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A NOMOGRAM TO PREDICT THE MALIGNANT TRANSFORMATION RISK OF OPMDS USING CHAIR SIDE DIAGNOSTIC AIDS AND HISTOPATHOLOGICAL EXAMINATION

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ABSTRACT

A nomogram is a graphical calculating device mainly used for the graphical computation of a mathematical function. It is basically a diagram consisting of scales representing the relationship between three or more variable quantities. The value of an unknown variable can be found by simple geometrical construction, by drawing a straight line intersecting the other scales at appropriate values. Oral Potentially Malignant Disorders (PMD) includes a variety of lesions and conditions characterised by an increased risk of malignant transformation to oral squamous cell carcinoma. A biopsy (histopathological examination) is considered to be the gold standard for the definitive diagnosis of an OPMD and its malignant progression. There are various chair side diagnostic aids like vital staining, light based detection systems and other non invasive diagnostic aids like exfoliative cytology like brush biopsy which can serve as adjuvants for diagnosis of these disorders and for proceeding with treatment planning such as need for biopsy for the definitive diagnosis. There are also various molecular and genetic markers which can be used in the diagnosis of OPMDs and oral cancer. This review highlights about various OPMDs, chair side diagnostic tools and aims to device a nomogram to predict the risk of malignant transformation of OPMDs using chair side diagnostic aids and histopathological examination.

Key words: Nomogram, OPMDs, risk, malignancy

INTRODUCTION

The World Health Organisation (WHO) in 1978 had initially proposed the terms "precancerous lesions" and "precancerous conditions" and precancerous lesion was defined as 'a morphologically altered tissue in which cancer is most likely to occur than its apparently normal counterpart ' and precancerous condition was 'a generalised state where there was an increased risk of cancer' **[1]**. A workshop in 2005 redefined all oral lesions with a potential for malignant transformation to be grouped under the title "Potentially Malignant Disorders **[2]**. The traditional terminologies of premalignant lesions and premalignant conditions have been abandoned. Oral Potentially Malignant Disorders (PMD) includes a variety of lesions and conditions characterised by an increased risk of malignant transformation to oral squamous cell carcinoma. The histopathological features of a given lesion, especially the presence of epithelial dysplasia are currently the most useful indicators of malignant transformation risk **[3]**. In this regard, the clinical features of PMD can show considerable variation within the same histopathologically defined entity that may be critical to the likelihood of progression towards malignancy **[4]**. It has been reported in literatures that The International Agency for Research on Cancer (IARC) and the World Health Organisation (WHO) have stated that out of 15 million oral cancer cases, one third of it can be prevented by timely intervention with the help of appropriate screening strategies. Oral cancer is the sixth most common malignancy reported worldwide and makes around 40 % of the cancers globally **[5]**.

According to the new classification of the WHO, OPMDs are defined as "clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal oral mucosa" **[6]**. The latest WHO monograph on head and neck tumours in 2005 had used the terminology 'epithelial precursor lesions' and defined it as 'altered epithelium with an increased likelihood for progression to squamous cell carcinoma' **[7]**. It is also mentioned that word 'altered' in the definition means epithelial dysplasia. A new term 'potentially premalignant oral epithelial lesion' (PPOEL) has recently been used as a broad term to define both histologic and clinical lesions that have potential for malignant transformation. This encompasses a broad variety of lesions like leukoplakia, erythroplakia, erythro-leukoplakia, lichen planus, oral submucous fibrosis and oral dysplasia.

There have been various chair side diagnostic tools which serve as adjuncts for detection of dysplasias in these lesions which could aid in timely intervention **[8]**. These adjunctive aids could be broadly divided into three categories as optical imaging devices, those with high resolution microscopy (in vivo microscopy) and vital staining techniques that use various dyes to delineate any altered mucosa. These optical devices work detect changes in the optical properties of the surface epithelium and submucosa. These changes are based on light absorption, scattering or fluorescence of the tissue **[9]**. In vivo microscopy uses specific probes for real-time imaging of morphometric features at a gross level that for an impression of nuclear and cellular features of the lining mucosa **[10]**. Vital staining is also one of the most efficient chair side diagnostic aid for detecting dysplasia in various OPMDs **[11]**. It can be done as supravital or intravital staining. Supravital staining is a method of staining used in microscopy to examine living cells that have been removed from an organism. It differs from intravital staining, which is done by injecting or otherwise introducing the stain into the body. There have been various stains used for vital staining which include toluidine blue, methylene blue, lugol's iodine, rose bengal, acetic acid **[12]**. The gold standard for detection of dysplasia in OPMDs is histopathological examination as it is generally accepted that the histopathological features of a given lesion, especially the presence and degree of epithelial dysplasia, are currently the most useful indicators of malignant transformation risk **[13]**. For an overall accurate assessment of the malignant transformation risk of these OPMDs, it is essential that all the clinical, molecular and histopathological features should be evaluated properly.

Aim

To devise a nomogram to predict the malignant transformation risk of OPMDs into oral cancer by using chair side diagnostic aids and histopathological examination.

METHODOLOGY

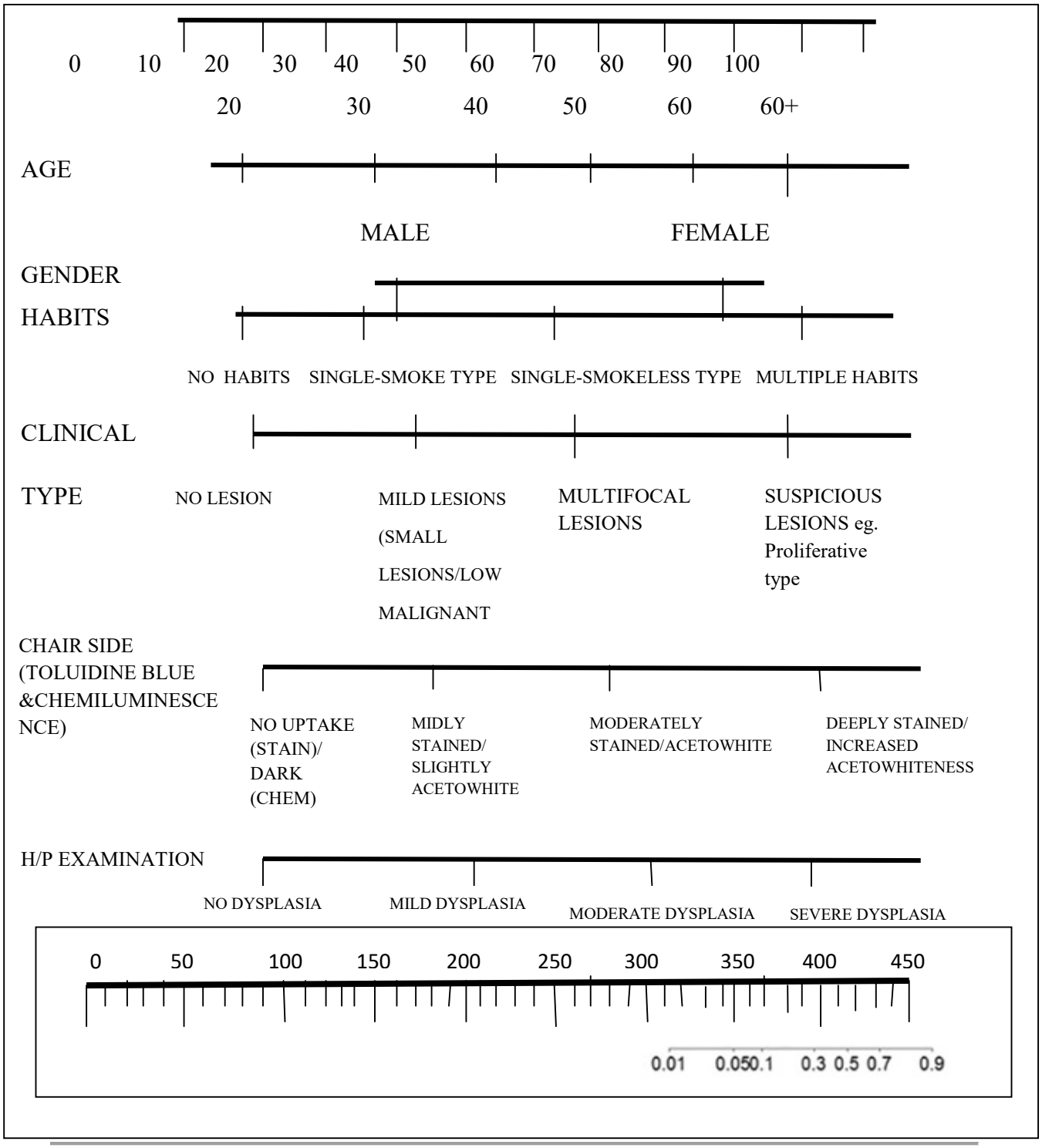
A retrospective analysis of patients clinically diagnosed with OPMDs who underwent chair side examination with a combination of toluidine blue and chemiluminescence and later histopathological examination were chosen. A risk prediction model using a nomogram which consisted of a scale ranging from 0 to 100 with the following variables:

i) Age
ii) Gender
iii) Habits
iv) Clinical diagnosis

v) Chair side examination (Toluidine blue & chemiluminescence)

vi) Histopathological examination (Biopsy)

Each of the variables was plotted against the scale and the total points were calculated. The minimum and the maximum score of the given data set were analysed and the probability scale ranged between 230 to 420.



Eg: Consider the following case scenario

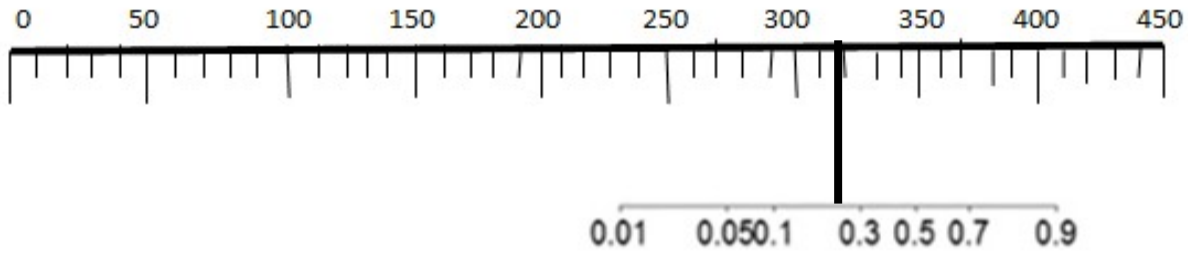
A 35-year old male patient with habit of gutkha chewing for the past 20 yrs.

Clinical diagnosis: OSMF with leukoplakia

Chair side (TB+Chem) examination: Moderately stained with acetowhite hue

H/P Report: Moderate epithelial dysplasia

- Age :35 =**38 points**
- Gender : Male =**28 points**
- Habit : Single-smokeless type tobacco = **55 points**
- Clinical type : OSMF with leukoplakia=**62 points**
- Chair side =**55 points**
- H/P examination=**62 points**
- **TOTAL : 300 PTS**



Risk of malignant transformation as in this case is around 20 %

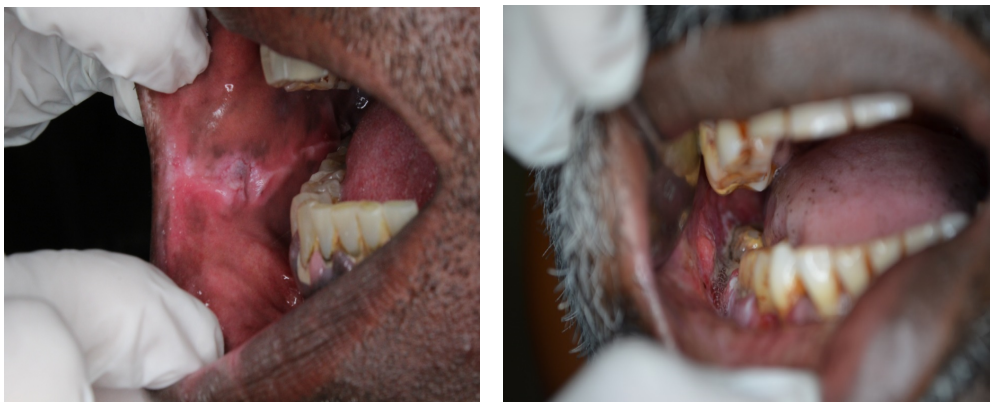


Figure 1: Clinical presentation of OPMDs

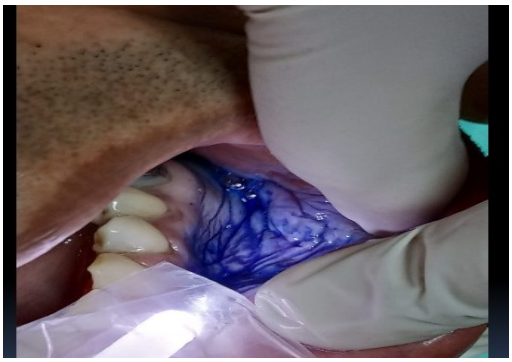


Figure 2: Chair side diagnosis using a combination of toluidine blue and chemiluminescence

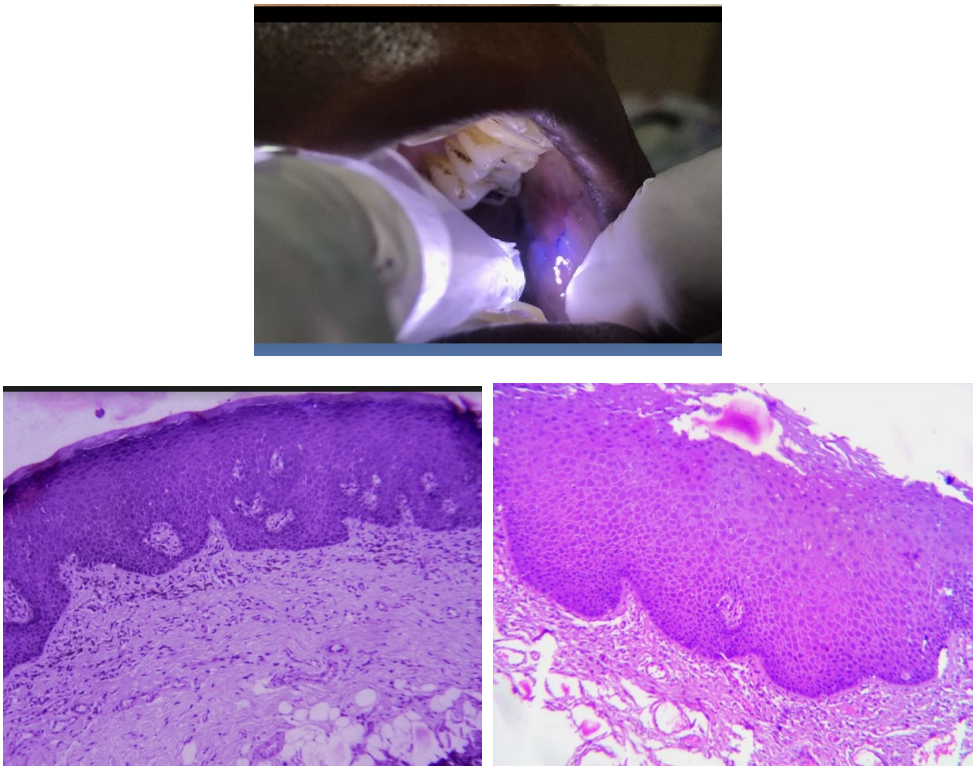


Figure 3: Histopathological examination (Presence or absence of epithelial dysplasia)

DISCUSSION

A nomogram is a graphical calculating device, a pictorial representation consisting of a scale with one or more variables; it depicts the numerical probability of an event. Medical nomograms use biologic and clinical variables, like tumour grade and patient age, to graphically depict a statistical prognostic model that generates a probability of a clinical event, such as cancer recurrence or death, for a given individual **[14-16]**. A nomogram construction first involves choosing of a relevant clinical question which requires a mathematical model to answer, followed by determining the variables which influence the outcome based on priori clinical hypothesis. The next step involves choosing a statistical model like a Cox Proportional hazards regression model. Then a process of validation is done which involves testing on populations to assess the performance. There are various nomograms in the medical field for calculation of body mass index, hba1c test and post test probabilities for gestational diabetes. In oral medicine, there are various nomograms published in the literature like for estimating the malignant transformation risk of leukoplakia, oral cancer, temperomandibular joint disc perforation. Kim et al constructed a nomogram to predict the risk of temperomandibular joint disc perforation using clinical and imaging findings (magnetic resonance imaging). Age, disc shape, bone marrow signal, joint

space narrowing and changes of condyle and fossa were the variables considered and plotted against a scale from 0 to 100 points. The total points ranged from 0 to 350 and numerical probability was estimated. Nomogram was constructed with a prediction model from multivariate binary logistic regression analysis and the suitability of the model assessed with Hosmer-Lemeshow goodness -of-fit test **[17]**. Wang *et al*. constructed several types of survival models using a set of 979 patients with oral cavity squamous cell carcinoma. Covariates were age, sex, tobacco use, stage, grade, margins, and subsite. The best performing model was externally validated on a set of 431 patients and the outcome was locoregional recurrence free survival. They found that lognormal model showed the best results. An online nomogram was built from this model for the estimation of locoregional failure-free survival with and without postoperative radiotherapy **[18]**. Another study was done to construct a nomogram for prediction of the malignant transformation risk of leukoplakia, which was a retrospective analysis of patients diagnosed with oral leukoplakia and confirmed histopathologically. The candidate risk factors for malignant transformation of leukoplakia were screened from clinicopathological variables were age, histologic grade, site of lesion and smoking habits using the Cox proportional hazard regression analysis. The nomogram model was generated based on the COX regression results and was validated through Harrell concordance index (c-index) and calibration plots and suggested that patients with leukoplakia who were over 50 years old, non-smokers with dysplasia, and lesions involving the lip, the floor of mouth, and tongue had an enhanced risk for malignant transformation. The established nomogram model had the predictive value of malignant progression and aided in the treatment strategy and screen of high risk patients **[18]**.

CONCLUSION

Nomograms are risk prediction models for predicting the prognostic and treatment planning process of various diseases. There are well established nomogram models in oral medicine for predicting the malignant transformation risk of certain OPMDs, prognosis of oral cancer, TMJ pathologies etc. Hence construction of nomograms and appropriate standardisation is required for the validity and generalisability to varied population groups which can play an important role in the clinical decision making process.

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