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Original Research Article

Clinical and Biochemical Correlates of Disease Severity in Oral Submucous Fibrosis: A Prospective Observational Study

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Conflict of interest: Nil

Abstract

Background: Oral submucous fibrosis is a chronic, progressive, and potentially malignant disorder associated with areca nut and related chewing habits. In addition to progressive fibrosis and functional restriction, patients may demonstrate measurable haematological and biochemical alterations.

Methods: This prospective observational study included 100 patients with oral submucous fibrosis managed in the Department of Otorhinolaryngology from December 2023 to January 2026. Clinical evaluation included symptom profile, site involvement, stage, and mouth opening. Laboratory assessment included complete blood count, erythrocyte sedimentation rate, serum protein, C-reactive protein, serum iron, and serum lactate dehydrogenase. Mouth opening was reassessed at 1 month, 3 months, and 6 months.

Results: The mean age was 33.05 ± 8.19 years, and 74.0% of patients were male. Stage III was the most common stage (31.0%). Baseline mouth opening declined progressively from Stage I to Stage IV. Increasing stage was associated with longer chewing duration and greater chewing amount per day. Haemoglobin, mean corpuscular volume, mean corpuscular Haemoglobin, platelet count, serum protein, and serum iron declined progressively with advancing stage, whereas total leukocyte count, erythrocyte sedimentation rate, C-reactive protein, and serum lactate dehydrogenase increased progressively.

Mouth opening showed strong positive correlation with Haemoglobin, mean corpuscular volume, mean corpuscular Haemoglobin, platelet count, serum protein, and serum iron, and strong negative correlation with age, complaint duration, chewing burden, total leukocyte count, erythrocyte sedimentation rate, C-reactive protein, and serum lactate dehydrogenase. Follow-up demonstrated progressive improvement in mouth opening, with greater improvement in earlier stages.

Conclusion: Oral submucous fibrosis showed a clear association between increasing clinical severity, greater habit burden, worsening functional limitation, and progressive haematological and biochemical derangement. Combined clinical and biochemical assessment may provide a broader estimate of disease burden and may assist severity assessment and follow-up.

Keywords: Oral submucous fibrosis; OSMF; areca nut; mouth opening; serum iron; lactate dehydrogenase.

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Introduction

Oral submucous fibrosis is a chronic, progressive disorder of the oral cavity characterized by juxta-epithelial inflammation followed by fibro-elastic changes in the lamina propria and deeper connective tissues, resulting in mucosal stiffness, fibrous band formation, and progressive restriction of mouth opening. [1]

It is also recognized as a potentially malignant disorder with documented malignant transformation risk. [2,3] The burden of disease remains substantial in populations with areca nut exposure, and cumulative habit burden is regarded as a major determinant of disease occurrence and progression. [1,4,5] Clinically, patients may present with burning sensation, intolerance to spicy food, mucosal blanching, reduced cheek flexibility, and progressive trismus. [6,7]

Functional restriction of mouth opening is particularly important because it reflects disease severity and day-to-day disability. [7]

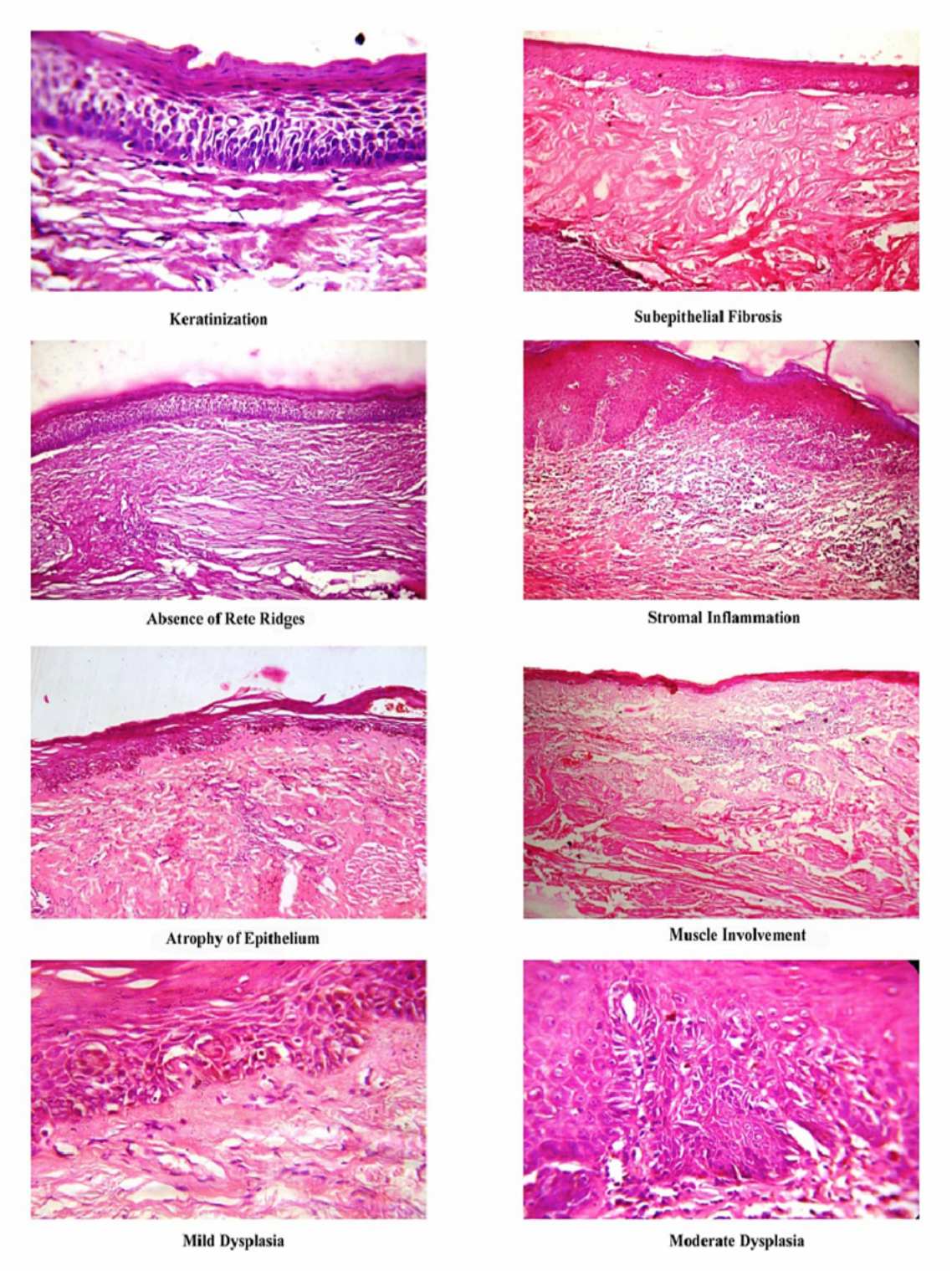

Figure 1: Histological Changes in OSMF from Fibrosis to Dysplasia

In addition to local fibrosis, several studies have reported alterations in haematological indices, inflammatory markers, serum proteins, iron status, and lactate dehydrogenase in affected patients, suggesting that oral submucous fibrosis may have measurable systemic correlates. [8-16]

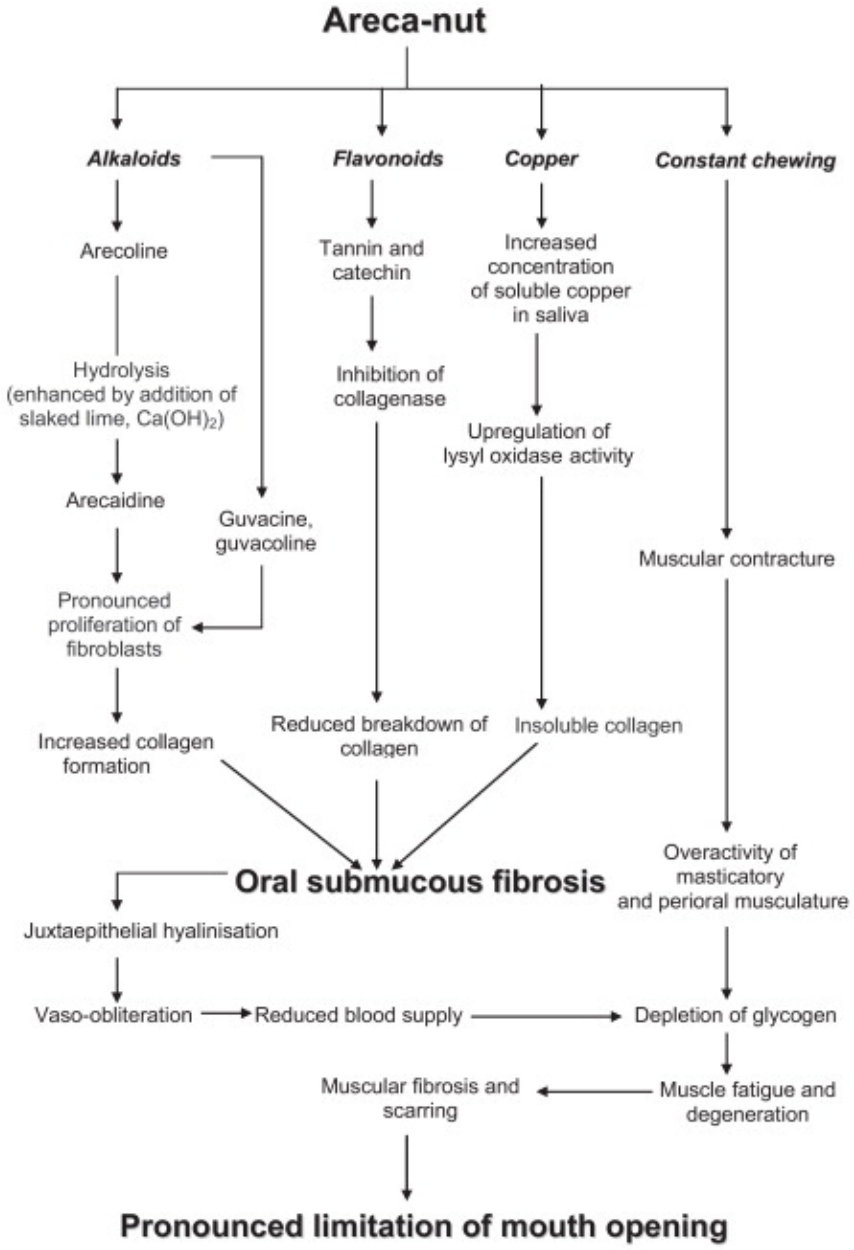

Figure 2: Molecular and Cellular Pathogenesis of OSMF

Clinical assessment alone may not fully capture disease burden in oral submucous fibrosis. The present study assessed the clinical and biochemical profile of patients with oral submucous fibrosis and examined the relationship between clinical severity and haematological and biochemical parameters.

Materials and Methods

Study design and setting: This prospective observational study was conducted in the Department of Otorhinolaryngology among patients presenting with burning sensation in the mouth, absence of taste sensation, difficulty in mouth opening, and fibrous bands in the oral cavity.

Study duration: The study was conducted during December 2023 to January 2026.

Participants: All eligible cases of oral submucous fibrosis diagnosed during the study period were considered for inclusion. Diagnosis was based on detailed history and clinical examination with specific attention to the buccal mucosa, retromolar trigone, and anterior pillar of the palatine tonsil, posterior pharyngeal wall, soft palate, and uvula.

Inclusion Criteria: Patients aged 10 to 60 years diagnosed with oral submucous fibrosis and willing to participate after written informed consent were included.

Exclusion Criteria: Patients with pre-existing malignant lesions, previously operated oral submucous fibrosis, prior radiotherapy, or restricted mouth opening due to causes other than oral submucous fibrosis were excluded.

Sample size and sampling: The sample size was 100 patients. Consecutive sampling was used, and all eligible consenting patients were enrolled until the target sample size was achieved.

Data Collection: A structured proforma was used to record demographic profile, chief complaints with duration, medical and operative history, chewing and smoking exposure, tobacco-infused toothpaste use, mouth opening in millimetres, site-wise clinical findings, fibrous bands, ulcers or lesions, and associated symptoms including burning sensation, difficulty in chewing, and difficulty in swallowing. Follow-up mouth opening was recorded at 1 month, 3 months, and 6 months.

Laboratory investigations: Laboratory investigations included complete blood count, erythrocyte sedimentation rate, serum protein, C-reactive protein, serum iron, and serum lactate dehydrogenase.

Treatment Protocol: Management was stage-based. Stage I disease was managed with habit cessation, antioxidants, topical corticosteroids, and physiotherapy. Stage II disease received habit cessation, antioxidants, intralesional steroids, and physiotherapy.

Stage III disease was treated with habit cessation, systemic antioxidants, intralesional steroids with hyaluronidase, and vigorous physiotherapy. Advanced disease underwent fibrotomy-based surgical evaluation with physiotherapy; incisional biopsy was performed in one patient.

Statistical Analysis: Categorical variables were summarized as frequency and percentage. Continuous variables were summarized as mean ± standard deviation. Associations between categorical variables were assessed using the chi-square test. Other suitable statistical tests were applied as required, and $p < 0.05$ was considered statistically significant.

Ethical Considerations: Ethical approval was obtained from the Research Ethics Committee of the institution, and written informed consent was obtained from all participants before inclusion in the study.

Results

Demographic and habit-related profile: A total of 100 patients with oral submucous fibrosis were included. The age range was 21 to 58 years, with a mean age of 33.05 ± 8.19 years. Most patients were in the 21-30 year age group (46.0%), followed by the 31-40 year age group (34.0%). Males constituted 74.0% of the cohort. Mean age increased significantly across stages, from 24.30 ± 2.22 years in Stage I to 43.45 ± 7.13 years in Stage IV ($p < 0.001$). Gender distribution also varied significantly across stages ($p = 0.006$), with male patients more commonly represented in advanced disease.

Chewing habit was present in all patients. Gutkha was used by 36.0%, areca nut by 35.0%, and pan masala by 29.0%. Smoking was present in 19.0%, whereas tobacco toothpaste use was uncommon (2.0%). Chewing duration and chewing amount per day increased significantly with advancing stage, from 2.67 ± 1.07 years and 2.63 ± 0.63 per day in Stage I to 11.10 ± 3.21 years and 8.35 ± 2.13 per day in Stage IV (both $p < 0.001$). Complaint duration also increased progressively across stages, with an overall mean duration of 12.53 ± 7.96 months.

Table 1: Baseline clinical and habit-related characteristics according to OSMF stage

Variable	Stage I (n=27)	Stage II (n=22)	Stage III (n=31)	Stage IV (n=20)	p-value
Age (years)	24.30 ± 2.22	29.59 ± 2.52	36.42 ± 4.33	43.45 ± 7.13	<0.001
Male sex, n (%)	17 (63.0)	12 (54.5)	29 (93.5)	16 (80.0)	0.006
Chewing duration (years)	2.67 ± 1.07	5.09 ± 1.11	7.90 ± 2.02	11.10 ± 3.21	<0.001
Chewing amount/day	2.63 ± 0.63	4.32 ± 0.84	6.35 ± 1.56	8.35 ± 2.13	<0.001
Baseline mouth opening (mm)	39.52 ± 2.61	31.50 ± 3.02	19.90 ± 3.30	10.60 ± 2.16	<0.001

Presenting complaints and symptom profile: Burning sensation was the most common chief complaint, present alone in 41.0% and in combination with restricted mouth opening in 35.0% of patients. Restricted mouth opening alone was present in 18.0%, and severe restricted mouth opening in 6.0%. Among associated symptoms, burning sensation was present in 76.0%, difficulty in chewing in 56.0%, absence of taste in 31.0%, and difficulty in swallowing in 23.0%.A clear stage-wise shift in symptom pattern was observed. Early-stage disease was dominated by burning sensation, whereas advanced stages were characterized by restricted mouth opening, difficulty in chewing, difficulty in swallowing, and loss of taste.

All major symptom associations with stage were statistically significant ($p < 0.001$).

Clinical findings and disease stage: Stage III was the most common clinical stage (31.0%), followed by Stage I (27.0%), Stage II (22.0%), and Stage IV (20.0%). Mean baseline mouth opening was 25.89 ± 11.14 mm and declined significantly with

advancing stage, from 39.52 ± 2.61 mm in Stage I to 10.60 ± 2.16 mm in Stage IV ($p < 0.001$).

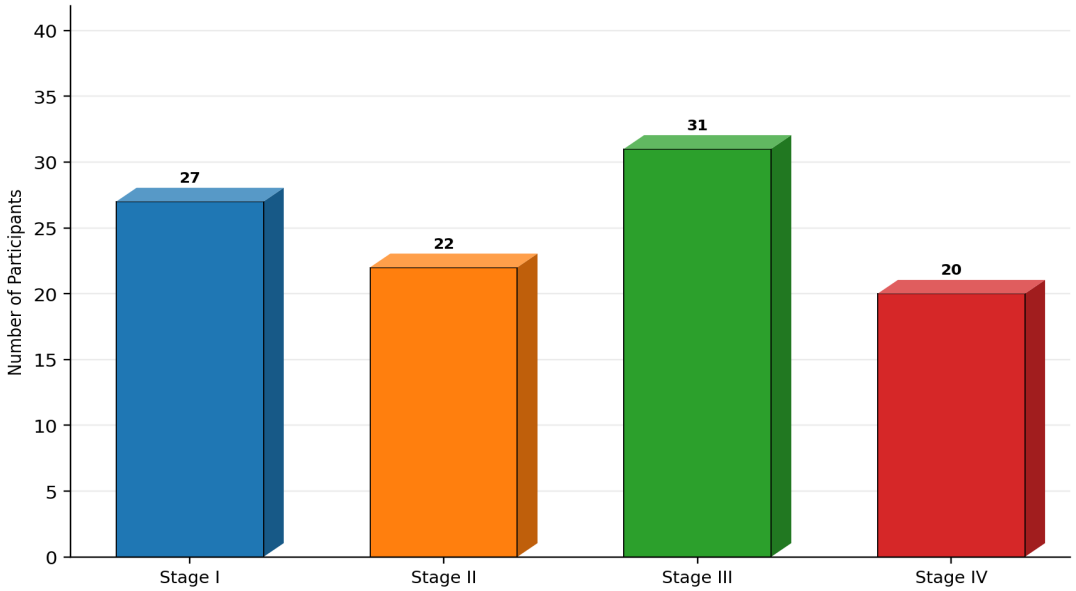

Figure 3: Distribution of OSMF stage among study participants.

All patients had fibrous bands and buccal mucosal involvement.

Erythaematous mucosa was the most common mucosal appearance overall (45.0%), followed by pale mucosa (36.0%), blanching (11.0%), and marble-like change (8.0%). Retromolar trigone involvement was present in 57.0%, palatoglossal arch involvement in 41.0%, soft palate involvement in 20.0%, uvular involvement in 13.0%, and posterior pharyngeal wall involvement in 7.0%.

These sites were increasingly involved in advanced stages.

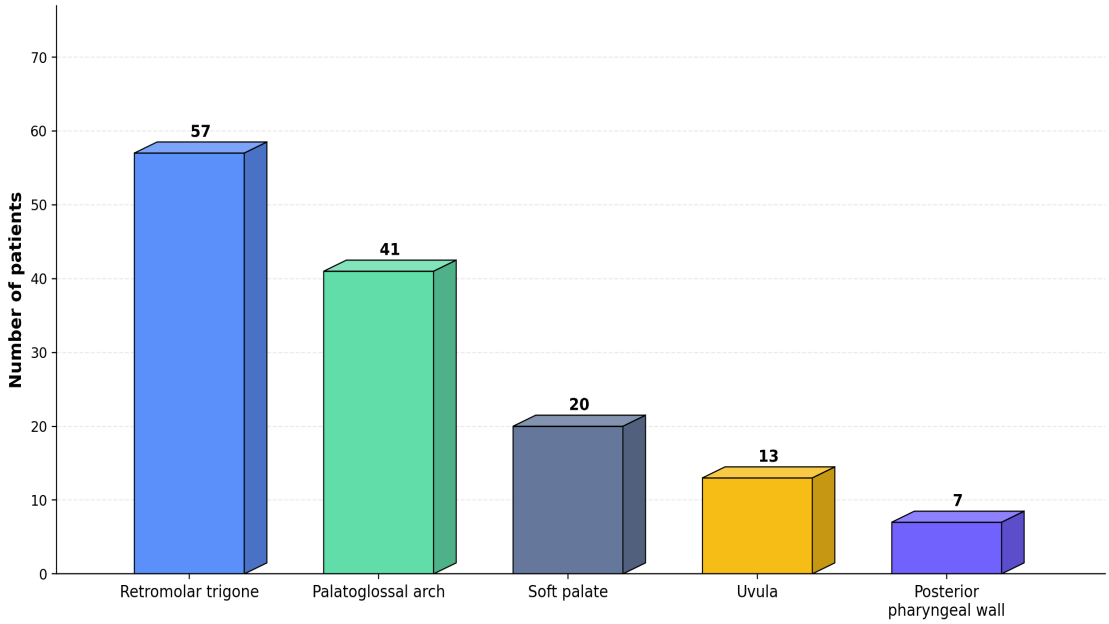

Figure 4: Distribution of site involvement in OSMF.

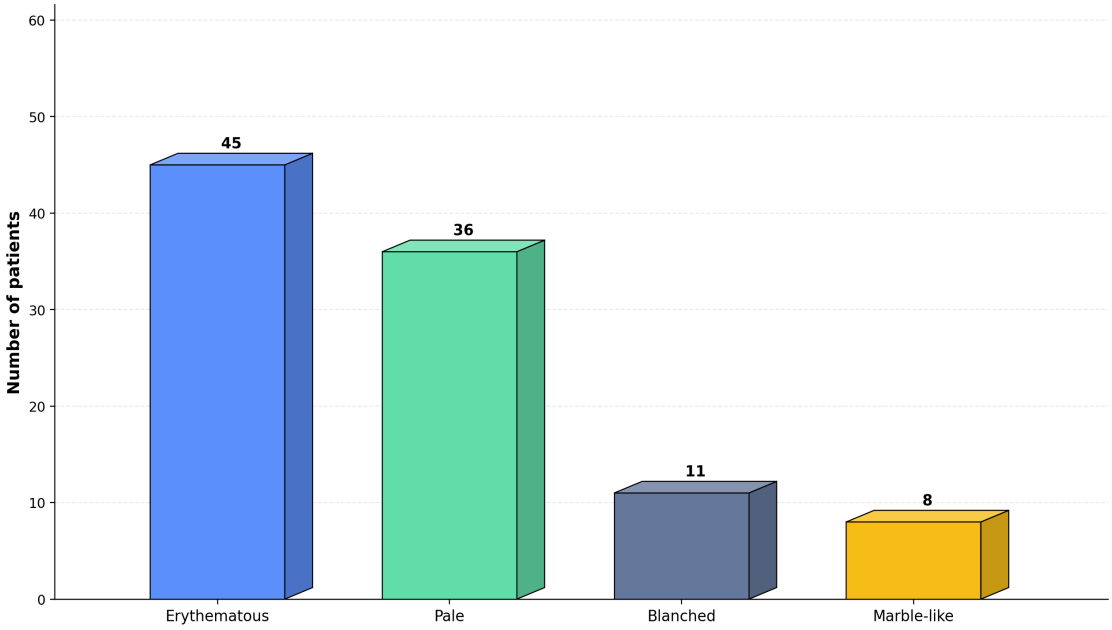

Figure 5: Distribution of mucosal colour among study participants.

Haematological and biochemical profile: The mean Haemoglobin level was 12.47 ± 1.49 g/dL, mean corpuscular volume was 78.95 ± 6.88 fL, mean corpuscular Haemoglobin was 26.72 ± 2.76 pg, total leukocyte count was 6762.00 ± 1140.86 cells/µL, platelet count was 3.31 ± 0.64 lakh/µL, and erythrocyte sedimentation rate was 23.08 ± 10.57 mm/hr.

Mean serum protein was 6.76 ± 0.62 g/dL, mean C-reactive protein was 4.53 ± 3.60 mg/L, mean serum iron was 70.37 ± 16.35 µg/dL, and mean serum lactate dehydrogenase was 307.30 ± 74.26 U/L. Stage-wise analysis showed progressive decline in Haemoglobin, mean corpuscular volume, mean corpuscular Haemoglobin, platelet count, serum protein, and serum iron with increasing disease stage. In contrast, total leukocyte count, erythrocyte sedimentation rate, C-reactive protein, and serum lactate dehydrogenase increased progressively from Stage I to Stage IV. All associations were statistically significant ($p < 0.001$).

Table 2: Key haematological and biochemical parameters according to OSMF stage

Parameter	Stage I (n=27)	Stage II (n=22)	Stage III (n=31)	Stage IV (n=20)	p-value
Haemoglobin (g/dL)	14.24 ± 0.37	13.08 ± 0.45	11.93 ± 0.41	10.26 ± 0.59	<0.001
Total WBC/TLC (cells/µL)	5481.48 ± 233.76	6213.64 ± 313.65	7329.03 ± 521.02	8215.00 ± 862.84	<0.001
ESR (mm/hr)	11.70 ± 2.05	17.95 ± 3.18	26.35 ± 5.02	39.00 ± 5.16	<0.001
Serum protein (g/dL)	7.43 ± 0.11	7.08 ± 0.20	6.54 ± 0.27	5.83 ± 0.30	<0.001
CRP (mg/L)	1.11 ± 0.31	2.31 ± 0.62	5.42 ± 1.53	10.20 ± 2.39	<0.001
Serum iron (µg/dL)	89.92 ± 3.68	77.57 ± 5.36	63.15 ± 6.41	47.23 ± 5.04	<0.001
Serum LDH (U/L)	216.93 ± 18.33	280.00 ± 27.19	338.55 ± 25.00	410.90 ± 33.24	<0.001

Treatment and follow-up outcome: Treatment intensity increased with stage. Stage I patients were managed conservatively, Stage II and Stage III mainly required intralesional therapy with physiotherapy, and most Stage IV patients underwent fibrotomy-based surgical evaluation with physiotherapy.

The association between treatment modality and stage was statistically significant ($p < 0.001$). Serial follow-up demonstrated progressive improvement in mouth opening.

Mean mouth opening increased from 25.89 ± 11.14 mm at baseline to 26.97 ± 11.37 mm at 1 month, 27.94 ± 11.30 mm at 3 months, and 28.60 ± 11.48 mm at 6 months.

Mean improvement from baseline was 1.08 ± 0.54 mm at 1 month, 2.05 ± 0.77 mm at 3 months, and 2.71 ± 1.09 mm at 6 months.

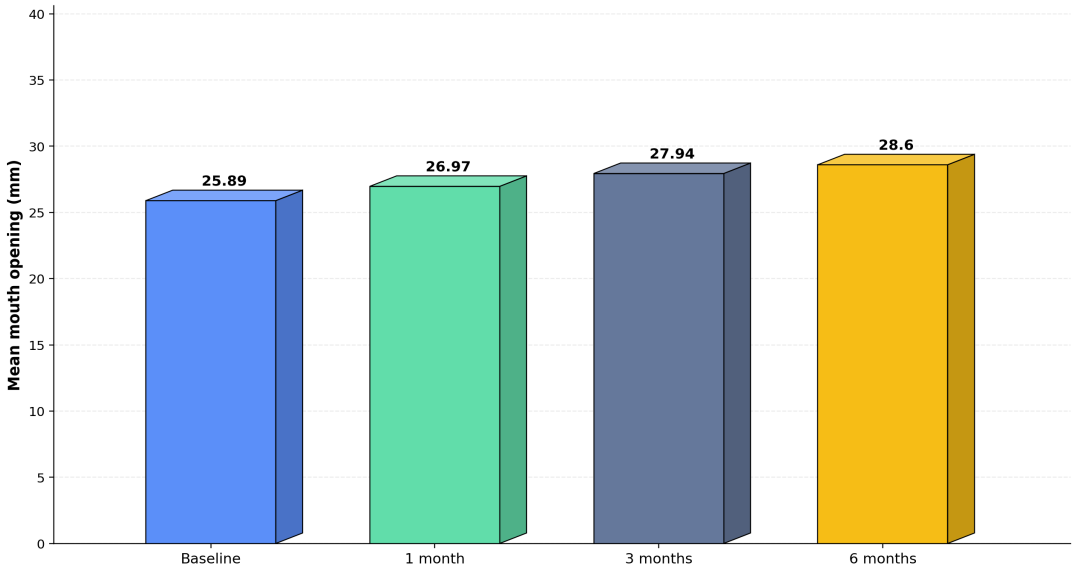

Figure 6: Serial change in mean mouth opening during follow-up.

Stage-wise analysis showed improvement in all groups. At 6 months, mouth opening reached 41.85 ± 2.13 mm in Stage I, 35.50 ± 2.77 mm in Stage II, 22.61 ± 3.87 mm in Stage III, and 12.40 ± 2.95 mm in Stage IV. The greatest mean improvement at 6 months was seen in Stage II (4.00 ± 0.69 mm), whereas the least improvement was seen in Stage IV (1.80 ± 0.95 mm). Differences across stages remained statistically significant at all follow-up intervals ($p < 0.001$).

Table 3: Serial change in mouth opening during follow-up according to OSMF stage

OSMF stage	Baseline (mm)	1 month (mm)	3 months (mm)	6 months (mm)
Stage I (n=27)	39.52 ± 2.61	40.52 ± 2.53	41.15 ± 2.18	41.85 ± 2.13
Stage II (n=22)	31.50 ± 3.02	33.27 ± 2.91	34.55 ± 2.82	35.50 ± 2.77
Stage III (n=31)	19.90 ± 3.30	20.94 ± 3.36	22.00 ± 3.64	22.61 ± 3.87
Stage IV (n=20)	10.60 ± 2.16	11.10 ± 2.57	12.05 ± 2.76	12.40 ± 2.95
p-value	<0.001	<0.001	<0.001	<0.001

Correlation of mouth opening with clinical and laboratory parameters: Baseline mouth opening showed strong negative correlation with age (r = -0.903), complaint duration (r = -0.882), chewing duration (r = -0.887), chewing amount per day (r = -0.869), smoking duration (r = -0.476), and smoking amount per day (r = -0.487). It showed strong positive correlation with Haemoglobin (r = 0.970), mean corpuscular volume (r = 0.975), mean corpuscular Haemoglobin (r = 0.977), platelet count (r = 0.969), serum protein (r = 0.963), and serum iron (r = 0.982). Strong negative correlations were seen with total leukocyte count (r = -0.939), erythrocyte sedimentation rate (r = -0.956), C-reactive protein (r = -0.935), and serum lactate dehydrogenase (r = -0.974).

Discussion

This prospective observational study showed that oral submucous fibrosis predominantly affected young and middle-aged adults, with marked male predominance and universal chewing exposure. Clinical severity increased with age, symptom duration, chewing burden, and smoking exposure. Stage III was the most frequent clinical stage, and mouth opening declined sharply across stages. Advancing stage was accompanied by progressive reduction in Haemoglobin, mean corpuscular volume, mean corpuscular Haemoglobin, platelet count, serum protein, and serum iron, together with rising total leukocyte count, erythrocyte sedimentation rate, C-reactive protein, and serum lactate dehydrogenase. Serial follow-up demonstrated improvement in mouth opening across all stages, with better gains in earlier disease.

The age distribution observed here is consistent with previous reports showing that oral submucous fibrosis commonly affects younger and middle-aged individuals. [4,6] Male predominance in the present cohort is also in keeping with earlier clinical series. [6,7] Universal chewing exposure supports the established etiological role of areca nut-related habits in oral submucous fibrosis. [1,4,5] The stage-wise decline in mouth opening aligns with the functional staging observations of Haider et al., who identified mouth opening as a practical marker of disease extent and severity. [7] The progressive hematinic compromise observed

here is comparable to reports by Abidullah et al., Patil and Joshi, Bhardwaj et al., and Karthik et al., all of whom described lower Haemoglobin and iron-related indices in oral submucous fibrosis. [8-11] Inflammatory marker elevation in the present cohort is directionally similar to findings reported by Gosavi and Torkadi and by Sharma et al. [12,13] The progressive rise in serum lactate dehydrogenase is also concordant with previous clinical and meta-analytic work suggesting elevated lactate dehydrogenase in oral submucous fibrosis. [14-16] The decline in serum protein with increasing stage is closer to the pattern reported by More et al., although biochemical protein behavior in oral submucous fibrosis remains heterogeneous across studies. [17,18]

The present findings suggest that oral submucous fibrosis should not be viewed solely as a localized fibrotic oral disorder. Progressive restriction of mouth opening was accompanied by worsening hematinic, nutritional, inflammatory, and tissue-injury markers, indicating that clinical severity and laboratory derangement evolve in parallel. Mouth opening therefore appears to function not only as an index of trismus but also as a practical surrogate of overall disease burden. In routine care, combined clinical staging and targeted biochemical assessment may improve severity assessment and follow-up planning, particularly in patients with advanced fibrosis or prolonged chewing exposure.

The study included 100 consecutively enrolled patients with stage-wise analysis and serial follow-up of mouth opening. Limitations include the single-centre design, lack of a healthy control group, absence of histopathological correlation in the clinico-biochemical analysis, and restriction to select haematological and biochemical markers. In addition, most clinico-biochemical comparisons were observational and cross-sectional, which limits causal interpretation.

Conclusion

Oral submucous fibrosis showed a clear association between increasing habit burden, progressive reduction in mouth opening, wider site involvement, and worsening haematological and biochemical parameters. Earlier-stage disease demonstrated better functional recovery during follow-up than advanced-stage disease. Combined clinical and biochemical assessment may therefore offer a broader and more objective estimate of disease severity than clinical examination alone.

Declarations

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Author contributions

Dr Kachoriya Taral contributed to study conception and design, data collection, clinical assessment, data compilation, interpretation of results, and manuscript drafting.

Dr Kanwar Vikrant Singh contributed to patient evaluation, data review, manuscript revision, and intellectual input.

Dr Pranshuta Sehgal contributed to study supervision, methodological guidance, critical revision of the manuscript, and final approval of the version to be published.

All authors read and approved the final manuscript.

Ethics approval and consent to participate: Ethical approval was obtained from the Research Ethics Committee of the institution, and written informed consent was obtained from all participants before inclusion in the study.

Consent for publication: Consent for publication was obtained from the participants wherever applicable. No identifying personal information is included in the manuscript.

Availability of data and materials: The data supporting the findings of this study are available from the corresponding author on reasonable request.

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