Association of Habits with Clinical Symptoms in Oral Submucous Fibrosis Patients - A Retrospective Study

Running title: Evaluating habits and clinical symptoms in OSMF patients

Sai Sudha Mahajan
Saveetha Dental College and hospital,
Saveetha Institute of Medical and Technical Sciences,
Saveetha University,
Chennai-600077
Email ID: *151807005.sdc@saveetha.com*

Hannah R
Senior lecturer
Saveetha Dental College and hospital,
Saveetha Institute of Medical and Technical Sciences,
Saveetha University,
Chennai-600077
Email ID: hannahr.sdc@saveetha.com

Pratibha Ramani
Professor and Head of Department of Oral Pathology,
Saveetha Dental College,
Saveetha Institute of Medical and Technical Sciences,
Saveetha University,
Chennai-600077
Email ID: *pratibaramani@saveetha.com*

Corresponding author:
Hannah.R
Senior lecturer
Saveetha Dental College and hospital,
Saveetha Institute of Medical and Technical Sciences,
Saveetha University,
Chennai-600077
Email ID: hannahr.sdc@saveetha.com

Abstract:
Oral Submucous Fibrosis (OSMF) is a potentially malignant disorder and its early diagnosis is essential to reduce malignant transformation into oral squamous cell carcinoma (OSCC) and thereby reduce morbidity and mortality. This study assessed the chewing habits of the patients visiting Saveetha Dental College and Hospitals with regard to consumption of areca nut and its products, frequency and duration of habits as well as clinical symptoms and signs in OSMF. The aim of this study was to associate the habits with clinicopathological findings in OSMF patients. An institutional based retrospective study was conducted among 64 cases clinically diagnosed with OSMF. A detailed habit history and clinical signs and symptoms were recorded and appropriate statistical analysis was done. The study included 62 OSMF cases of both the gender groups; males (87.5%) and females (12.5%) of age group between 22 to 65 years. In this study, the most common habit was noted to be pan chewing and the commonest clinical symptoms was found to be restricted mouth opening (39%) and associated pain symptoms (28%). A very common clinical site for this lesion was found to be the buccal mucosa bilaterally (79.69%). The habit patterns and clinical features of OSMF are important to facilitate prompt diagnosis and management in order to monitor its clinical severity and progression to OSCC.

Keywords: Oral submucous fibrosis; Potentially malignant; Clinical symptoms; Restricted mouth opening; Pan chewing; Areca nut.

INTRODUCTION

Oral submucous fibrosis (OSMF), is a chronic, progressive, irreversible, scarring disease of the oral cavity and extending up to the pharynx. (Ali *et al.*, 2013 ; Haider *et al.*, 2000) It has been given the term 'atrophic idiopathic mucosae oris'; coined by Sir Schwartz in 1952. (Nanavati, Nanavati and Nanavati, 2015 ; Ahmad *et al.*, 2006) It is a common oral potentially malignant disorder (OPMD) among the South East Asian population with a malignant transformation rate between 7 to 13%. (Gupta and Ramani, 2016 ; Jayaraj *et al.*, 2015 ; Gifrina Jayaraj, Ramani, *et al.*, 2015) OSMF is found to be the most common among the population of the Indian sub-continent with a prevalence rate of 0.2 to 0.5% consisting of over 2.5 to 10 million cases since 2015. (Sridhar *et al.*, 2016 ; Ali *et al.*, 2014) (Singh, Gaikwad and Sapra, 2015 ; Saraswathi *et al.*, 2006 ; Jayaraj *et al.*, 2015 ; Hannah *et al.*, 2018) It commonly affects both the genders, the male to female ratio being 1:3 with a male predominance occuring between the third to fifth decade of life. (Saraswathi *et al.*, 2006 ; Jayaraj *et al.*, 2015 ; Sivaramakrishnan and Ramani, 2015)

OSMF is multifactorial in etiology, found to be associated with habits such as areca nut or betel-quid chewing, containing high levels of chemical constituents like alkaloids and flavonoids that interfere with the molecular processes of deposition and degradation of extracellular matrix molecules like collagen. (Gheena and Ezhilarasan, 2019 ; Hema Shree *et al.*, 2019 ; Jangid *et al.*, 2015) TGF beta is known to play a significant role where its synthesis takes place at the site of inflammation. (Wollina *et al.*, 2015 ; Gifrina Jayaraj, Sherlin, *et al.*, 2015) The hallmark of this lesion being it preceded by vesicle formation, associated with juxta-epithelial inflammatory reaction followed by fibro-elastic changes of lamina propria such as blanching of the

mucosa along with epithelial atrophy leading to stiffness of oral mucosa, causing trismus and inability to eat. (Ali *et al.*, 2014 ; Singh, Gaikwad and Sapra, 2015 ; Ranganathan *et al.*, 2001 ; Reddy *et al.*, 2011; Hazarey *et al.*, 2007 ; Cai *et al.*, 2019 ; Angadi and Rekha, 2011 ; Wollina *et al.*, 2015 ; Sherlin, *et al.*, 2015) The lesion is known to have multiple site involvement including the bilateral involvement of buccal mucosa, the lip mucosa, palatal mucosa, faucial pillars and the mucosa of the floor of the mouth. (Niessen *et al.*, no date ; Thangaraj *et al.*, 2016 ; Viveka *et al.*, 2016)

Several literatures have been published to correlate the clinical features with the habits including the signs and symptoms of OSMF which have found evidence of the oral lesion to have potential to transform into malignancy such as OSCC, if untreated or inadequately treated. (Sridharan *et al.*, 2019 ; Sridharan, Ramani and Patankar, 2017 ; Swathy, Gheena and Varsha, 2015). Therefore, this study aims to associate habit with clinical symptoms and severity in oral submucous fibrosis patients..

MATERIALS AND METHODS

Study design and study setting
This retrospective study was conducted by the department of oral and maxillofacial pathology in Saveetha dental college and hospital, Chennai, to evaluate the habits and clinical symptoms of oral submucous fibrosis patients from June 2019 to March 2020. The study was initiated after approval from the institutional Scientific review board.

Study population and sampling
After assessment in the university patient data registry, case records of 62 patients with clinically diagnosed oral submucous fibrosis were included in the study and evaluated. The inclusion criteria for the study were patients with clinically diagnosed OSMF; patients with complaints of burning sensation and restricted or limited mouth opening; patients with a history of areca nut chewing habit. The exclusion criteria of the study was patients with other oral lesions excluding OSMF such as oral squamous cell carcinoma and other oral potentially malignant disorders. Cross verification of data for errors was done with the help of an external examiner.

Data collection

A single calibrated examiner evaluated the digital case records of the 62 oral submucous fibrosis patients from June 2019 to March 2020. Demographic details like age, gender along with habit history, site of the lesion and clinical symptoms were also recorded. All consecutive case records of patients with oral submucous fibrosis were included in the study and their data retrieved.

Statistical Analysis
The collected data was validated, tabulated and analysed with Statistical Package for Social Sciences for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA) and results were obtained. Categorical variables were expressed in frequency and percentage. Chi-square test was used to test associations between categorical variables. P value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

The study group included both male (87.5%) and female (12.5%) OSMF participants (figure.1)
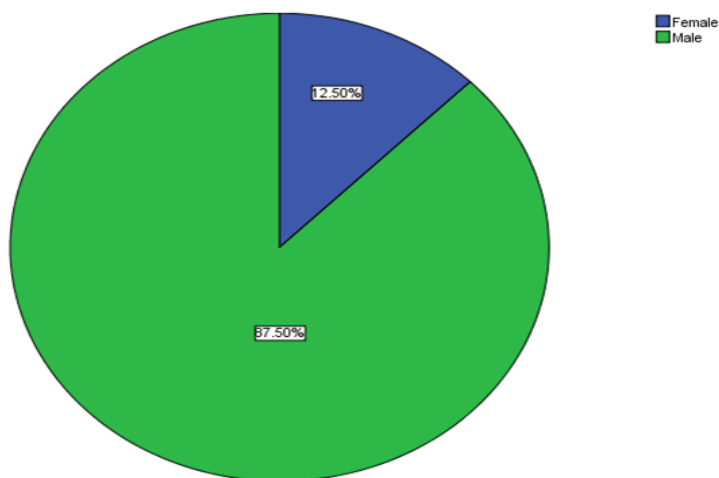

Figure 1: Pie chart depicting the gender distribution of oral submucous fibrosis patients. 87.5% of the participants were males (green) and 12.5% were females (blue).

between the age group 22 to 65 years . The most common age group was 31-40 years followed by 21 to 30 years (Figure 2).
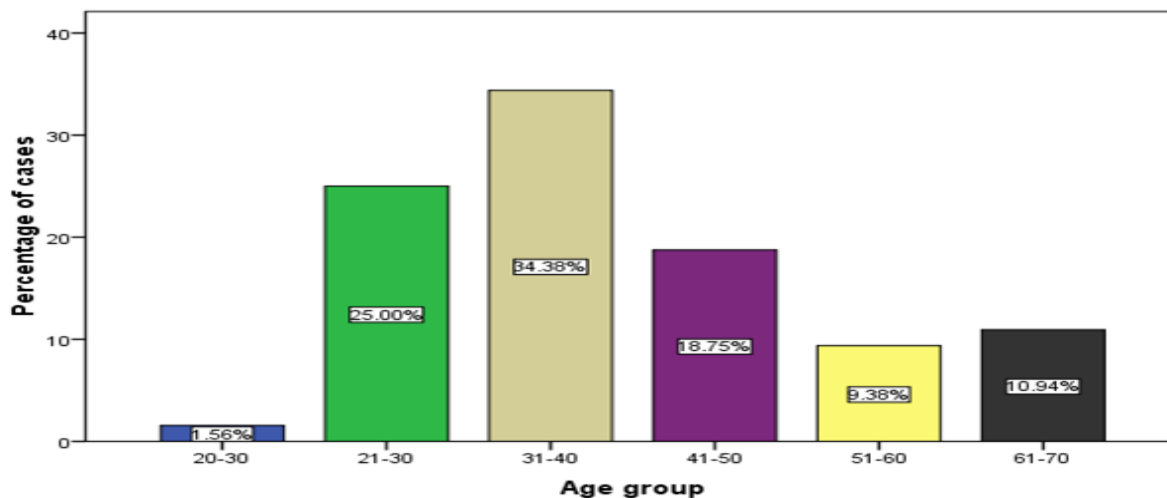

Figure 2: Bar chart representing the age distribution of the oral submucous fibrosis patients. X axis represents the age groups and Y axis represents the percentage of cases. Maximum of the study participants belonged to 31 - 40 years of age(grey) followed by 25% belonging to 21 - 30 years of age(green).

The habits prevalent among oral submucous fibrosis patients were areca nut (32.81%); mawa (7.8%); Hans (15.6%); pan (39%); Gutkha (4.7%) (Figure 3).
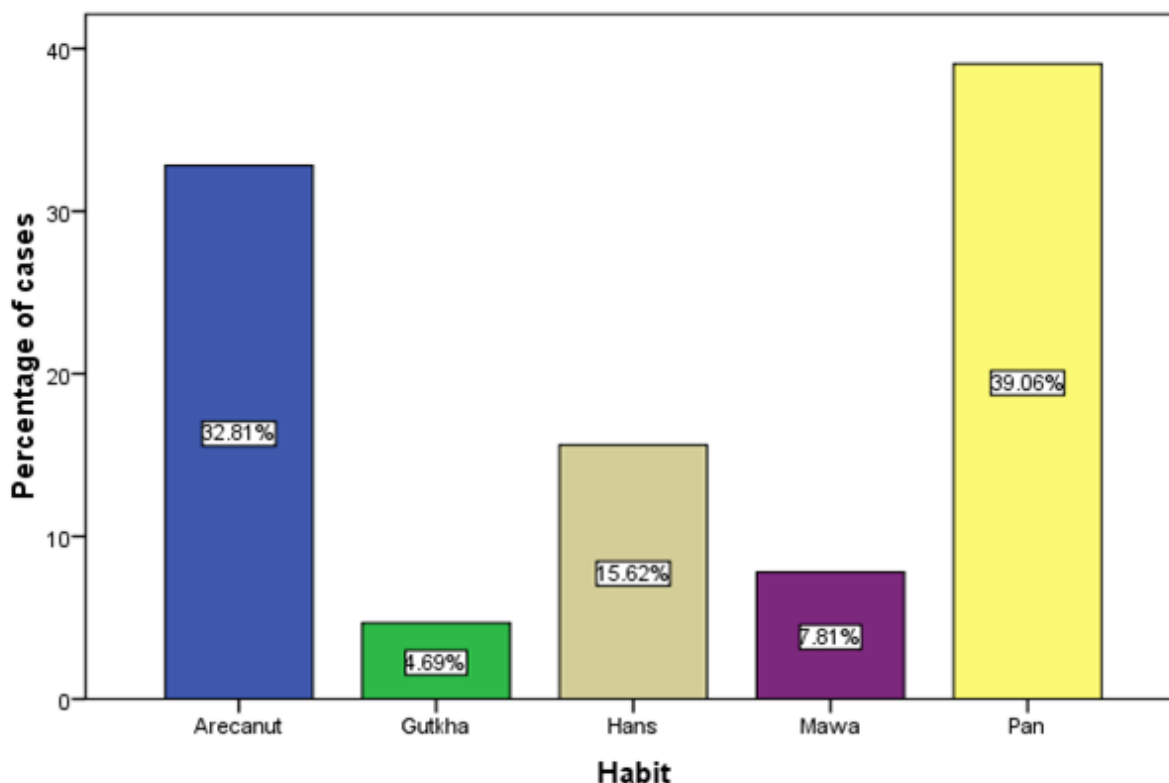

Figure 3: Bar graph representing the frequency distribution of habits among oral submucous fibrosis patients. X axis depicts the habits and Y axis the percentage of cases. The most prevalent habit was pan chewing 39.06% (yellow), followed by areca nut 32.61% (blue), Hans 15.62% (grey), mawa 7.8%(peuple) and Ghutkha 4.69%(green).

Among the participants, the duration of habit ranged between 10 months to 23 years where a majority of cases had 2 years of habit ranged between 10-15% in this study.

The clinical symptoms such as restricted mouth opening were found to be present in 39% of cases followed by associated pain symptoms in among 28 % of cases. The burning sensation was seen in upto 17% of cases. OSMF was an accidental finding in 12% of cases who complained of other symptoms such as swelling, missing teeth and stains on teeth (Figure 4).
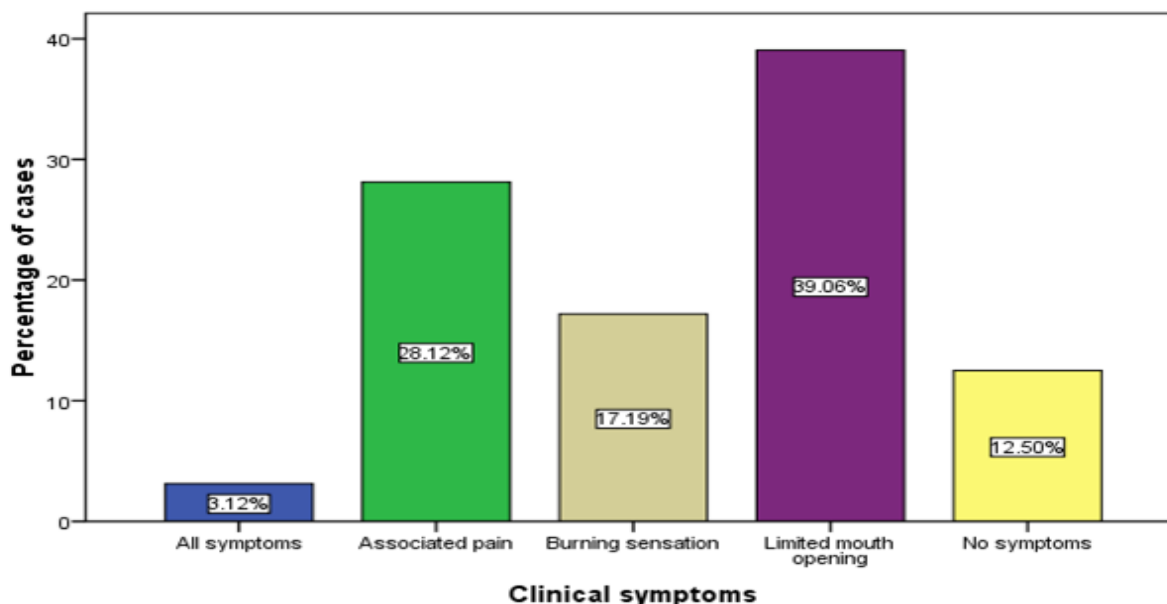
Figure 4: Bar graph representing the frequency distribution of clinical symptoms among oral submucous fibrosis patients. X axis represents the clinical symptoms and Y axis the percentage of cases. The most common symptom being limited mouth opening among 39% (purple), followed by associated pain 28.12%, Burning sensation 17.2% and no clinical symptoms was seen in 12.5% of the cases.

The most common site in the oral cavity for its clinical presentation was the buccal mucosa bilaterally (80%) (Figure 5).
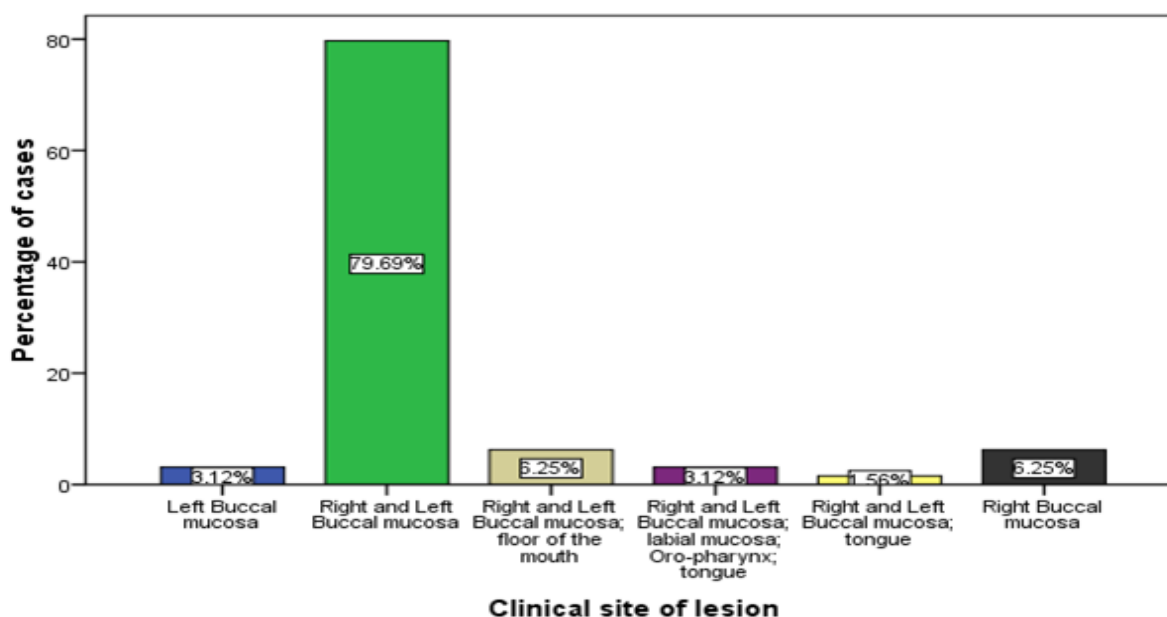
Figure 5: Bar graph representing the frequency distribution of clinical site of occurrence of oral submucous fibrosis. X axis represents the clinical site of the lesion and Y axis represents the percentage of cases. 79.7% of the cases were found bilaterally in both the right and left buccal mucosa(green), 6.2% were found only in the right buccal mucosa(black) and another 6.2% had involvement of the floor of the mouth (grey).

The most common clinical finding was found to be the blanching of the mucosa and palpable fibrotic bands. It was found that the duration of clinical symptoms vary common during 1 year in 25% of cases and 1 week in less than 15% of cases; 10 years in less than 10% of cases; more than 5% cases showed clinical symptoms for a duration of 3 days, 4 days, 3 weeks, 2 months, 3 months and 6 months. Less than 5% cases had clinical symptoms for 5 days, 10 days, 1 month, 2 years and 5 years.

A statistical chi-square test was done to find the association between OSMF habits and its clinical symptoms. (Figure 6)
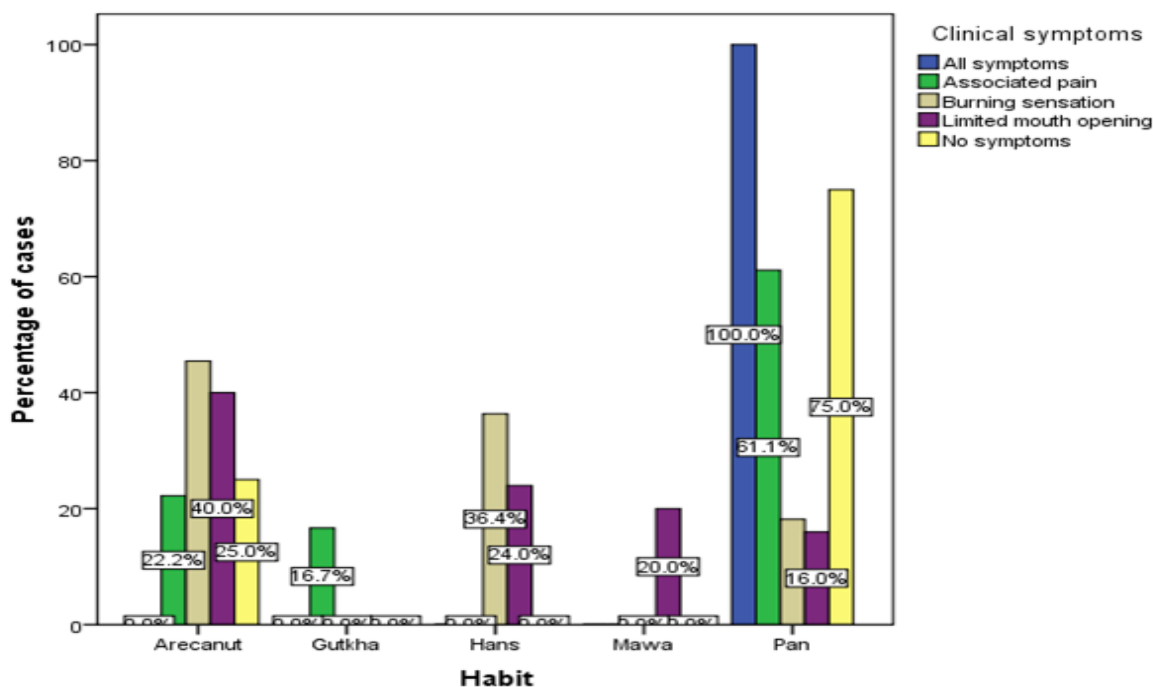

Figure 6: Bar graph representing the association of habits with clinical symptoms among oral submucous fibrosis patients. X axis represents the habits and Y axis the percentage of cases. Chi square analysis showed statistical significance with (Chi square value 37.760) p=0.002 (p<0.05), indicating a significant increase in all symptoms and symptoms of pain among those with habit of pan chewing. Limited mouth opening and burning sensation was more common among areca nut users.

A positive association was found between panchewing and associated pain symptoms(61%) and Burning sensation and restricted mouth opening being more common among those with areca nut habit. The P value was 0.002 (p<0.05) showing statistical significance (Figure 6). Age and clinical symptoms also showed statistical significance with all symptoms being more prevalent among 31-40 years of age(Figure 7).
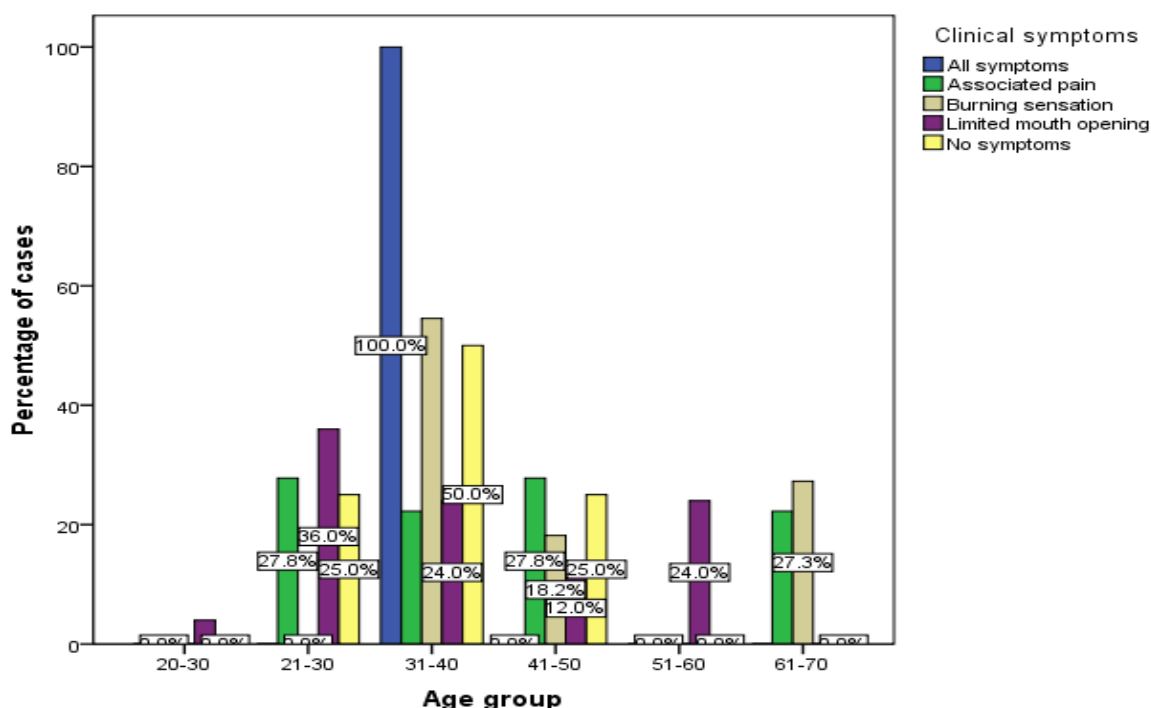
Figure 7: Bar graph representing the association of age groups with clinical symptoms among oral submucous fibrosis patients. X axis represents the age groups and Y axis the percentage of cases. Overall symptoms were more prevalent among the 31-40 age group. Chi square analysis showed statistical significance with (Chi square value 31.909) p=0.044 (p<0.05), indicating a significant increase in all symptoms and burning sensation among those belonging to 31-40 years of age.

In this study, the OSMF patients were increasingly more under the age of 29 years and above 63 years suggesting that the habit is very common in younger and older age groups. males were found to be more commonly affected than females. This finding is in accordance with the study by Sridhar *et al* and Ahmad M *et al* implicating that such occurrences could be due to the presence of habits more commonly in males than females among the South Asian population. (Sridhar *et al.*, 2016; Ahmad, M. S. *et al.* 2006)

The areca nut products like pan (fig. 3) are found to have a significant correlation with the clinical site of the lesion which revealed the buccal mucosa bilaterally. (fig.5) This occurrence of the oral lesion particularly the buccal mucosa bilaterally implicates a greater frequency of OSMF patients with the usage of areca nut products like pan habitually placed in the cheek region of the mouth. (Nanavati, Nanavati and Nanavati, 2015)Pan chewing showed significant correlation with associated pain symptoms proving evidence that the clinical severity such as trismus and burning sensation including associated pain is having a link with the site and extent of the lesion in OSMF patients. This finding is similar to the study by Reddy V *et al* and Ali *et al. (Ali et al., 2013)* (Reddy *et al.*, 2011) The probability of the associated pain symptoms would have risen as a result of chemical constituents present in the pan which could induce ulceration and accompanied pain sensation.In this study and also in most other studies, the very common clinical symptoms was restricted mouth opening followed by pain. (Nanavati, Nanavati and Nanavati,

2015) This is also in consensus with the results of study by Angadi *et al,* where it was found that restricted mouth opening was a more common clinical feature followed by burning sensation (Angadi and Rekha, 2011)Although pain and burning sensation are the initial clinical symptoms, patient do not report to the hospital until they develop difficulty in opening the mouth. This finding just implies that most of the patients are not aware of the presence of the disease until they are told about OSMF and its consequences. Presence of palpable fibrous bands and blanching were the principal clinical findings evident in most cases of OSMF and is also a relevant diagnostic criteria.As this study was restricted to an institutional study, the samples analysed are from a particular regional data and the sample size of this study is limited owing to its limitations. Probably a larger sample size would have helped to yield a much significant result. The study may guide to establish a better clinical approach in relation with its associated habits.

CONCLUSION

Within the limits of this study, the habits and its clinical symptoms show significant association, with Pain being more common among those with the habit of pan chewing and restricted mouth opening among the areca nut users. This will help in understanding the pathogenesis of OSMF better and in turn help in preventing its malignant transformation.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

References

1. Ahmad, M. S. *et al.* (2006) 'Epidemiological and etiological study of oral submucous fibrosis among gutkha chewers of Patna, Bihar, India', *Journal of the Indian Society of Pedodontics and Preventive Dentistry*, 24(2), pp. 84–89.

2. Ali, F. M. *et al.* (2013) 'Oral submucous fibrosis: Comparing clinical grading with duration and frequency of habit among areca nut and its products chewers', *Journal of cancer research and therapeutics*, 9(3), pp. 471–476.

3. Ali, F. M. *et al.* (2014) 'Oral submucous fibrosis and its dermatological relation', *Indian dermatology online journal*, 5(3), pp. 260–265.

4. Angadi, P. V. and Rekha, K. P. (2011) 'Oral submucous fibrosis: a clinicopathologic review of 205 cases in Indians', *Oral and maxillofacial surgery*, 15(1), pp. 15–19.

5. Cai, X. *et al.* (2019) 'Oral submucous fibrosis: A clinicopathological study of 674 cases in China', *Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 48(4), pp. 321–325.

6. Haider, S. M. *et al.* (2000) 'Clinical and functional staging of oral submucous fibrosis', *The British journal of oral & maxillofacial surgery*, 38(1), pp. 12–15.

7. Hazarey, V. K. *et al.* (2007) 'Oral submucous fibrosis: study of 1000 cases from central India', *Journal of oral pathology & medicine: official publication of the International*

Association of Oral Pathologists and the American Academy of Oral Pathology, 36(1), pp. 12–17.

8. Nanavati, S., Nanavati, P. and Nanavati, M. (2015) 'Clinico-pathological study of 170 cases of oral sub-mucous fibrosis', *McGill journal of medicine: MJM: an international forum for the advancement of medical sciences by students*, 3(9), pp. 137–144.

9. Niessen, F. A. *et al.* (no date) 'Early discontinuation of empirical antibiotic treatment in neutropenic patients with acute myeloid leukaemia and high-risk myelodysplastic syndrome'. doi: 10.21203/rs.2.17037/v3.

10. Ranganathan, K. *et al.* (2001) 'Mouth opening, cheek flexibility and tongue protrusion parameters of 800 normal patients in Chennai, South India. A base line study to enable assessment …'. scienceopen.com. Available at: https://www.scienceopen.com/document?vid=610ad2ac-f235-4611-bb95-3733dab2a2d4.

11. Reddy, V. *et al.* (2011) 'Oral Submucous Fibrosis: Correlation of Clinical Grading to various habit factors'. unknown, 3(1). Available at: http://dx.doi.org/ (Accessed: 13 June 2020).

12. Saraswathi, T. R. *et al.* (2006) 'Prevalence of oral lesions in relation to habits: Cross-sectional study in South India', *Indian journal of dental research: official publication of Indian Society for Dental Research*, 17(3), pp. 121–125.

13. Singh, S., Gaikwad, P. and Sapra, G. (2015) 'Clinico-Pathological Evaluation and Correlation of Stages of Oral Submucous Fibrosis with Different Habits', *J Interdiscipl Med*. pdfs.semanticscholar.org. Available at: https://pdfs.semanticscholar.org/1676/d0fd11bd0ff3afc75782ed365318af9f24d6.pdf.

14. Sridhar, C. *et al.* (2016) 'Evaluation of Habit Patterns and Clinical Findings of Oral Submucous Fibrosis in South Indian Population', *Journal of pharmaceutical and biomedical sciences*, 6(7). Available at: http://lawarencepress.com/ojs/index.php/JPBMS/article/view/292 (Accessed: 13 June 2020).

15. Wollina, U. *et al.* (2015) 'Oral submucous fibrosis: an update', *Clinical, cosmetic and investigational dermatology*, 8, pp. 193–204.

16. Gheena, S. and Ezhilarasan, D. (2019) 'Syringic acid triggers reactive oxygen species–mediated cytotoxicity in HepG2 cells', *Human & Experimental Toxicology*, pp. 694–702. doi: 10.1177/0960327119839173.

17. Gupta, V. and Ramani, P. (2016) 'Histologic and immunohistochemical evaluation of mirror image biopsies in oral squamous cell carcinoma', *Journal of Oral Biology and Craniofacial Research*, 6(3), pp. 194–197.

18. Hannah, R. *et al.* (2018) 'Awareness about the use, ethics and scope of dental photography among undergraduate dental students dentist behind the lens', *Research Journal of Pharmacy and Technology*. A & V Publications, 11(3), pp. 1012–1016.

19. Hema Shree, K. *et al.* (2019) 'Saliva as a Diagnostic Tool in Oral Squamous Cell Carcinoma - a Systematic Review with Meta Analysis', *Pathology oncology research: POR*, 25(2), pp. 447–453.

20. Jangid, K. *et al.* (2015) 'Ankyloglossia with cleft lip: A rare case report', *Journal of Indian Society of Periodontology*, 19(6), pp. 690–693.

21. Jayaraj, G., Sherlin, H. J., *et al.* (2015) 'Cytomegalovirus and Mucoepidermoid carcinoma: A possible causal relationship? A pilot study', *Journal of oral and maxillofacial pathology: JOMFP*, 19(3), pp. 319–324.

22. Jayaraj, G., Ramani, P., *et al.* (2015) 'Inter-observer agreement in grading oral epithelial dysplasia – A systematic review', *Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology*, pp. 112–116. doi: 10.1016/j.ajoms.2014.01.006.

23. Jayaraj, G. *et al.* (2015) 'Stromal myofibroblasts in oral squamous cell carcinoma and potentially malignant disorders', *Indian journal of cancer*, 52(1), pp. 87–92.

24. Sherlin, H. *et al.* (2015) 'Expression of CD 68, CD 45 and human leukocyte antigen-DR in central and peripheral giant cell granuloma, giant cell tumor of long bones, and tuberculous granuloma: An immunohistochemical study', *Indian Journal of Dental Research*, p. 295. doi: 10.4103/0970-9290.162872.

25. Sivaramakrishnan, S. M. and Ramani, P. (2015) 'Study on the Prevalence of Eruption Status of Third Molars in South Indian Population', *Biology and Medicine*. doi: 10.4172/0974-8369.1000245.

26. Sridharan, G. *et al.* (2019) 'Evaluation of salivary metabolomics in oral leukoplakia and oral squamous cell carcinoma', *Journal of oral pathology & medicine: official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology*, 48(4), pp. 299–306.

27. Sridharan, G., Ramani, P. and Patankar, S. (2017) 'Serum metabolomics in oral leukoplakia and oral squamous cell carcinoma', *Journal of cancer research and therapeutics*, 13(3), pp. 556–561.

28. Swathy, S., Gheena, S. and Varsha, S. L. (2015) 'Prevalence of pulp stones in patients with history of cardiac diseases', *Research Journal of Pharmacy and Technology*. A & V Publications, 8(12), pp. 1625–1628.

29. Thangaraj, S. V. *et al.* (2016) 'Molecular Portrait of Oral Tongue Squamous Cell Carcinoma Shown by Integrative Meta-Analysis of Expression Profiles with Validations', *PloS one*, 11(6), p. e0156582.

30. Viveka, T. S. *et al.* (2016) 'p53 Expression Helps Identify High Risk Oral Tongue Pre-malignant Lesions and Correlates with Patterns of Invasive Tumour Front and Tumour Depth in Oral Tongue Squamous Cell Carcinoma Cases', *Asian Pacific journal of cancer prevention: APJCP*, 17(1), pp. 189–195.