Abstract:
Oral potentially malignant disorders (OPMDs) are a group of chronic conditions affecting the oral mucosa with a risk of transformation to oral squamous cell carcinoma (OSCC). Oral leukoplakia, oral submucous fibrosis, oral lichen planus, and oral erythroplakia are the most common OPMDs observed in South Asian population. However, oral leukoplakia and oral lichen planus are commonly encountered OPMDs in clinical practice in Bangladesh, possibly, owing to specific lifestyle habits. Although the exact aetiology is unknown, use of smokeless tobacco, smoking, and chewing of betel quid containing areca nut, are considered as common risk factors for OPMDs. Early diagnosis is very important and can be lifesaving, as at a late stage, OPMDs are more likely to progress into severe dysplasia or even into squamous cell carcinoma. In fact, OPMDs have a significantly increased risk of progressing to cancer, mostly in South Asian population, including Bangladesh. This review provides an overview of the OPMDs in Bangladeshi population.

Keywords: Oral leukoplakia, oral lichen planus, oral submucous fibrosis, smoking, smokeless tobacco.

Introduction
Oral squamous cell carcinoma (OSCC) is the most common malignant neoplasm of the oral cavity. OSCC is regarded as one of the most frequent cancers worldwide, the prevalence of which ranks the highest among all cancers in men in the Indian subcontinent or South Asia. About 60 to 70% of OSCC patients from South Asia receive cancer treatment only in the advanced stage, which leads to high mortality rate from OSCC. Therefore, five-year survival of OSCC directly related to the stage at which the initial diagnosis is made. Apparently, OSCC preceded by visible clinical changes in the oral mucosa usually in the form of white or red patches, known as oral potentially malignant diseases (OPMDs). The term “OPMD” usually used to describe clinical condition that has the potential to develop in to oral carcinoma. OPMDs have a significantly increased risk of progressing to cancer, mostly in South Asian population. The risk varies depending on the range of patients or lesion-related factors. It is difficult to predict the risk of progression in any individual, and the clinicians make a judgment based on their assessment of each case.

However, prevention and early diagnosis of such OPMDs have the potential not only to decrease the incidence but also to improve the survival of those who develop oral cancer. Most patients from South Asia are malnourished and frequent user of Betel quid as pan and areca nut, which are culturally acceptable mostly in the older population. Such practice leads to the development of OPMDs and increase the mortality rate of HNSCC patients. Inadequacy of public understanding of the signs, symptoms, risk factors, along with lack of sufficient information for primary identification by health care providers, are considered to be responsible for the delay in diagnosis and initiation of treatment. Several studies on oral health status performed in people from India, Pakistan, Asia, UK and...
USA, but not much from Bangladesh. This review provides an updated and comprehensive information about the OPMDs in Bangladesh.

**Epidemiology**

The spectrum of OPMDs includes a large number of disorders, such as, oral leukoplakia (OL), erythroplakia, oral lichen planus (OLP), oral submucous fibrosis (OSMF), erythroleukoplakia, oral lichenoid reactions, palatal lesions in reverse smokers, oral lupus erythematosus, graft-versus-host disease (GvHD), dyskeratosis congenita and epidermolysis bullosa. The prevalence of OPMDs varies globally, which may be attributed to difference in the associated risk factors, and cultural, dietary, and environmental factors. A systematic review including 22 epidemiological surveys estimated that the global prevalence of OPMDs was 4.47% (95% CI = 2.43–7.08). The highest prevalence of OPMDs was reported in Asian populations (10.54%; 95% CI=4.60-18.55), with the prevalence of OL and OSMF were 7.77% (95% CI = 2.86-14.80), and 4.96% (95% CI = 2.28-8.62), respectively. However, the lowest prevalence of OPMDs (0.11%, 95% CI = 0.004-0.37), was observed in North America. A panel of South Asian pathologists reported a new OPMD found among betel quid users, termed as “oral verrucous hyperplasia.” This novel lesion consisting of both exophytic and verrucous phenotypes, has been observed specifically in betel quid chewers in South Asian populations.

The most frequent sites for OPMDs in populations from the Indian subcontinent are buccal mucosa accompanied by tongue, palate and floor of the mouth. The average age of population with OPMDs has been 50-59 years, which is roughly five years younger than oral cancer patients. However, an earlier research showed that 1-5% of OPMDs have an effect on the younger age group of 30 years. One of the reasons for this could be the fact that younger population these days more likely to be exposed to a range of harmful extrinsic and intrinsic etiological elements, such as, age, sex, hereditary features, unhealthy diets, smoking, alcohol consumption, and microbial infections. A study from India has shown that among 400 OPMD cases, 78% (312/400) were men and 22% (88/400) women, suggesting male predilection. The mean age of the sufferers were 33.50 ± 13.24 years for males and 42.60 ± 14.18 years for females. Out of 400 patients mostly (342 cases) had OSMF, 39 had OL, 14 had OLP, 1 had erythroplakia, and 1 had discoid lupus erythematosus. Studies on Bangladeshi population suggested that OL and OLP are the most commonly diagnosed OPMDs, and buccal mucosa is the most common site (Table 1). The mean age of OPMD patient seems to be relatively younger, ranging between 39 to 56 years, and males are predominantly affected.

**Table 1:** Details of published studies on Bangladeshi population reporting incidence of OPMDs.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age group (mean age) years</th>
<th>Habits described</th>
<th>Gender Distribution</th>
<th>Total oral lesion cases</th>
<th>OPMD Cases</th>
<th>Site distribution</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahman AMFS et. al., 2005</td>
<td>25 - 70 (43.5±8.8)</td>
<td>Betel quid with smokeless tobacco users (mostly) &amp; Tobacco smoking (less)</td>
<td>Male = 47 Female = 16</td>
<td>80 Oral Leukoplakia-44 Oral Lichen planus-11</td>
<td>Buccal mucosa ~ 65% Tongue ~ 24.2% Lip ~ 24% Retro-molar area ~ 11.8%</td>
<td>44/80 (~55%) 11/80 (~14%)</td>
<td></td>
</tr>
<tr>
<td>Pearson N et al., 2001</td>
<td>40 – 83 (56)</td>
<td>Tobacco smoking &amp; Betel quid with smokeless tobacco users</td>
<td>Male = 77 Female = 60</td>
<td>137 Oral Leukoplakia-34</td>
<td>Buccal mucosa ~52% Tongue ~21% Lip ~13% Alveolar Ridge ~ 8% Palate Gingiva ~ 2% Mouth Floor ~ 2%</td>
<td>34/137 (~25%)</td>
<td></td>
</tr>
<tr>
<td>Bhuiyan I et. al., 2010</td>
<td>20 – 60 (39.03±12.3)</td>
<td>Not mentioned</td>
<td>Male = 53 Female = 27</td>
<td>80 Oral Lichen planus-16</td>
<td>Not specified</td>
<td>16/80 (~20%)</td>
<td></td>
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</tbody>
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Risk Factors

The major risk factors for OPMDs are well characterized, these include, tobacco (both smoked and smokeless), chewing betel quid containing areca nut, and excess alcohol consumption. In addition, the association of human papillomavirus (HPV) has also been documented. A study from India reported detection of oncogenic and non-oncogenic types of HPV in OLP, suggesting an association between HPV and OLP. Another study from Bangladesh reported association of HPV with approximately 20% of head and neck squamous cell carcinoma cases. These studies indicate possible association of HPV with the OPMDs, however, its exact role in the development of OPMDs remains unknown.

The most common smokeless tobacco (SLT) products used in South Asia, include, Betel quid or Paan with tobacco leaves, Gutkha, Naswar, Chaini, Misri and chewable tobacco. It has been suggested that SLT substances produce more than thirty carcinogenic agents. The carcinogenic agents in tobacco has been thought to act by inducing changes at both genetic and local levels, providing a favorable local environment for the hyperplastic transformation of the buccal cells. Ninety percent of the world’s SLT burden lies in South Asian countries, including, India, Pakistan, Bangladesh and Sri Lanka. These countries employ different forms of SLT products, often dictated by regional influences. Unfortunately, the use of SLT regarded as culturally and socially appropriate habit in South Asia. A recent systematic review on SLT have identified a link between SLT and oral cancer, and have suggested that a gap in knowledge regarding the effects of SLT use and the development of OPMDs exist, particularly, in the South Asia context.

Majority of the uneducated people with a low socio-economic background in Bangladesh, start using smokeless tobacco, such as betel quid and areca nuts at their early age. This practice more commonly seen in women compared to men. Women in South Asia generally stay indoors, while most men go out for work. This could be one of the reasons, for which, women may have more chance to chew betel quid or areca nuts for a longer duration, thus increasing their risk of development of OPMDs. Moreover, a significant number of people in Bangladesh are cigarette smokers, mostly men. Potential causes for mass amount of tobacco use could be poverty, financial instability, ignorance, lack of health education, and lack of implementation of sufficient government regulations. Although tobacco smoking is considered as a risk factor for oral leukoplakia, it is not strongly associated with oral submucous fibrosis or erythroplakia in the Indian Subcontinent, possibly, due to the lack of direct long-term exposure of tobacco to the oral mucosa. However, alcohol drinking has been associated with elevated risks of OL, OSMF and erythroplakia. The high dosage of Vitamin/iron supplements appeared to be another risk factor for multiple OPMDs. Among the above-mentioned factors, smokeless tobacco (SLT) chewing identified as a major risk factor for multiple oral premalignant lesions. One of the reasons could be due to SLT’s long exposure to the oral mucosa. In the Indian subcontinent, many individuals often swallow the SLT, especially, chewing tobacco fluid, and keep the chewing tobacco inside their mouth overnight.

Studies performed on Bangladeshi expats living in United Kingdom, have suggested that the prevalence of practicing similar social habits of using SLT, including betel quid, areca nuts are significantly high. An earlier research found that 95% of first generation Bangladeshi women (older population) living in the West Yorkshire (United Kingdom - UK) were betel quid chewer, of which, 89% added areca nuts to the betel quid. Another study showed approximately, 85% of Bangladeshi adult men living in Birmingham, aged 36 years and above, used SLT, while 82% of Bangladeshi women reported chewing betel quid with other SLTs. Similarly, another study from Tower hamlet, London, suggested that 86% of Bangladeshi women and 71% of Bangladeshi men living there, had habits of using tobacco and betel quid, of which, 64% of women and 42% of the men added chewing tobacco and areca nut to their betel quid. In fact, betel quid and areca nut chewing was considered to be highest among the first-generation Muslim community, and even among the first and second generations Hindu and Jain males living in UK. All the above studies suggest that Bangladeshi expats are literally using two risk factor agents at a time as social habit, SLT and areca nuts; these certainly increase the risk of development of OPMDs and oral cancer.

Common OPMDs diagnosed in Bangladesh

Oral leukoplakia, oral erythroplakia, oral submucous fibrosis, oral lichen planus, and actinic cheilitis (AC) are
commonly seen OPMDs in the Asian populations. OPMDs in these groups of people are mostly associated with cigarette smoking, areca nut, betel quid and smokeless tobacco chewing. Since betel quid and areca nut chewing are common habitual attributes in South Asian population, including Bangladeshis, the prevalence of OPMDs is high. The buccal mucosa, lower and upper buccal grooves, floor of the mouth, and the ventral surface of the tongue are commonly affected sites among South Asian populations due to the placement of betel quid and areca nut at these locations. A study from India suggested that OSMF was being the most common (8.06%), and erythroplakia was the least prevalent (0.24%) OPMDs observed in Indian population. However, OL seems to be the most common OPMD observed in Bangladeshi population, especially, with the smoking, smokeless tobacco, and areca nut users. Another study from Bangladesh by Rahman AMFS et al. suggested that OLP is also commonly diagnosed OPMD in Bangladesh but less common than OL. The incidence of OSMF is less common in Bangladeshi population, compared to OL and OLP. However, this study did not extensively observed the prevalence of OSMF, which may lead to confusion about the actual prevalence of the OSMF in Bangladesh. In fact, OPMDs and their sequels may cause heavy impairment in the quality of life of patient individually, and may implement economic burden to the society as a whole.

**Oral leukoplaikia**

The term leukoplaikia used to recognize white plaques of questionable risk excluding known disorders that carry no risk for cancer development. The OL manifests as white patches in the oral mucosa with surface of the patches slightly raised above the surrounding surfaces (Figure 1A). Clinically, leukoplaikia categorized into two groups: (a) homogeneous leukoplaikia, a lesion with uniform smooth appearance that may show slight variations but clear overall structure; and (b) non-homogeneous leukoplaikia, mainly known as white lesion and red lesion (erythroleukoplaikia) with irregular structure that may contain ulceration and may present with speckled, nodular or verrucous topography. Histological characteristics of both types of leukoplaikia are complex and can include ortho-keratosis or para-keratosis of varying degrees. Accumulation of chronic inflammatory cells within connective tissue also seen at carcinoma in situ stage (Figure 1B). Non-homogeneous leukoplaikias bear a greater possibility of transform in to malignancy.

**Fig.-1:** (A) Clinical presentation of homogenous oral leukoplaikia of a 50 years old female having history of 20 years of SLT chewing, showing thick white patches on the right side of lower buccal mucosa extending from buccal surface to the lower gingiva. (B) Histological features show hyperkeratotic lining epithelium with increased thickness of the pickle cell layer (Acanthosis). Reteridges present. Accumulation of chronic inflammatory cells in connective tissue stroma (Haematoxylin & Eosin staining, 100X magnification).
Tobacco in different forms found to be the prime aetiologic factor for leukoplakia. Smokers have an elevated risk of developing leukoplakia compared with non-smokers, as more than 80% of patients with leukoplakia are smokers.

**Oral Lichen Planus**

Oral Lichen planus (OLP) is an inflammatory keratotic dermatosis with an overall age-standardized prevalence of 1.27% (0.96% in men and 1.57% in women) observed worldwide. This is a T-cell mediated autoimmune disease, in which the cytotoxic CD8+ cells lead to the apoptosis of the basal cells of the oral epithelium. The OLP is common in all cultures around the world, and comprises more than 0.5% of all dermatological visits. Although the exact aetiology is unknown, OLP is often considered as a hypersensitivity reaction. Strong association with emotional stress, antihypertensive drugs, NSAIDs, infectious disease, and glucose metabolism disturbances reported as associated risk factors for OLP. Different clinical forms of OLP are detected, such as, reticular, erosive, atrophic, bullous, and plaque types. Among these, reticular type is the most common form, which present as a series of fine white striae bilaterally in a symmetrical pattern on the buccal mucosa, also known as Wickham striae, often surrounded by dextrate erythematous border (Figure 2A). Wickham striae is also observed on the ventral surface of the tongue. Plaque like form of lichen planus commonly found among the tobacco smokers. However, the erosive oral lichen planus has a greater risk of potential to transforms into malignancy.

Histopathology of the OLP consists of hyperkeratosis, basal layer vacuolization of apoptotic keratinocytes and a T cell infiltrate at the interface of the epithelium-connective tissue (Figure 2B). The epithelium undergoes progressive remodeling over time, resulting in decreased thickness, and a rete ridge resemble of saw tooth.

**Oral Submucous Fibrosis**

Oral submucous fibrosis (OSMF) is a systemic chronic scarring condition observed in the oral mucosa. More precisely, OSMF is a chronic, devious disease, which affects the connective tissue of the oral mucosa, and involves the submucosa, resulting loss of fibro-elasticity. Often, the OSMF linked with inflammatory juxta-epithelial reaction, accompanied by a fibro-elastic modification in the lamina propria. OMSF typically observed in the buccal mucosa, cheeks, soft palate and retro-molar regions, and occasionally in the pharynx and oesophagus. The exact aetiology of the OSMF is unknown and thought to be multifactorial in origin.

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**Fig.-2:** (A) Classical presentation of a reticular type of oral lichen planus (OLP) with Wickham striae in a 55 years old male showing fine white striae on the left side of the posterior part of buccal mucosa. (B) Histological features show epithelial hyperkeratosis with increased thickness of the pickle cell layer (Acanthosis). Partial hydropic degeneration of the basal layer with sub-epithelial chronic lymphocytic inflammatory infiltrate into the connective tissue (Haematoxylin & Eosin staining, 100X magnification).
Areca nut believed to be the major aetiological factor for the development of OSMF. Other factors may include, tobacco, chilies, lime-juice, tobacco, nutritional deficiencies such as iron, zinc, and copper, immunological disorders, collagen disorders, and genetic predisposition. In addition, Indian food habits, especially, intake of heavy spicy food, known to play a critical role in the development of OSMF.

Majority of the patients complain of burning sensation during intake of hot & spicy food. Clinically the advanced lesions appear as palpable fibrous white band in the buccal mucosa and in a circular fashion around the mouth opening and lips (Figure 3A). The mucosal membrane inside the mouth become stiff and restrict mouth opening, which causes difficulty in mastication, speech and swallowing. Salivary flow also decreased and the tongue movement restricts gradually.

Histologically, OSMF presents as atrophic epithelium with fine, fibrillar collagen bundles formation accumulating within the connective tissue lamina propria (Figure 3B), followed by abundant infiltration of chronic inflammatory cells.

Transformation from OPMD to Oral Squamous cell carcinoma (OSCC)
Extrinsic factors, such as, tobacco, betel quid, and exposure to UV ray may stimulate the malignant transformation. An earlier study suggest that the different microenvironment alteration in OPMDs create susceptible environment to transform into malignancies, such as OSCC. Chronic inflamed OPMDs usually show higher incidence of OSCC transformation. Although OE is less frequent than OL, the probability of malignant transformation is higher, more than 90% of these red lesions show serious epithelial dysplasia or carcinoma in situ. The malignant transformation rate for OSMF varies from 4 per cent to 8 per cent. An earlier meta-analysis suggested that Human Papilloma Virus (HPV) specially HPV 16 and/or 6 Infection is most prevalent in OPMDs, and may lead to malignant transformation. Furthermore, impaired immune response, such as, acquired immunodeficiency syndrome (AIDS) and Non-Hodgkin Lymphoma can also induce OPMD to OSCC.

The pathogenesis of OPMD transforming in to OSCC is a multifactorial condition. OPMDs gradually progress

Fig.-3: (A) Clinical presentation of advanced oral sub-mucous fibrosis (OSMF) of a 52 years old female showing blanching and fibrosis of the left sided buccal mucosa having marble like appearance. Blanching is associated with rupture of small vesicles to form erosion. The white fibrous band is extending from the posterior end to near lip border of the buccal mucosa. (B) Histological features show atrophic squamous epithelium with loss of reteridges. Collaginisation of the sub-epithelial connective tissue scantly infiltration of chronic inflammatory cells (Haematoxylin & Eosin staining, 100X magnification).
in a diverse tissue microenvironment where they evolve sustainably and gradually taking the characteristics of oral squamous cell carcinoma (OSCC). The malignant transition of OPMD to OSCC includes many critical factors such as angiogenesis, lymphangiogenesis, genetic changes, and mutational factors. Furthermore, some extrinsic factors disrupt the architectural orientation of epithelium, disruption of internal stromal tissue homeostatic in the affected area thought to be the main pathologic cause for transformation of OPMD to OSCC. Simultaneous coordination between inflammatory cells of the epithelium and the tissue microenvironment thought to play a vital role in the carcinogenic mechanism.

The transition of OPMDs to OSCC showed elevated expression of FGF-2 (Fibroblast Growth Factor-2) and its receptors, and FGF-3 in the tumour microenvironment. Activated Cancer-associated fibroblasts (CAFs) and myofibroblasts (MFs) were present in the OPMD and OSCC microenvironments, however, the number of CAFs and MFs escalate as the disease progresses from OPMD to OSCC. Thus, CAFs and MFs act as potential indicators for OPMD to OSCC transition. In addition to immune cells, the extracellular matrix (ECM) composition may also play as a significant indicator of OPMD developing to malignant condition.

**Diagnosis of Potentially malignant disorders**

In general, OPMDs diagnosed clinically in Bangladesh. For the confirmatory diagnosis, biopsy and histopathological examination are performed, and later to plan for proper treatment. In case of large lesions, incisional biopsy mostly performed. If the lesion is small, an excisional biopsy is the treatment of choice. Toluidine blue used to stain correct biopsy sites and vizilite. Another method of diagnosis is Mirror Image Biopsy, which is capable of identifying the clinically normal-looking oral mucosa having pre-existence of dysplastic changes in a large proportion in oral cancer patients. Therefore, the mirror image biopsy could be an effective diagnostic method for early detection of dysplastic changes in seemingly normal preconditioned mucosa.

Another study from India reported that progressive increase of serum and salivary sialic acid noted in patients with OPMDs and OSCC, indicating serum and salivary sialic acid as potential biomarkers for OPMD and OSCC. Moreover, overall serum cholesterol, HDL and Apo A1 levels used as diagnostic tools as they have shown to decrease significantly in OSMF patients and Leukoplakia patient, but no difference observed in lichen planus patients. Therefore, lipid profile could be used as a potential diagnostic tool, especially for diagnosing OSMF and Leukoplakia.

**Management of OPMD**

Adequate treatment of potentially malignant disorders rely on patient age, early detection and avoidance of malignant transformation, structural causes, behavioral history, duration, type and clinical characteristics, natural history and histopathological characteristics. Regardless of individual risk factors, all patients diagnosed with OPMD should receive counseling. The aim is to reduce their future risk of malignancy through cessation of tobacco, moderation of alcohol, and use of betel quid (areca nut) among Asian patients. If there are no signs of dysplasia, conservative therapy recommended regardless of the clinical form of the lesion. Conservative therapy includes the use of vitamins, green tea, lycopene, protease inhibitors and anti-inflammatory medicines. In cases of moderate or severe dysplasia, conservative and surgical therapies are recommended.

In the case of OSMF patients, 5 mg dispersible tablets of Prednisolone as mouthwash using three times a day found to work well, especially in ulcerative condition to reduce the symptoms.

For treating OL, primarily traditional conservative treatments include, Enameloplasty to smoothen the sharp teeth, Vitamin therapy such as, vitamin A, C & E for the proliferation and natural arrangement of the epithelium layers, â carotenes to avoid oncogenic free radicals, and nystatin when candida infection is superimposed. In addition, surgical excision by cryosurgery or laser therapy are considered as general surgical therapy for leukoplakia. A meta-analysis of interventional studies suggests that oral leukoplakia excision can reduce transformation risk. Therefore, current convention recommend high risk lesions such as erythroplakias, erythroleukoplakias or leukoplakias with moderate or severe dysplasia should be excised in the absence of any surgical contraindications.

While there is no precise therapy for OLP, certain medications may help to alleviate associated clinical
conditions. Topical and systemic medications may cure non-ulcerative OLP. Corticosteroids are the single most effective medication category for lichen planus management. A study from India suggested that both hydroxychloroquine and griseofulvin have shown clinical improvement and better response in patients with OLP. Another study from Bangladesh by Hadiuzzaman M, et al in 2013, reported that a patient having a 10-year history of chronic OLP, remained nonresponsive after the application of topical triamcinolone acetonide and systemic steroids, and later went for surgical excision, after which, the patient got cured, and no relapse observed after 2 years of follow up. Therefore, if the topical and systemic applications fail for OLP, surgical excision might be the treatment of choice.

Conclusion:
It is estimated that most cancer deaths worldwide could be avoided by early detection, as this more likely to offer a better likelihood to pursue early and successful treatment. The key goal of secondary prevention is to detect OPMDs early when they are handled most effectively. In Bangladesh, due to lack of public education, and lack of expertise among medical professionals, OPMDs are frequently remained undiagnosed. Clinical presentation and lesion diagnosis are not sufficient to assess the premalignant existence as not all OPMDs progress to malignancy. Therefore, more research is very much required in Bangladesh to explore and understand the true epidemiology of OPMDs and treat them adequately.

Authors contribution
MAI performed the literature search and wrote the first draft, corrected versions and agreed the final manuscript. SMAS critically revised the manuscript and provided clinical and histological pictures, and agreed the final version. MHS devised and organised the manuscript, assisted in electronic search of the published literature, critically revised all versions and agreed the final manuscript.

Informed consent
Informed consent obtained from the patients only for the use of clinical photos.

Conflict of interest
None.

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References


