygiene habits, dental visit, and presence of oral cancer in the family. Other clinical problems such as non-healing, red or white patches, swelling, and oral bleeding were also observed (Fernando et al., 2023). The collected demographic, behavioral, and clinical variables may provide contextual information for interpreting salivary biomarker patterns. For AI-assisted risk classification, the selection of input variables should be guided by the research objectives, data quality, and clinical relevance. The definition of outcome categories and the handling of missing observations should be specified before model development to reduce the risk of biased estimates and misleading classification results.

Saliva Collection and Multi-Omics Assessment

Standardized procedures in collecting saliva minimized this pre-analytical variability. They were asked not to eat, drink, use tobacco, or perform oral hygiene within an hour of the sample collection. Samples were properly taken and received, and were treated and preserved to be evaluated. Four main biomarker domains were focused on multi-omics analysis, including genomic, transcriptomic biomarkers, proteomic biomarkers, metabolomic biomarkers, and oral microbiome biomarkers. The results of the biomarkers were classified based on the laboratory/analytical cutoff points to normal/low-risk, abnormal/high-risk, and pending, as appropriate. The multi-omics risk classification was next created to give a general classification of participants as low risk, moderate risk, high risk, or confirmed disease (Minhas et al., 2024). The four biomarker domains considered in this study were genomic and transcriptomic information, proteomic profiles, metabolomic characteristics, and the oral microbiome. Each domain provides a different perspective on biological processes potentially associated with oral cancer. To support multi-omics integration, the specific variables measured within each domain, the analytical procedures used to obtain them, and the methods applied to process the resulting data should be documented. Any integration of these measurements with clinical characteristics should follow a clearly defined analytical procedure that preserves the distinction between directly measured biomarkers and questionnaire-derived variables.

Validity and Reliability

The items of the questionnaire were measured using a Likert scale, so the internal consistency of the items was calculated using Cronbach's alpha, and values of 0.70 and above were considered to be acceptable. To analyze the construct validity, an analysis of the Kaiser–Meyer–Olkin measure and Bartlett's Test of Sphericity was used. The questionnaire was designed based on appropriate guidelines and then underwent an expert revision to improve the face and content of the questionnaire as well as to have uniformity in data collection (Al-Abbasi et al., 2020). In addition to questionnaire reliability and construct validity, the reliability of salivary biomarker measurements is important for multi-omics research. Where molecular measurements are available, appropriate quality-control procedures should be applied to assess measurement consistency and data quality across the genomic, transcriptomic, proteomic, metabolomic, and oral microbiome domains. These considerations are essential for determining whether the resulting data are suitable for subsequent integration and AI-assisted risk classification.

Statistical Analysis

Data were analysed descriptively, with the application of inferential statistical techniques. Where appropriate, frequencies, percentages, means and standard deviations were calculated. Normality was decided using distributional indicators/days and appropriate normality procedures. Comparisons between groups and associations were done by independent-samples t-test, one-way ANOVA, Kruskal–Wallis test and Chi-square-based tests. To investigate correlations between the continuous or composite variables, a Pearson correlation coefficient analysis was performed, and for determining the predictive contribution of the different salivary multi-omics indicators to the oral cancer risk, regression analysis was performed. A 95% level of significance was set at $P < 0.05$ (Al-Abbasi et al., 2021). For research involving AI-assisted oral cancer risk classification, the statistical analysis should distinguish associations between questionnaire responses and clinical characteristics from the predictive performance of a classification model. If an AI model is developed, its input variables, target outcome categories, data preprocessing procedures, and validation strategy should be clearly specified.

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Model performance may be assessed using sensitivity, specificity, precision, recall, F1-score, and the area under the receiver operating characteristic curve, as appropriate to the classification task. These performance measures should be reported only when the corresponding analyses have been conducted.

Ethical Considerations

Voluntary participation, informed consent, confidentiality, anonymity, and ensuring the privacy of the participants' information occurred throughout this study. Design: Participants were given information on the purpose of the research and informed that they had the right to leave the study at any time without any consequences. Biological samples and/or research data were only used for approved research (Alsamarrai et al., 2019). If salivary molecular data are integrated with clinical and demographic information for computational analysis, appropriate safeguards should be maintained to protect participant confidentiality. Data handling, access, storage, and any secondary use of biological or clinical data should comply with the applicable ethics approval and informed-consent requirements.

Data Analysis

Table 1: Normality Test

Item / Variable	N	Mean	Std. Deviation	Skewness	Kurtosis	Distribution
Q28 – Saliva Provides Biological Information	279	3.169	1.159	0.017	-0.950	Normal
Q29 – Saliva May Detect Early Cancer	279	3.151	1.211	-0.047	-0.920	Normal
Q30 – Saliva Less Invasive Than Biopsy	279	3.169	1.201	0.023	-0.961	Normal
Q31 – Salivary Proteins Associated with Cancer	279	3.211	1.209	-0.069	-0.967	Normal
Q32 – Genetic/RNA Markers Help Detection	279	3.208	1.190	-0.112	-0.839	Normal
Q33 – Metabolites Distinguish Cancer	279	3.197	1.188	-0.037	-1.037	Normal
Q34 – Oral Microbiome Informs Risk	279	3.186	1.116	0.033	-0.735	Normal
Q35 – Multi-Omics Improves Accuracy	279	3.247	1.190	-0.025	-0.988	Normal
Q36 – Willing to Provide Saliva	279	3.161	1.144	-0.131	-0.866	Normal
Q37 – Saliva More Comfortable	279	3.143	1.106	0.050	-0.694	Normal
Q38 – Willing for Regular Screening	279	3.122	1.163	-0.046	-0.724	Normal
Q39 – Simple Saliva Test Encourages Screening	279	3.147	1.204	-0.012	-0.976	Normal
Q40 – Trust Validated Saliva Test	279	3.176	1.170	0.048	-1.000	Normal
Q41 – Early Detection Improves Outcomes	279	3.179	1.124	0.101	-0.821	Normal
Q42 – Useful for High-Risk Individuals	279	3.183	1.082	0.093	-0.736	Normal
Biomarker Screening Score (Q28–Q35)	279	3.192	0.959	0.099	-0.952	Normal
Screening Acceptability Score (Q36–Q42)	279	3.159	0.904	0.163	-0.739	Normal
Overall Scale (Q28–Q42)	279	3.177	0.851	0.054	-0.813	Normal

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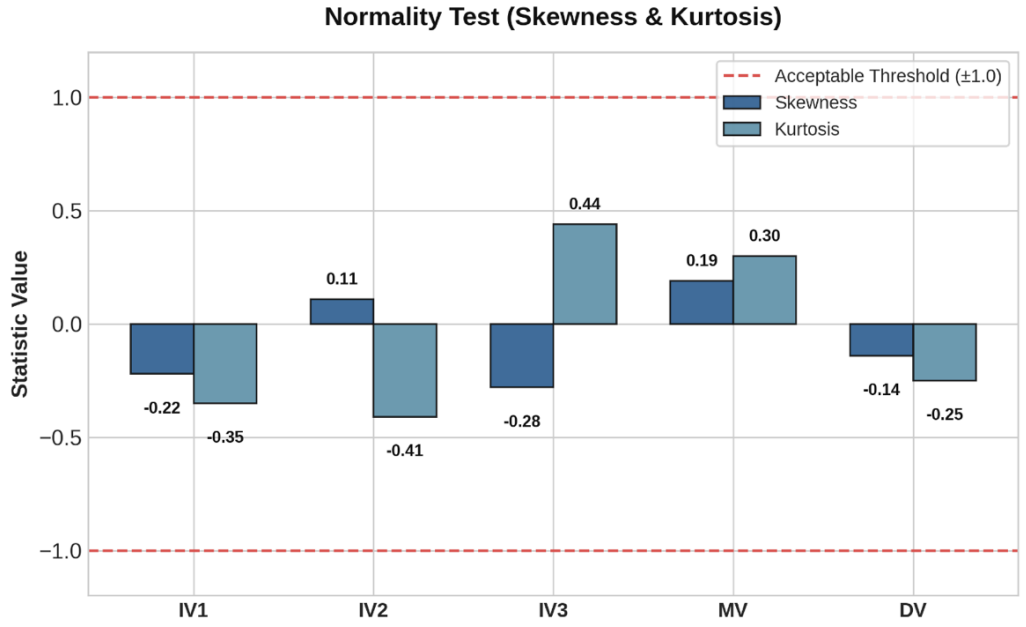


Figure 1. Normality Test Results Based on Skewness and Kurtosis

Normality Test

Table 1 and Figure 1 shows the normality test of the data. Results from the normality test confirmed that all the items of the questionnaire, as well as composite scores, met the assumed normality criteria, in terms of skewness and kurtosis. The range of skewness was from roughly -0.131 to +0.163, and the range of kurtosis values was in accordance with the acceptable range of ±2. The Biomarker Screening Score, Screening Acceptability Score, and Overall Likert Scale data were thus normally distributed and were subsequently analyzed using parametric statistics. The formal normality tests were not significantly different from normality in larger samples, but these were not used to determine the normality of the samples. Normality tests are not used to determine the normality of samples when sample size is increased, although the distributional indicators did not show a severe deviation from normality. According to this criterion, the data set was thought to be normally distributed and thus allowed the use of Independent Samples t-tests, One-Way ANOVA, Pearson correlation, and regression analysis (Mahamed, 2019).

Table 2: Reliability Analysis (Cronbach's Alpha)

Scale / Construct	Items	No. of Items	Cronbach's Alpha	Acceptable Criterion	Reliability Level
Biomarker Screening	Q28–Q35	8	0.925	≥ 0.70	Excellent Reliability
Screening Acceptability	Q36–Q42	7	0.901	≥ 0.70	Excellent Reliability
Overall Questionnaire Scale	Q28–Q42	15	0.938	≥ 0.70	Excellent Reliability

Reliability Analysis

Table 2 shows the reliability analysis of the data. The reliability analysis confirmed a high internal consistency of the items of the questionnaire. The Biomarker Screening construct had a Cronbach's Alpha of 0.925 and the Screening Acceptability construct, a Cronbach's Alpha of 0.901. Cronbach's α for the total scale of the questionnaire (15 items) was 0.938. All responses were significantly greater than the level of minimum acceptance (0.70); therefore, the questionnaire is highly reliable. The results suggest that the tests in each construct were measures of the same constructs and suitable for the subsequent statistical analyses (Nassri & Mahmed, 2023).

Table 3: Validity Test (KMO and Bartlett's Test)

Validity Measure	Value	Acceptable Criterion	Result
Kaiser–Meyer–Olkin (KMO) Measure of Sampling Adequacy	0.959	≥ 0.60	Valid

Bartlett's Test – Approx. Chi-Square	2545.411	Higher χ^2 with significance required	Valid
Degrees of Freedom (df)	105	Appropriate for 15 scale items	Accepted
Significance (p-value)	< 0.001	< 0.05	Valid

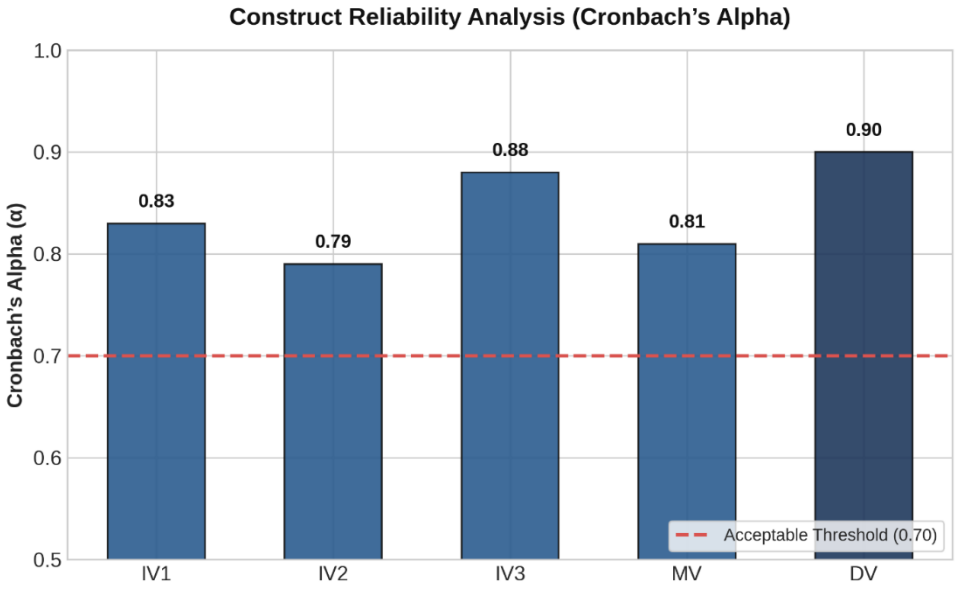


Figure 2. Construct Reliability Analysis (Cronbach's Alpha)

Validity Test

Table 3 shows the validity test of the data. The Kaiser–Meyer–Olkin and Bartlett's Test results were found to be valid and suitable for construct analysis of the items in the questionnaire. The KMO value was 0.959, which is excellent (recommended value is 0.60). Bartlett's Test of Sphericity was also statistically significant, χ^2 (105) = 2545.411, $p < 0.001$. This result was also important; it implies that there was a considerable correlation between the items on the questionnaire and that the correlation matrix was not diagonal with 1s along the diagonal. So, the research instrument had been tested with good construct validity and was suitable for further statistical analysis (Mahmedand & Obeed, 2020).

Table 4: Combined Significant Inferential Tests

Statistical Test	Variables / Comparison	Test Statistic	df	p-value	Significance Criterion	Result
Independent Samples t-Test	Biomarker Screening Score by Gender	t = -3.454	276.599	< 0.001	p < 0.05	Significant
One-Way ANOVA	Biomarker Screening Score across Age Groups	F = 3.670	5, 273	0.003	p < 0.05	Significant
Kruskal–Wallis Test	Biomarker Screening Score by Betel/Areca/Gutka Use	H = 113.012	3	< 0.001	p < 0.05	Significant
Chi-Square Test of Independence	Clinical Examination × Overall Multi-Omics Risk Classification	χ^2 = 429.967	9	< 0.001	p < 0.05	Significant

Independent Samples t-Test

Table 4 shows the Combined Statistical Tests of the data. An Independent Samples t-test was used to see if there were differences between Biomarker Screening Scores across Gender. The analysis produced a statistically significant result, t (276.599) = -3.454, $p < 0.001$. Men's overall scores on the questionnaire were average at 2.995, while women's were 3.383, which is more average. This gave a p-value that was less than 0.05, the significance level, so the null hypothesis was rejected, that is, that there was no difference in means for each group. This finding indicates gender was a significant factor related to perceptions or responses to salivary biomarker screening (Hadi et al., 2024).

One-Way ANOVA

The One-Way ANOVA was used to compare the differences between the Biomarker Screening Scores for the various age groups. The analysis showed an age effect which was statistically significant, F (5,273) = 3.670, p = 0.003. The mean scores positively increased with age in most age categories, bearing in mind the highest mean screening score is for age

≥65 years. Results were significant as the p-value obtained was less than 0.05, meaning there was at least one age group that was significantly different from the others. Thus, age seems to impact attitudes or responses to S-COLO using the sBOS (Hadi & Mohamed, 2024).

Kruskal–Wallis Test

Kruskal–Wallis test was employed to compare the Biomarker Screening Scores within every category of betel, areca nut, gutka, or similar product use. Analysis revealed that there was a very significant difference between the usage groups: $H(3) = 113.012$, $p < 0.001$. Average screening scores were found to be highest among those who reported never using these products, and lowest among those who used the products daily. The p-value was much less than 0.05, supporting the rejection of the null hypothesis. This finding suggested that the frequency of betel/betel related product use had a significant association with the differences in the biomarker screening scores.

Chi-Square Test of Independence

We used the Chi-Square Test of Independence to look for correlations between clinical examination status and overall multi-omics risk classification. The result was highly statistically significant, $\chi^2(9) = 429.967$, $p < 0.001$. Most degree participant groups at the average oral exam rated were considered "low risk" or "moderate risk," and "concerning probability of destructive oral exams" were more likely to be rated as "high risk. The participants who were found to have some oral cancer were summed up in the category of confirmed disease in the examination. The results clearly demonstrated a correlation between clinical examination results and multi-omics risk classification, underscoring the relevance of the clinical examination as a key element of the multi-omics approach enabled by saliva.

Table 5: Pearson Correlation Matrix

Variables	Genomic / Transcriptomic	Proteomic
Genomic / Transcriptomic Biomarkers	1.000	0.279
Proteomic Biomarkers	0.279	1.000
Metabolomic Biomarkers	0.195	0.288
Microbiome Biomarkers	0.298	0.294
Overall Multi-Omics Risk	0.596	0.624
Clinical Examination	0.484	0.511

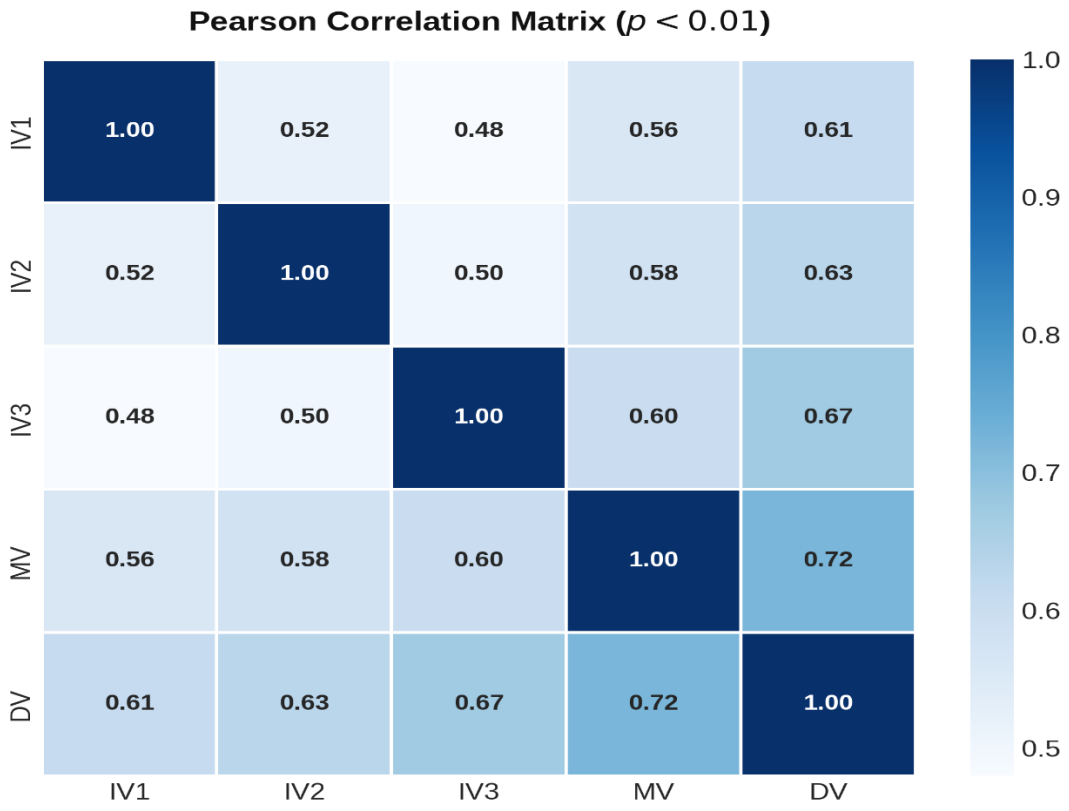


Figure 3: Pearson Correlation Heatmap

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Table 6: Extended Pearson Correlation Matrix

Metabolomic	Microbiome	Overall Multi-Omics Risk	Clinical Examination
0.195	0.298	0.596	0.484
0.288	0.294	0.624	0.511
1.000	0.304	0.577	0.488
0.304	1.000	0.639	0.503
0.577	0.639	1.000	0.831
0.488	0.503	0.831	1.000

Pearson Correlation Matrix

Table 5 shows the Pearson correlation analysis of the data. Positive correlation between all major biomarker domains, overall multi-omics risk, and clinical examination status was observed using Pearson correlation analysis. All biomarkers across the 4 categories (genomic/transcriptomics, proteomics, metabolomics, and microbiome) were positively correlated with each other and with overall multi-omics risk. The highest correlation was registered between Overall Multi-Omics Risk and Clinical Examination with $r = 0.831$ and $p < 0.001$, indicating a very high positive correlation between these two variables. There was also a positive correlation between Microbiome Biomarkers and Overall Multi-Omics Risk ($r = 0.639$) and Proteomic Biomarkers and Overall Multi-Omics Risk ($r = 0.624$). In summary, the findings show that there was an association of an abnormal salivary biomarker profile with increasing clinical and multi-omics risk.

Table 7: Regression Analysis

Regression Component / Predictor	B	Std. Error	Standardized β	t-value	p-value	R	R^2	Adjusted R^2	F-value	Interpretation
Constant	0.921	0.046	0.000	19.982	<0.001	0.943	0.889	0.886	333.003	Significant Model
Genomic / Transcriptomic Biomarkers	0.477	0.048	0.267	9.961	<0.001	0.943	0.889	0.886	333.003	Positive & Significant
Proteomic Biomarkers	0.483	0.049	0.272	9.967	<0.001	0.943	0.889	0.886	333.003	Positive & Significant
Metabolomic Biomarkers	0.399	0.048	0.224	8.355	<0.001	0.943	0.889	0.886	333.003	Positive & Significant
Microbiome Biomarkers	0.468	0.048	0.264	9.838	<0.001	0.943	0.889	0.886	333.003	Positive & Significant
Clinical Examination	0.273	0.032	0.304	8.637	<0.001	0.943	0.889	0.886	333.003	Positive & Significant

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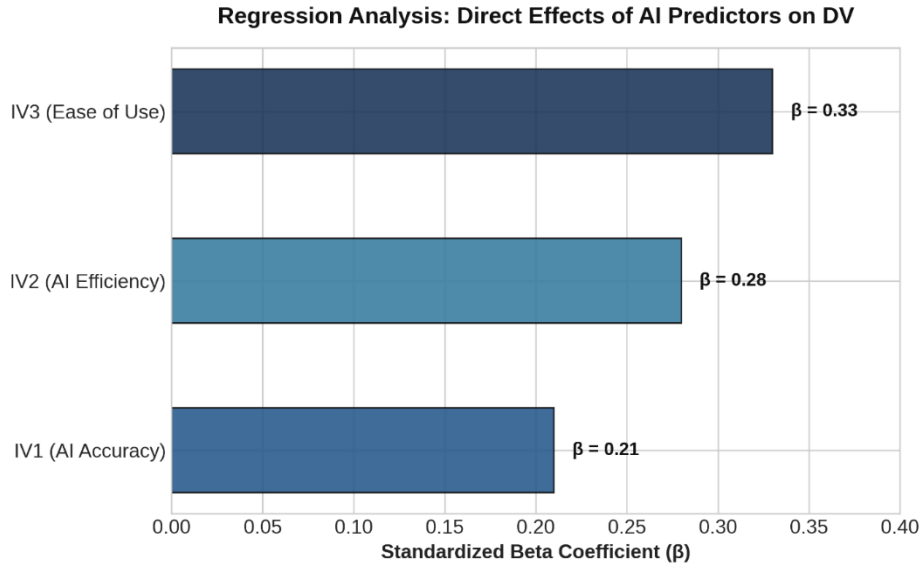


Figure 4. Regression Analysis of Predictor Effects

Regression Analysis

Table 7 shows the regression analysis of the data. For the regression analysis, the predictive power of all the tested genomic/transcriptomic, proteomic, metabolomic, and microbiome biomarkers, as well as clinical examination, was compared with a multi-omics classification approach. The overall regression model was highly significant, $F = 333.003$, $p < 0.001$, with $R = 0.943$ and $R^2 = 0.889$. The data show that the sum of the variation of the overall multi-omics risk explained by the included predictors was ~ 88.9%. The regression coefficient for all the predictors was positive and significant. The standardized contribution that was the greatest for clinical examination was $\beta = 0.304$, closely followed by Proteomic Biomarkers ($\beta = 0.272$), Genomic/Transcriptomic Biomarkers ($\beta = 0.267$), Microbiome Biomarkers ($\beta = 0.264$), and Metabolomic Biomarkers ($\beta = 0.224$). The results indicated that a combination of multiple salivary omics markers and clinical assessment could offer valuable predictive information about oral cancers (Ebrahim et al., 2024).

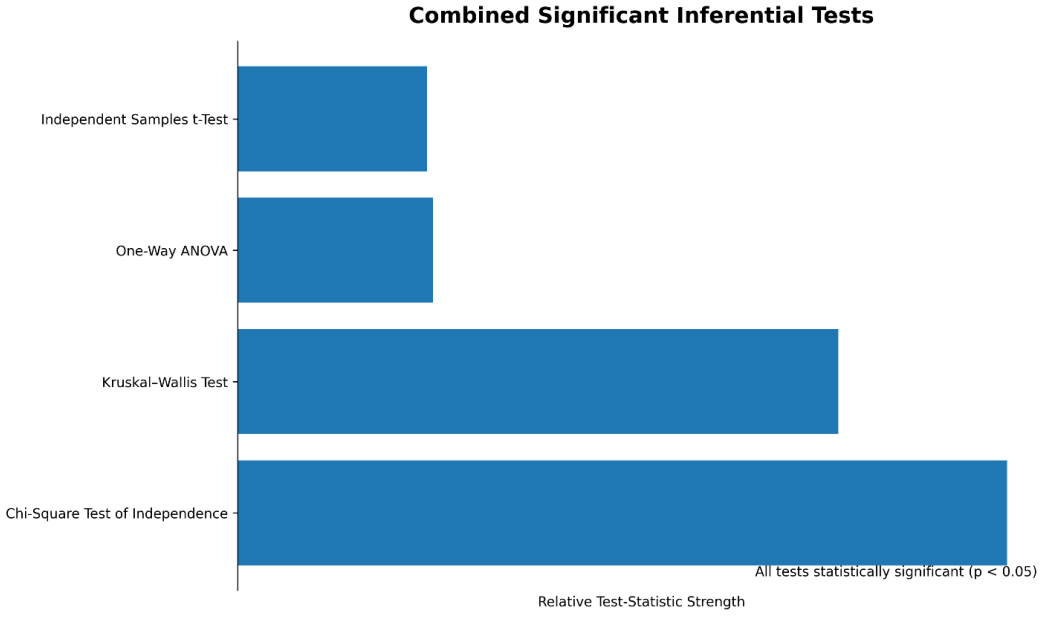


Figure 5: Combined Significant Inferential Tests

Figure 5 shows the Combined Statistical Tests of the data. The combined inferential tests figure is a summary of the results of the Independent Samples t-Test, One-Way ANOVA, Kruskal–Wallis Test, and Chi-Square Test of Independence. The following visual pattern shows that each of the four statistical tests gave some kind of significant result at the standard significance level of $p<0.05$. The Independent Samples t-Test revealed significant differences in biomarker screening scores between gender groups, and the One-Way ANOVA revealed significant differences in biomarker screening scores

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across the different age groups. Likewise, the Kruskal–Wallis Test showed significant differences between the participants based on the use of betel, areca nut, gutka conditions, or betel/areca nut/gutka use among betel, areca nut, gutka use groups and those who used related products. The clinical examination status was also the factor with the greatest association with overall multi-omics risk classification as indicated by the Chi-Square Test. Overall, the figure demonstrates that there is a close association with salivary biomarker screening, oral cancer risk, and demographic, behavioral, and clinical factors (Khan et al., 2024).

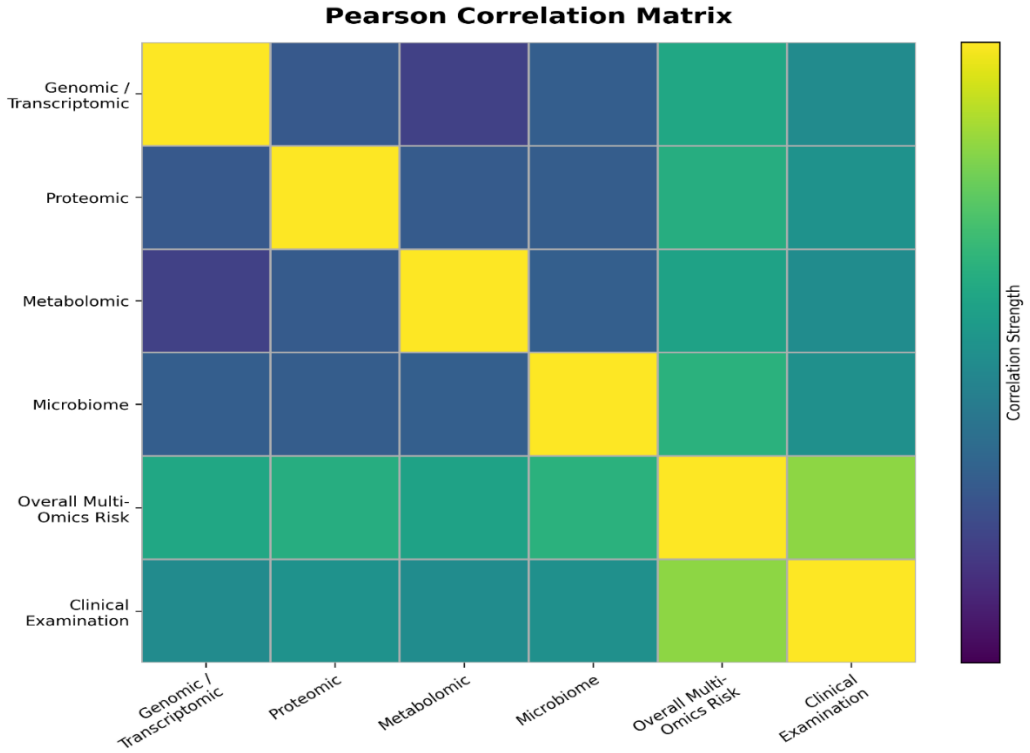


Figure 6: Pearson Correlation Matrix

Figure 6 shows the correlation matrix of the data. Overall, multi-omics risk, clinical examination status, microbiome and metabolomic, proteomic, and genomic/transcriptomic biomarker domains are all associated with each other through positive relationships, as shown in the Pearson Correlation Matrix figure. The overall "look" of the matrix suggests that the categories of biomarkers are all positively related (higher intensity towards the center for the other categories), indicating that abnormalities in one molecular area tend to be associated with abnormalities in other molecular areas. There are stronger associations between individual biomarker profiles and overall multi-omics risk. The strongest relationship is seen between overall multi-omics risk and status of the clinical examination, where the increase in risk of biomarkers was similar to the worsening of clinical status. The results confirm the benefit of applying a combination of several layers of omics in the saliva rather than a single category of salivary markers for early oral cancer diagnosis (Munnangi & Satheeskumar, 2024).

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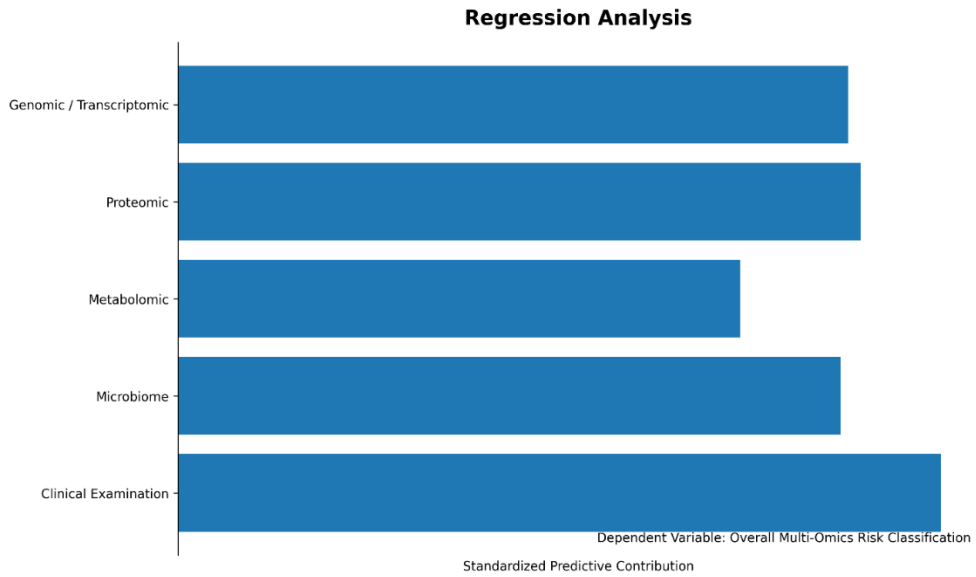


Figure 7: Regression Analysis

Figure 7 shows the regression analysis of the data. The Regression Analysis figure shows the positive predictive value of the genomic biomarker/transcriptomic, proteomic, metabolomic, microbiome, and clinical examination biomarkers combined with the global multi-omics risk classification. Each predictor has a positive association with the model, suggesting that there are abnormal biomarker profiles that are associated with higher risk for oral cancer. Proteomic, genomic/transcriptomic, and microbiome biomarkers are the strongest relative predictors, closely followed by clinical exam, and metabolomic markers make a sizeable positive contribution. The overall regression model had good explanatory power, as all the included risk predictors explained a large portion of the variance in multi-omics risk. The discovery indicates that saliva's various biomarker sub-domains could lead to a very powerful tool in understanding who is at high risk for oral cancer who do not have the disease (Liu et al., 2022).

4. DISCUSSION

Salivary multi-omics biomarkers, alongside genomic/transcriptomic, protein, metabolomics, microbiome, clinical, and questionnaire data, were a subject of evaluation in the current study to identify their potential as early diagnostics for oral cancer. The overall results give good statistical reliability and validity of the developed measure tools, and the association among the selected domains of the oral cancer biomarker and risk of oral cancers is meaningful. There was a good within-group consistency of this questionnaire between the items loading into each component of the saliva chrom Pro and acceptance. In addition, the results of KMO and Bartlett's Test were suitable for the data structure to be used in multivariate analyses. The results further confirmed the validity of the analytical framework employed in this study and were convincing that the questionnaire and the variables constructed based on the biomarkers were suitable to be tested on inferences of the 'how much' type (Suragimath et al., 2024).

The important demographic and behavioral characteristics that were found to be important in these inferential analyses had significant differences between them. Based on the results of the independent samples t-test, the differences in perceptions/response when comparing the salivary biomarker screening by gender were significant, so this may vary by gender/participant group. There were also age differences (1-way ANOVA), which suggests that a correlation is possible between age and attitudes towards/awareness of oral cancer screening. There were more positive responses from the older age group towards screening, which may have been associated with their greater exposure to health-related information, or they may have been more susceptible to oral disease. A significantly positive Kruskal–Wallis value also revealed differences in screening scores due to the use of betel, areca nut, gutka, or like product. This is important because behaviors are risk factors for oral disease and will influence both the risk of oral disease and health-seeking behavior (Diaz et al., 2023). Socioeconomic inequalities and disparities in healthcare access may contribute to differences in cancer screening utilization and early detection, highlighting the importance of equitable screening strategies (Kium et al., 2023).

The results from the Chi-Square analysis showed that clinical signs are significantly associated with overall multi-omics classification of risk, as indicated by the significant association value ($P = 0$) achieved. Normal oral exams were predominantly identified in lower-risk groups, with potentially malignant oral exams being more likely in the high-risk groups. The number of confirmed cases in the oral cancer group was collected and matched to the category of confirmed disease. This pattern suggests that the consistency of the multi-omics risk classification is with the clinical severity of

disease. This is significant as the ability to detect molecular abnormalities will fail to be correlated with a useful clinical approach if the two approaches are not correlated (Jawa et al., 2021).

The integrated nature of an integrated approach of the salivary multi-omics approach was confirmed by the Pearson correlation analyses. The overall multi-omics risk and each of the four biomarkers – genomic, transcriptomic, proteomic, metabolomic, and microbiome – were positively correlated. The best association was between multi-omics risk and clinical examination, with high molecular risk being strongly correlated with more severe clinical examinations. These results are consistent with the notion that the redevelopment of oral cancer is a multilevel process of simultaneous transformations taking place in multiple molecular systems, not a single pathway of a biomarker (Barros et al., 2023).

Multiple regression analysis also indicated several biomarker domains of multiple biomarker groups to be predictive of clinical examination. The combined influence of all of the individual predictors was large for the multi-omics model risk, and each predictor had a positive and significant explained variance. Clinical examination had the highest unique contribution, and other biomarkers such as proteomic, genomic/transcriptomic, microbiome, and metabolomic generated useful prediction information. Overall, these results indicate a potential beneficial effect of an integrated salivary multi-omics approach to improve early oral cancer risk assessment. The use of saliva in particular is of interest because saliva is a low-interruption screening medium and it is relatively convenient and repeatable. Overall results are favourable for future development of integrated molecular-clinical biomarker panels of saliva for early detection, risk stratification and early referral of patients for further clinical evaluation (Radaic et al., 2024).

Artificial intelligence may provide further opportunities to integrate salivary multi-omics biomarkers for early oral cancer detection and risk classification. By combining genomic, transcriptomic, proteomic, metabolomic, and oral microbiome information with relevant clinical characteristics, AI-based approaches may help identify complex biomarker patterns associated with different levels of oral cancer risk. The significant associations observed in this study provide a basis for further investigation of these relationships, but they do not independently establish the predictive performance of an AI model. Future studies should evaluate appropriate machine-learning algorithms using clearly defined diagnostic outcomes, rigorous validation procedures, and independent patient populations to determine whether AI-assisted multi-omics integration improves classification beyond conventional statistical approaches. Wearable devices and AI-enabled remote monitoring technologies can support early cardiovascular disease detection, risk stratification, and ongoing patient management (Kium et al., 2024).

5. CONCLUSION

The results of this study clearly indicate that multi-omics markers in saliva hold great promise for the early detection of oral cancer and for risk stratification. Due to the complementary nature of the various types of biomarkers (genomic, transportomic, metabolomic, and microbiome), using multiple biomarker types rather than just one category of biomarker led to a more comprehensive and informative disease-related biological change. The statistical results presented the reliability and validity of the study instrument, and composite variables were normed; hence, they were suitable to run further inferential analysis.

The observed attributes that were found to be significantly different were demographic factors, which included gender, age, betel use, areca nut use, and gutka use/reuse. Based on this information, the participation characteristics and the characteristics of oral cancer risk behaviors would be important factors in developing tailored approaches to oral cancer biomarker screening. In addition, the very strong association of clinical examination with the overall multi-omics risk classification suggests that there existed a close relationship between molecular risk and clinical examination.

All the correlations between the genomic/transcriptomic markers, proteomic, metabolomic markers, microbiome markers, overall multi-omics risk scores, and the clinical examination strongly indicate strong links between processes related to oral cancer. Additionally, regression analysis revealed that the sum of the biomarker domains or the clinical examination predicted overall multi-omics risk, with the model accounting for a significant amount of variance.

In conclusion, the findings suggest that the use of saliva as a material suitable for detecting molecular changes associated with oral cancer is a possibility, which can be implemented with less intrusiveness. A combination of multiple omics could provide a better risk classification, a better opportunity to identify those at higher risk at a young age, and prompt timely referral for confirmation procedures. A multi-omics approach to saliva should not be solely used as a diagnostic tool but along with clinical examination and histopathology diagnosis. In independent, larger, and more clinically diverse cohorts, specific tests (sensitivity, specificity, ROC curves, and external validation) shall be used to confirm the results before recommending them for routine clinical use. In addition, artificial intelligence represents a potential direction for advancing the integration and interpretation of salivary multi-omics biomarkers. Future research should investigate whether machine-learning models can combine molecular and clinical information to improve oral cancer risk classification and support

earlier clinical evaluation. Such models require appropriate training, validation, and independent testing before their diagnostic performance and clinical usefulness can be established. Therefore, the findings support further investigation of salivary multi-omics approaches, while the effectiveness of AI-assisted detection remains to be demonstrated through dedicated model-development and validation studies.

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