

Research Article

Association of Tobacco Use with Severity of Oral Submucous Fibrosis and Risk of Malignant Transformation: A Cross-Sectional Study

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ABSTRACT

Objective: To determine the association of tobacco and areca nut consumption patterns with the clinical severity of oral submucous fibrosis (OSMF) and histopathological indicators of malignant potential.

Study Design: Analytical cross-sectional study.

Place and Duration of Study: Tertiary care hospital, Lahore, Pakistan, from 1 January 2026 to 30 June 2026.

Methodology: A total of 120 patients with clinically diagnosed OSMF were enrolled through consecutive sampling. Tobacco and areca nut consumption patterns, habit duration, daily frequency, cumulative quid-years, clinical stage, interincisal distance, and histopathological findings were assessed. Malignant potential was defined as moderate or severe epithelial dysplasia or oral squamous cell carcinoma (OSCC). Associations were evaluated using Spearman correlation, ordinal logistic regression, and Firth penalized logistic regression.

Results: The mean age was 33.8 ± 8.7 years, and 79 (65.8%) patients were male. Smokeless tobacco was the most common exposure (42.5%), while 44 (36.7%) patients had stage IV disease. Among 116 habit users, cumulative quid-years showed a strong positive correlation with OSMF stage ($p = 0.80$, $p < 0.001$), whereas interincisal distance was inversely correlated ($p = -0.94$, $p < 0.001$). Habit duration (adjusted OR 1.48, 95% CI 1.30-1.69) and daily frequency (adjusted OR 2.08, 95% CI 1.65-2.63) were significantly associated with advanced disease (both $p < 0.001$). Histopathological malignant potential was identified in 14 (11.7%) patients, including three with OSCC. Greater cumulative exposure was associated with malignant potential (OR 1.20 per 10 quid-years, 95% CI 1.04-1.39; $p = 0.011$).

Conclusion: Greater cumulative tobacco and areca nut exposure was significantly associated with advanced OSMF and histopathological malignant potential. Detailed habit assessment, clinical staging, and appropriate histopathological evaluation may support early identification of high-risk patients.

Keywords: Oral Submucous Fibrosis, Smokeless Tobacco, Areca Nut, Epithelial Dysplasia, Oral Squamous Cell Carcinoma.

INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic, progressive, and potentially malignant disorder characterized by persistent inflammation,

excessive collagen deposition, and progressive fibrosis of the oral mucosa. The condition primarily affects the buccal mucosa, although the tongue, soft palate, and oropharynx may

also be involved. Clinically, OSMF manifests as mucosal blanching, burning sensation, palpable fibrous bands, restricted mouth opening, and impaired oral functions, including mastication, swallowing, and speech. Its irreversible fibrotic changes, functional consequences, and potential for malignant transformation represent considerable challenges for oral healthcare, particularly in South Asian populations [1].

The development of OSMF is strongly associated with prolonged areca nut consumption, particularly when combined with tobacco-containing products such as gutka, betel quid, and other commercially prepared chewing mixtures. Arecoline and other areca-derived alkaloids promote fibroblast activation, abnormal collagen synthesis, reduced collagen degradation, and extracellular matrix accumulation. Tobacco exposure may contribute additional carcinogenic effects through oxidative stress, DNA damage, chronic inflammation, and epithelial alterations. These processes contribute to progressive mucosal fibrosis and may facilitate the development of epithelial dysplasia and oral squamous cell carcinoma (OSCC) [2].

The magnitude of this public health problem is substantial in regions where areca nut chewing is culturally and socially prevalent. Yuwanati et al. conducted a systematic review and meta-analysis involving 53,213 areca nut chewers, among whom 929 cases of OSMF were identified. The pooled prevalence was approximately 5% (95% CI 3–8%), highlighting the considerable disease burden among exposed individuals [3]. The carcinogenic implications of these habits extend beyond fibrosis. Rungay et al. estimated that approximately 120,200 oral cancer cases worldwide in 2022 were attributable to smokeless tobacco or areca nut consumption, representing 30.8% of global oral cancer cases. South-central Asia had a particularly high attributable burden, emphasizing the importance of exposure prevention and early identification of oral potentially malignant disorders [4].

The severity of OSMF is influenced by multiple factors, including the type of chewing habit, duration of exposure, daily consumption frequency, and cumulative exposure. Progressive disease is generally accompanied by increased mucosal rigidity and reduced interincisal distance, which is an important clinical indicator of functional impairment. Warnakulasuriya et al. reported a pooled

adjusted relative risk of 7.9 (95% CI 7.1–8.7) for oral cancer associated with areca nut chewing, with evidence of increasing risk according to daily consumption and duration of use. These findings suggest that quantifying cumulative exposure may provide clinically relevant information beyond simply categorizing patients as tobacco or areca nut users [5].

Malignant transformation remains one of the most serious consequences of OSMF. Histopathological examination frequently demonstrates epithelial atrophy or hyperplasia, subepithelial fibrosis, chronic inflammatory infiltration, and varying degrees of epithelial dysplasia. Kujan et al., in a systematic review and meta-analysis of 6,337 patients, reported a pooled malignant transformation proportion of 4.2% (95% CI 2.7–5.6%), with an annual transformation rate of 0.73%. The authors also identified epithelial dysplasia as an important indicator of increased malignant potential, emphasizing the clinical significance of histopathological assessment and surveillance [6].

Accurate assessment of OSMF requires integration of clinical staging, oral functional examination, detailed exposure history, and histopathological findings. Contemporary clinical guidelines emphasize systematic documentation of chewing habits, measurement of mouth opening, evaluation of suspicious mucosal lesions, and appropriate biopsy to identify epithelial dysplasia or invasive malignancy. Identifying patients with substantial cumulative exposure and advanced clinical disease may facilitate targeted surveillance, early intervention, and individualized risk assessment [7].

In Pakistan, the widespread consumption of areca nut, gutka, naswar, and other smokeless tobacco preparations represents a major oral health concern. Hashmi et al. investigated areca nut exposure and clinicopathological characteristics among patients with OSCC in a Pakistani population, highlighting the relevance of these habits to the regional burden of oral malignancy [8]. However, locally applicable evidence integrating habit duration, consumption frequency, cumulative exposure, clinical OSMF staging, and histopathological malignant potential remains limited. Therefore, the present study aimed to determine the association of tobacco and areca nut use with OSMF severity and histopathological malignant potential, with particular emphasis on exposure intensity, advanced clinical stages, epithelial

dysplasia, and concurrent malignancy in a Pakistani patient population.

METHODOLOGY

This analytical cross-sectional study was conducted at tertiary care hospital in Lahore, Pakistan, over six months, from 1 January 2026 to 30 June 2026. The study aimed to evaluate the association of tobacco and areca nut consumption patterns with the clinical severity of oral submucous fibrosis (OSMF) and histopathological indicators of malignant potential. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Ethical approval was obtained from the Institutional Review Board/Ethical Review Committee [approval number to be inserted], and written informed consent was obtained from all participants before enrollment.

A total of 120 patients clinically diagnosed with OSMF were enrolled through non-probability consecutive sampling. The sample size was estimated using the single-population proportion formula, $n = Z^2 p(1-p)/d^2$, assuming a prevalence of 11.7%, a 95% confidence level, and a 6% margin of error. The calculated sample size was approximately 111 patients, which was increased to 120 to account for potentially incomplete records. Patients with a confirmed clinical diagnosis of OSMF, complete habit histories, and documented clinical staging were eligible. Patients with other oral mucosal or systemic fibrosing disorders that could interfere with clinical assessment, including oral lichen planus and systemic sclerosis, were excluded. Patients with a history of head and neck radiotherapy or chemotherapy and those with oral malignancies unrelated to OSMF-affected mucosa were also excluded.

Data were collected using a structured clinical assessment form documenting age, sex, educational status, socioeconomic status, alcohol consumption, concomitant leukoplakia, and tobacco or areca nut exposure. Habit patterns were categorized as areca nut only, smokeless tobacco, smoking, combined smoking and smokeless tobacco use, or no reported tobacco or areca nut use. Habit duration was recorded in years, daily consumption frequency was documented, and cumulative exposure was expressed as quid-years. Clinical severity was assessed using a four-stage OSMF classification (stages I–IV).

Maximum interincisal distance was measured in millimeters to assess restriction of mouth opening. Symptom duration was recorded in months. Histopathological findings were classified according to epithelial dysplasia severity as absent, mild, moderate, or severe, and the presence of oral squamous cell carcinoma (OSCC) was documented. The composite outcome, termed malignant potential, was defined as the presence of moderate or severe epithelial dysplasia or OSCC. This outcome represented histopathological abnormalities identified at assessment rather than prospectively observed malignant transformation.

Of the 120 enrolled patients, 116 reported tobacco and/or areca nut consumption and constituted the primary exposure-analysis population. Four patients without either habit were described separately and included in sensitivity analyses, with exposure duration and frequency assigned values of zero. Data completeness was assessed before analysis. Continuous variables were evaluated for normality using the Shapiro–Wilk test and graphical examination of Q–Q plots. Normally distributed variables were summarized as mean $\pm$ standard deviation, whereas skewed variables were reported as median and interquartile range. Categorical variables were presented as frequencies and percentages.

Associations between habit duration, daily frequency, cumulative quid-years, OSMF stage, and interincisal distance were assessed using Spearman rank correlation coefficients, with 95% confidence intervals estimated through 5,000 bootstrap resamples. Differences in continuous variables across OSMF stages and habit categories were examined using the Kruskal–Wallis test. Pairwise comparisons were performed using Mann–Whitney U tests with permutation-based inference where appropriate. The association between habit type and clinical stage was additionally evaluated using a permutation-based chi-square test. Multivariable proportional-odds ordinal logistic regression was performed to examine the independent associations of habit duration and daily frequency with OSMF stage, adjusting for age and sex. Additional models incorporated symptom duration and habit type. Associations with interincisal distance were assessed using linear regression with heteroscedasticity-robust standard errors. Regression estimates were presented as odds ratios (ORs) or regression coefficients with corresponding 95% confidence intervals.

Patients with and without malignant potential were compared using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables. The discriminatory ability of continuous exposure variables was evaluated using the area under the receiver operating characteristic curve (AUC), with bootstrap 95% confidence intervals. Trends in malignant potential across OSMF stages were assessed using the Cochran–Armitage trend test. Because only 14 patients met the composite outcome definition, Firth's penalized logistic regression was applied using one predictor per model to reduce small-sample estimation bias. Three prespecified hypotheses—cumulative quid-years and OSMF stage, habit type and OSMF stage, and habit duration and malignant potential—were evaluated with Holm adjustment for multiple comparisons. All remaining analyses were considered exploratory. Statistical analyses were performed using R software, version

4.6.1. All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant, subject to the specified multiplicity adjustments.

RESULTS

The study included 120 patients with oral submucous fibrosis (OSMF), with a mean age of 33.8 ± 8.7 years; 79 (65.8%) were male. Of these, 116 (96.7%) reported areca nut and/or tobacco use and constituted the primary exposure-analysis population. Four participants reported neither exposure, were all classified as stage I, and had no composite malignant-potential outcome. Smokeless tobacco was the most frequent habit category (51/120, 42.5%). Overall, 44 patients (36.7%) had stage IV disease, and 14 (11.7%; reported 95% CI 7.1–18.6%) met the composite outcome definition. Three patients (2.5%) had prevalent oral squamous cell carcinoma (OSCC), all in the smokeless-tobacco group (Table 1).

Table 1. Baseline Demographic, Exposure and Clinical Characteristics (N = 120)

Characteristic	Value
Age, years; mean $\pm$ SD	33.8 $\pm$ 8.7
Male / female	79 (65.8%) / 41 (34.2%)
Education: none / primary / secondary / higher	13 (10.8%) / 29 (24.2%) / 55 (45.8%) / 23 (19.2%)
Socioeconomic status: low / middle / high	43 (35.8%) / 50 (41.7%) / 27 (22.5%)
Areca nut only	25 (20.8%)
Smokeless tobacco	51 (42.5%)
Smoking	14 (11.7%)
Mixed use	26 (21.7%)
Neither areca nut nor tobacco	4 (3.3%)
Alcohol use	10 (8.3%)
Concomitant leukoplakia	15 (12.5%)
OSMF stage I / II / III / IV	35 (29.2%) / 27 (22.5%) / 14 (11.7%) / 44 (36.7%)
Epithelial dysplasia: none / mild / moderate / severe	88 (73.3%) / 19 (15.8%) / 11 (9.2%) / 2 (1.7%)
Prevalent OSCC	3 (2.5%)
Composite malignant-potential outcome	14 (11.7%)
Habit duration, years; median (IQR), n = 116	9.0 (6.0–12.0)
Daily habit frequency; median (IQR), n = 116	5.0 (3.0–7.0)
Cumulative quid-years; median (IQR), n = 116	40.0 (20.0–70.0)
Symptom duration, months; median (IQR), N = 120	19.0 (9.5–26.0)
Interincisal distance, mm; median (IQR), N = 120	25.5 (14.0–34.0)

Data are n (%) unless indicated otherwise. Composite outcome as defined in the source manuscript; see verification notes on endpoint components.

Among the 116 habit users, disease severity increased with habit duration, daily frequency

and cumulative quid-years. Median habit duration rose from 6.0 years (IQR 3.5–8.5) in

stage I to 12.0 years (IQR 9.0–14.0) in stage IV. Corresponding median cumulative exposure increased from 15.0 to 75.0 quid-years, whereas median interincisal distance decreased from 38.0 to 13.0 mm. Cumulative quid-years had the strongest reported exposure correlation

with stage (Spearman $\rho = 0.80$, 95% CI 0.71–0.86), followed by daily frequency ($\rho = 0.60$) and habit duration ($\rho = 0.59$). Interincisal distance correlated inversely with stage ($\rho = -0.94$). Age was not associated with stage ($\rho = -0.08$, $p = 0.323$) (Table 2; Figure 1).

Table 2. Exposure and Clinical Characteristics by OSMF Stage Among Habit Users (N = 116)

Variable	I (n=31)	II (n=27)	III (n=14)	IV (n=44)	ρ (95% CI)	p
Duration (years)	6.0 (3.5–8.5)	8.0 (5.0–8.5)	9.0 (8.0–10.0)	12.0 (9.0–14.0)	0.59 (0.44–0.71)	<0.001
Daily frequency	3.0 (2.0–4.5)	5.0 (3.5–5.5)	5.0 (4.0–6.0)	7.0 (5.0–8.0)	0.60 (0.46–0.71)	<0.001
Quid-years	15.0 (9.0–21.5)	35.0 (19.5–41.0)	43.5 (39.2–54.8)	75.0 (56.0–96.0)	0.80 (0.71–0.86)	<0.001
Symptom duration (months)	7.0 (2.0–11.0)	16.0 (10.0–18.5)	23.0 (21.2–24.0)	27.5 (24.8–33.2)	0.86 (0.81–0.90)	<0.001
Interincisal distance (mm)	38.0 (34.5–40.0)	29.0 (27.5–30.5)	20.5 (20.0–22.8)	13.0 (11.0–15.0)	–0.94 (–0.95 to –0.92)	<0.001
Age (years)	33.0 (28.5–38.0)	33.0 (28.0–38.0)	35.5 (31.5–41.2)	32.0 (25.0–38.2)	–0.08 (–0.26–0.10)	0.323

Cells by stage show median (IQR); ρ is Spearman correlation with OSMF stage. Reported p-values are Kruskal–Wallis across stages. Figures show stage medians, not patient-level distributions.

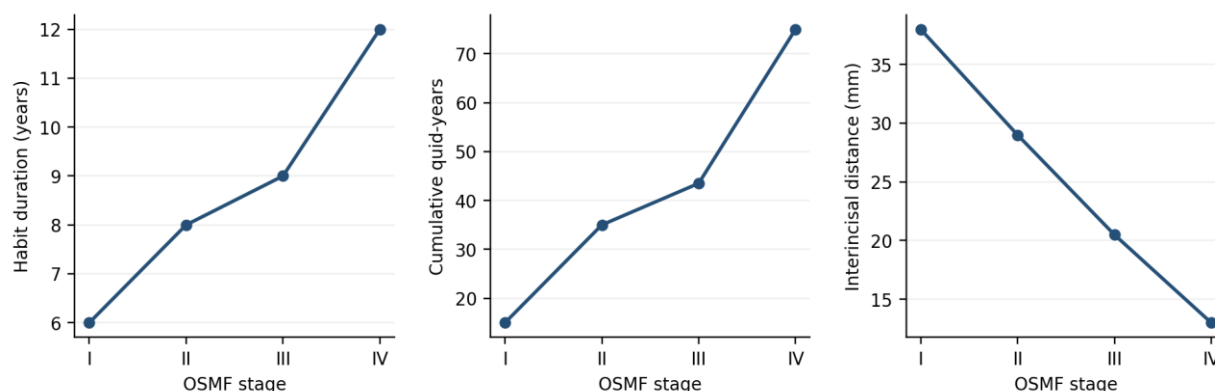


Figure 1. Reported Median Habit Duration, Cumulative Quid-Years and Interincisal Distance by OSMF Stage. Lines Connect Group Medians for Visualization and Do Not Represent Longitudinal Change.

Stage distribution varied across habit categories (Kruskal–Wallis $p = 0.004$). Stage IV was observed in 14/26 (53.8%) mixed users, 22/51 (43.1%) smokeless-tobacco users, 4/14 (28.6%) smokers and 4/25 (16.0%) areca-nut-only users. Mixed users also reported higher daily frequency (median 6.5 uses/day), and habit duration and frequency differed across

exposure categories ($p = 0.013$ and 0.005 , respectively). Although the unadjusted association between habit type and stage was present, habit-type contrasts were not statistically significant after adjustment for duration and daily frequency (Table 3; Figure 2).

Table 3. OSMF Stage Distribution and Exposure Characteristics by Habit Category (N = 116)

Category	n	Stage I	Stage II	Stage III	Stage IV	Duration (years)	Frequency/day	Mouth opening (mm)
Areca nut only	25	11 (44%)	6 (24%)	4 (16%)	4 (16%)	8.0 (4.0–9.0)	4.0 (3.0–5.0)	30.0 (23.0–36.0)
Smokeless tobacco	51	11 (22%)	13 (25%)	5 (10%)	22 (43%)	9.0 (8.0–12.5)	5.0 (3.0–7.0)	21.0 (14.0–33.0)
Smoking	14	7 (50%)	2 (14%)	1 (7%)	4 (29%)	7.0 (3.5–10.8)	5.0 (2.2–7.0)	28.0 (15.8–38.0)
Mixed	26	2 (8%)	6 (23%)	4 (15%)	14 (54%)	9.0 (7.0–12.8)	6.5 (5.0–8.0)	15.5 (13.2–27.5)

Stage cells are n (%) within habit category; continuous variables are median (IQR). Reported Kruskal–Wallis p-values: stage 0.004; duration 0.013; frequency 0.005; mouth opening 0.045.

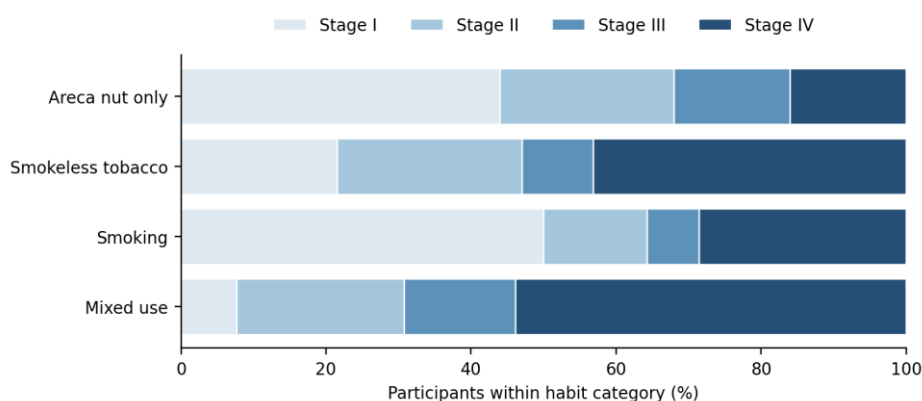


Figure 2. Percentage Distribution of OSMF Stage by Exposure Category (N = 116). Percentages were Calculated from the Reported Stage Counts.

The composite malignant-potential outcome was recorded in 14 of 116 habit users: 8/51 (15.7%) smokeless-tobacco users, 3/26 (11.5%) mixed users, 2/25 (8.0%) areca-nut-only users and 1/14 (7.1%) smokers. Habit-category differences were not statistically significant (reported permutation $p = 0.75$). Compared with those without the composite outcome, affected participants had longer habit duration (median 11.0 versus 8.0 years; $p =$

0.011), greater cumulative exposure (64.5 versus 36.0 quid-years; $p = 0.001$) and greater daily frequency (6.0 versus 5.0 uses; $p = 0.042$). Cumulative quid-years showed an AUC of 0.77 (95% CI 0.67–0.86) for distinguishing participants with versus without this cross-sectional composite outcome. The outcome became more frequent across stages, reaching 9/44 (20.5%) in stage IV (Cochran–Armitage trend $p = 0.011$) (Table 4; Figure 3).

Table 4. Exposure and Clinical Features by Composite Malignant-Potential Outcome Among Habit Users (N = 116)

Characteristic	Absent (n=102)	Present (n=14)	p	AUC (95% CI)
Habit duration (years)	8.0 (5.2–12.0)	11.0 (9.2–11.8)	0.011	0.71 (0.61–0.81)
Daily frequency	5.0 (3.0–7.0)	6.0 (5.0–8.0)	0.042	0.67 (0.54–0.79)
Quid-years	36.0 (18.0–59.0)	64.5 (54.2–90.2)	0.001	0.77 (0.67–0.86)
Symptom duration (months)	18.5 (10.0–25.0)	25.0 (19.0–29.5)	0.046	0.66 (0.52–0.79)
Age (years)	33.0 (28.0–39.0)	31.0 (27.2–41.8)	0.953	0.49 (0.33–0.66)

Leukoplakia	11 (10.8%)	3 (21.4%)	0.373	—
Alcohol use	8 (7.8%)	2 (14.3%)	0.346	—
Male sex	63 (61.8%)	12 (85.7%)	0.134	—
OSMF stage IV	35 (34.3%)	9 (64.3%)	0.041	—

Continuous characteristics are median (IQR), compared with Mann–Whitney U tests; binary characteristics are n (%), compared with Fisher exact tests. AUC is the reported rank-discrimination statistic, not prospectively validated prediction performance.

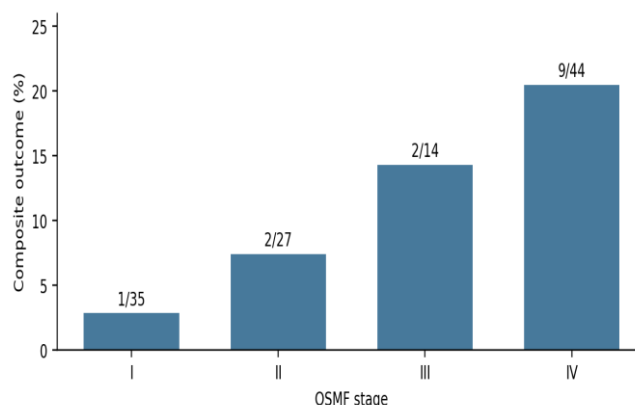


Figure 3. Prevalence of the Composite Malignant-Potential Outcome by OSMF Stage Among All 120 Participants. Numerators/Denominators Appear Above the Bars; These are Cross-Sectional Prevalences, Not Malignant-Transformation Rates.

In proportional-odds ordinal regression adjusted for age and sex, each additional year of habit duration was associated with higher odds of a more advanced OSMF stage (OR 1.48, 95% CI 1.30–1.69; $p < 0.001$), as was each additional reported daily use (OR 2.08, 95% CI 1.65–2.63; $p < 0.001$). Both associations persisted after additional adjustment for symptom duration (duration OR 1.40, 95% CI 1.18–1.65; frequency OR 1.87, 95% CI 1.41–

2.49). In single-predictor Firth penalized logistic models addressing the 14 composite-outcome events, the odds increased with habit duration (OR 1.19 per year, 95% CI 1.04–1.39; $p = 0.013$) and cumulative exposure (OR 1.20 per 10 quid-years, 95% CI 1.04–1.39; $p = 0.011$), while daily frequency was borderline ($p = 0.052$). These estimates are exploratory and should not be interpreted as adjusted independent causal effects (Table 5).

Table 5. Reported Regression Associations Among Habit Users (N = 116)

Outcome / predictor	OR (95% CI)	p
Ordinal stage model: adjusted for age and sex		
Habit duration, per year	1.48 (1.30–1.69)	<0.001
Daily frequency, per use/day	2.08 (1.65–2.63)	<0.001
Age, per year	1.00 (0.96–1.06)	0.860
Male versus female	2.00 (0.88–4.57)	0.098
Ordinal stage model: with additional symptom duration		
Habit duration, per year	1.40 (1.18–1.65)	<0.001
Daily frequency, per use/day	1.87 (1.41–2.49)	<0.001
Symptom duration, per month	1.39 (1.25–1.54)	<0.001
Habit type (versus smokeless tobacco), duration/frequency adjusted		
Areca nut only	0.78 (0.27–2.24)	0.647
Mixed use	0.91 (0.31–2.63)	0.856
Smoking	0.42 (0.10–1.72)	0.227

Composite outcome: single-predictor Firth models (14 events)		
Habit duration, per year	1.19 (1.04–1.39)	0.013
Daily frequency, per use/day	1.25 (1.00–1.60)	0.052
Quid-years, per 10	1.20 (1.04–1.39)	0.011
Stage IV versus I–III	3.28 (1.09–10.81)	0.034
Leukoplakia, yes versus no	2.42 (0.55–8.75)	0.221

OR, odds ratio; CI, confidence interval. Stage odds ratios refer to greater ordinal stage; composite-outcome Firth models were fitted with one predictor per model, not simultaneously multivariable-adjusted.

DISCUSSION

The present study demonstrated a significant association between cumulative areca nut and tobacco exposure, clinical severity of OSMF, and histopathological malignant potential. Among 120 patients, the mean age was 33.8 ± 8.7 years, 65.8% were male, and 36.7% had stage IV disease. These findings are comparable to those of Deosthale et al., who evaluated 70 patients with OSMF and reported a mean age of 33.2 ± 12.66 years, male predominance of approximately 75%, and stage III disease in 62.86%. Their findings also demonstrated an association between prolonged adverse habits and advanced clinical disease [9].

In our study, habit duration, daily frequency, and cumulative quid-years were positively correlated with OSMF stage ($p = 0.59, 0.60$, and 0.80 , respectively; all $p < 0.001$). Median cumulative exposure increased from 15.0 quid-years in stage I to 75.0 in stage IV. These findings support a dose-dependent relationship between carcinogenic exposure and fibrotic progression. Jasim et al., in a meta-analysis involving 19,312 participants, reported a pooled odds ratio of 8.18 (95% CI 5.27–12.72) for the association between betel quid chewing and oral potentially malignant or malignant disorders [10]. Similarly, Ko et al. reported that severe betel-quid use disorder was associated with substantially greater oral cancer risk, with a reported risk estimate of 42.3, emphasizing the clinical relevance of exposure intensity [11]. A particularly important finding was the strong inverse correlation between interincisal distance and OSMF stage ($p = -0.94$, $p < 0.001$). Median mouth opening decreased from 38.0 mm in stage I to 13.0 mm in stage IV. Shete et al., in a retrospective study of 120 histopathologically confirmed OSMF cases, reported significantly reduced mouth opening

among patients with epithelial dysplasia ($p = 0.001$), supporting the clinical relevance of functional restriction when evaluating advanced disease [12].

Smokeless tobacco was the predominant exposure category (42.5%), while mixed users had the highest proportion of stage IV disease (53.8%), followed by smokeless-tobacco users (43.1%). However, differences between habit categories were no longer statistically significant after adjustment for habit duration and daily frequency. This suggests that exposure intensity may explain part of the crude association between habit type and clinical severity. The observed relationship is consistent with the broader dose-response evidence summarized by Warnakulasuriya et al., who identified increasing oral cancer risk with greater areca nut consumption and longer exposure duration [5].

The composite malignant-potential outcome was identified in 14 patients (11.7%), while 3 patients (2.5%) had prevalent OSCC. Nayanar et al. reported a pooled malignant transformation proportion of 5.5% among 5,428 OSMF patients [13]. Murthy et al. also confirmed the malignant potential of OSMF in their systematic review [14]. Importantly, these longitudinal transformation estimates are not directly comparable with our cross-sectional composite-outcome prevalence, which incorporates histopathological features and prevalent disease rather than incident malignancy.

Epithelial dysplasia was documented in 32 patients (26.7%), including 13 (10.8%) with moderate or severe dysplasia. Turton et al. emphasized the prognostic relevance of dysplasia assessment while acknowledging limitations in currently available biomarkers [15]. Ferraz et al. further demonstrated that binary histopathological grading may offer better discrimination of malignant progression than conventional multilevel classification [16]. Ramos-García et al. additionally identified p53 overexpression as a potentially useful marker for assessing malignant progression in oral potentially malignant disorders [17].

Cumulative exposure was associated with the composite outcome, with an AUC of 0.77 (95% CI 0.67–0.86). Each additional 10 quid-years was associated with increased odds of the outcome (OR 1.20, 95% CI 1.04–1.39). However, this discrimination estimate requires prospective validation before clinical prediction can be claimed. Jones et al. highlighted the limitations of current therapeutic evidence for OSMF [18], while More et al. emphasized the importance of comprehensive disease management [19]. Walsh et al. supported structured clinical assessment for identifying potentially malignant oral lesions [20], and Chhabra et al. emphasized habit cessation and ongoing surveillance [21].

The principal limitations include the cross-sectional design, modest sample size, self-reported exposure history, and only 14 composite-outcome events, which restricted multivariable analysis. Nevertheless, the findings suggest that cumulative tobacco and areca nut exposure, reduced mouth opening, and advanced clinical stage may help identify OSMF patients requiring closer histopathological evaluation and surveillance in Pakistani clinical settings.

CONCLUSION

Greater duration, frequency, and cumulative exposure to tobacco and areca nut were associated with increased OSMF severity, reduced mouth opening, and histopathological malignant potential. Cumulative exposure emerged as a particularly relevant indicator of disease severity. These findings support early habit cessation, comprehensive clinical assessment, and targeted histopathological surveillance in patients with advanced OSMF.

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