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A Comparative Study Using WHO and Binary Oral Epithelial Dysplasia Grading Systems in Leukoplakic Lesions

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Abstract

Objectives: This study aimed to compare the reproducibility and consistency of the World Health Organization (WHO) and Binary oral epithelial dysplasia grading systems when applied to leukoplakic lesions, the most common oral potentially malignant disorders (OPMDs).

Methods: In this retrospective, cross-sectional study, clinical data and microscopic slides of 89 leukoplakia cases were reviewed. Two pathologists independently graded each sample using both WHO and Binary systems. Inter-observer agreement was evaluated using kappa statistics. The relationship between variables and the grade of dysplasia was analyzed using T-test and Chi-square test at $p<0.05$.

Results: The mean age of cases was 53.93 ± 13.84 years, with a slight female predominance. The lesions were most commonly located on the tongue (38.2%) and buccal mucosa (37.08%). The inter-observer agreement was higher for the Binary system (kappa index= 0.62) compared to the WHO system (kappa index= 0.46). The highest agreement was observed for cellular features such as the increased number of cell nucleoli (0.74) and cell pleomorphism (0.73), while keratin pearls showed the lowest agreement (0.21).

Conclusion: The Binary classification system demonstrated superior consistency and reproducibility compared to the WHO system due to fewer grading categories. However, its detailed numerical requirements and time-consuming nature may limit its widespread adoption, which is why the WHO system is more commonly used.

Keywords: WHO; Binary; Classification; Grading; Dysplasia; Leukoplakia; Oral cavity

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Introduction

Squamous cell carcinomas (SCC) comprise roughly 90% of head and neck neoplasms and have a high morbidity rate and a five-year survival rate below 50% mostly due to late diagnosis.[1] The majority of these lesions are preceded by oral potentially malignant disorders (OPMDs), a category of conditions that pose a greater likelihood of progressing into SCC than normal oral tissue.[2,3] The term "potentially malignant" is favored over the commonly used term "premalignant" because it recognizes that progression to malignancy is not inevitable but represents an elevated risk.[4] OPMDs include several conditions, such as oral leukoplakia (OL), erythroplakia, erythroleukoplakia, submucous fibrosis, palatal lesions from reverse smoking, smokeless tobacco keratosis, lichen planus, discoid lupus erythematosus, actinic cheilitis, Fanconi anemia, dyskeratosis congenita, and xeroderma pigmentosa.[5,6] The OL, the most prevalent OPMD globally with a prevalence of 1-5%, is described by the World Health Organization (WHO) as a white plaque of uncertain risk, following the exclusion of other diseases or conditions that do not elevate cancer risk.[7] In a 2020 meta-analysis of 32 studies, an estimated overall mean rate of malignant transformation (MT) for OL was 9.3%.[8]

Histological analysis and grading of dysplasia are the gold standard for diagnosis, establishing prognosis, and assessing the rate of MT. The criteria for grading oral epithelial dysplasia (OED) include both architectural and cytological changes.[3,6] Epithelial dysplasia manifests as an abnormal or atypical proliferation of epithelial cells, causing a lesion with disrupted differentiation and maturation.[5] Although progression to cancer is more likely with higher grades of dysplasia, lower grades can also transform into malignant disease.[9,10] The grading of dysplasia plays a crucial role in determining the treatment approach for these lesions.[9]

Approximately 15 OED grading systems have been developed, showing varying degrees of effectiveness.[5] One significant challenge with these systems is the limited reproducibility caused by the considerable variability among examiners, both within and between them.[5] To mitigate this bias, the WHO introduced a three-tiered scale (mild, moderate, and severe dysplasia), combining severe dysplasia and carcinoma in situ into one category. However, managing lesions classified as moderate dysplasia remains challenging with this system.[2] Kujan et al. simplified the classification of epithelial architectural and cytological changes defined by the WHO by proposing a binary grading system that categorizes lesions into low-risk and high-risk groups for malignant transformation.[11] Some authors believe that the binary system is currently the most effective OED grading method, as it is clinically relevant, reproducible, and accurately predicts which lesions may progress to malignancy.[5] This study aimed to compare the Binary and WHO systems, the two commonly used classification systems, in terms of their reproducibility and ability to provide consistent results when applied to leukoplakic lesions as the most common OPMDs.

Methods

This retrospective cross-sectional study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.DRC.REC.1399.145). The archived files of oral and maxillofacial pathology department, Shahid Beheshti University of Medical Sciences were reviewed and all cases with a clinical diagnosis of leukoplakia were selected. Clinical data such as age, gender, and lesion location were recorded based on the gathered files, and microscopic slides were reviewed in all cases. Cases with microscopic diagnosis of SCC or hyperkeratosis/epithelial hyperplasia were excluded from the study. Two pathologists (an oral pathologist (A) and a general pathologist (B)) graded 89 leukoplakias using both grading systems. Each sample was assigned to a mild, moderate, or severe group based on the WHO system and to a low-risk or high-risk group based on the binary system. Inter-observer agreement was evaluated with the use of kappa statistics similar to previous studies[12] as follows: <0 = poor agreement, 0-0.2 = slight agreement, 0.21-0.40 = fair agreement, 0.41-0.60 = moderate agreement, and >0.61= good agreement.

Statistical analyses were performed by SPSS version 25. The Kappa statistical index was utilized to evaluate the degree of agreement between the two pathologists concerning each of the cellular and structural features. The relationship between variables and the grade of dysplasia was analyzed using T-test and Chi-square test. Moreover, p-values less than 0.05 were considered statistically significant.

Results

The archived files of 89 patients diagnosed with leukoplakia were included in the study. Forty cases (45%) were males and 49 cases (55%) were females. Their ages ranged from 27 to 90 years with a mean age of 53.93 ± 13.84, and the most common decade was the 6th decade of life (26%). Tongue (38.2%) and buccal mucosa (37.08%) were common sites. Mild, moderate, and severe inflammation was observed in 32.5%, 29.5%, and 23.5% of the cases, respectively. Moreover, 89% of the samples exhibited hyperkeratosis and 17% exhibited pigmentation. Based on the T-test for age (p = 0.510) and the Chi-square test for hyperkeratosis (p = 0.9), pigmentation (p = 0.579), inflammation (p = 0.099), sex (p = 0.383), and lesion location (p = 0.088), no significant relationship was found between these variables and the grade of dysplasia. Tables 1 and 2 represent the grading results conducted by both pathologists using each classification system. In addition, OED was most frequently observed at a mild level, with moderate and severe cases being less common (Figures 1, 2, and 3). The percentage of agreement between the two pathologists was calculated based on the Kappa index, and its rate was higher in the Binary system (0.62) than in the WHO system (0.46) (Table 3). According to Cohen's kappa coefficient, the concordance of the diagnosis of the two pathologists was in the good category for the Binary system and in the moderate category for the WHO system. The highest level of agreement was related to the feature of increased number of cell nucleoli (0.74) and cell pleomorphism (0.73). The lowest level of agreement was related to keratin pearls (0.21).

Table 1 - Grading results of pathologist A

	WHO system	Binary system	
		Low risk	High risk
Mild	56 (62.9%)	56 (100%)	-
Moderate	21 (23.6%)	10 (47.6%)	11 (52.4%)
Severe	12 (13.5%)	1 (8.3%)	11 (91.7%)
Total	89 (100%)	67 (75.3%)	22 (24.7%)

Table 2 - Grading results of Pathologist B

	WHO system	Binary system	
		Low risk	High risk
Mild	59 (66.3%)	56 (94.9%)	3 (5.1%)
Moderate	22 (24.7%)	13 (59.1%)	9 (40.9%)
Severe	8 (9%)	-	8 (100%)
Total	89 (100%)	69 (77.5%)	20 (22.5%)

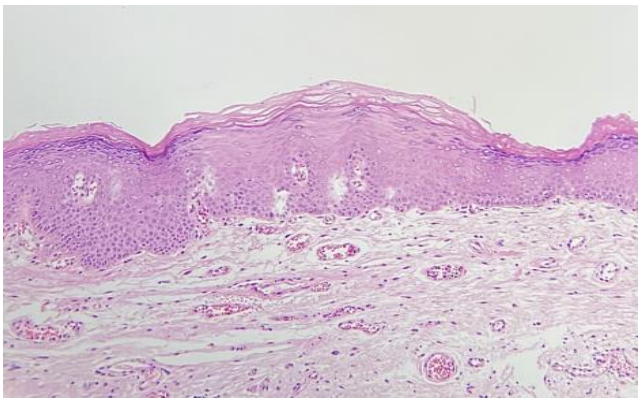

Figure 1: Mild dysplasia. Hyperortokeratosis and superficial granular layer are visible. Basilar hyperplasia and cell hyperchromatism are evident in the basal and parabasal layers of the epithelium (H&E ×100).

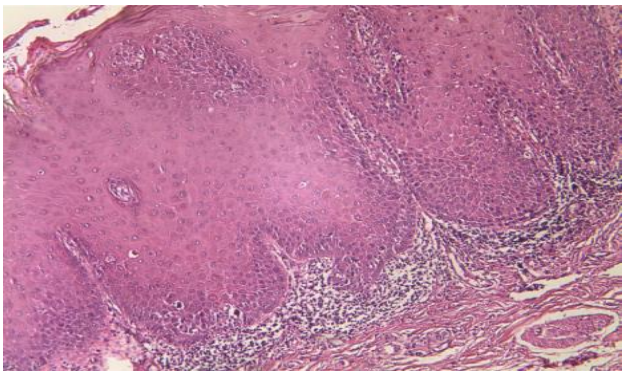

Figure 2: Moderate dysplasia. Bulbous red ridges are seen. Cellular changes and individual cell keratinization are evident up

to the mid portion of the epithelium. Inflammation is present in the lamina propria (H&E ×100).

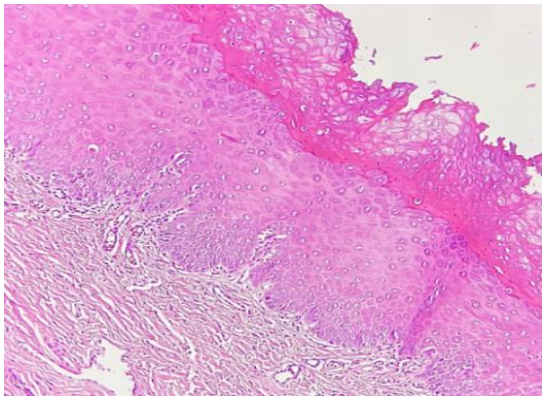

Figure 3: Severe dysplasia/carcinoma in situ. A thick orthokeratinized layer is seen. Prominent structural and cellular changes, including the change in the shape of rete ridges, pleomorphism of cells and nuclei, individual cell keratinization, and hyperchromatism above the mid portion of the epithelium are clearly visible (H&E ×100).

Table 3 - Degree of agreement among the pathologists

	Grade	Pathologist A	Pathologist B	Kappa value
WHO system	Mild	56 (63%)	59 (66.3%)	0.46
	Moderate	21 (23.6%)	22 (24.7%)	
	Severe	12 (13.5%)	8 (9%)	
Binary system	Low risk	22 (24.7%)	20 (22.5%)	0.62
	High risk	67 (75.3%)	69 (77.5%)	

Discussion

Numerous efforts have been dedicated to identifying an appropriate algorithm for accurately predicting the progression of potentially malignant lesions. According to the WHO, the malignant transformation rate of OL ranges between 1 and 2%, with reported values varying from 0.1 to 36.4%.[1] Several factors potentially associated with an increased risk of malignant progression include age, gender, lesion size and subtype, color, location, texture, duration, presence of Candida infection, habits, race, geographical region, and grade of dysplasia.[4,5] Based on the results of this study, there was no significant relationship between the severity of dysplastic changes and demographic factors such as age, gender, and lesion location. This is consistent with findings from both Jayasooriya et al. and Nankivell et al.[10,13] However, a systematic review by Warnakulasuriya and Ariyawardana indicated that women and older individuals have a higher risk of malignant transformation in OL lesions compared to men and younger individuals.[14] Additionally, some studies have suggested that lesions on the lateral border of the tongue are more prone to malignancy.[5] Furthermore, according to available studies, the grading of dysplastic lesions is considered the most critical factor and plays an independent role in determining the prognosis of these lesions.[5,13]

In the present study, there was greater concordance in the classification results of the slides by two pathologists using the Binary system (kappa coefficient = 0.62) compared to the WHO system (kappa coefficient = 0.46). This is consistent with findings from Kujan et al.'s study (0.35-0.65 for Binary vs 0.06-0.43 for WHO) and Nankivell et al.'s study (0.59 for Binary vs 0.49 for WHO).[10,15] However, in Krishnan et al.'s study, despite the Binary system showing the highest level of agreement, the kappa coefficient was only 0.201, indicating a fair agreement rate.[12] In the present study, the highest level of agreement was related to the features of an increased number of cell nucleoli (0.74) and cell pleomorphism (0.73). Keratin pearls and abnormally superficial mitosis, which exhibited the highest conformity rates in Nankivell's study [10], had the lowest agreement levels in this study. This study, along with Krishnan's, demonstrated greater agreement among pathologists regarding cellular features compared to structural features. Conversely, Kujan's and Nankivell's studies reported higher agreement rates among pathologists for structural features than for cellular features.[10, 16]

Different results among studies may originate from variations in pathologists' experience, interpretations of features, and inconsistencies in calibration. Another cause of these differences is the number of grades in each system; In the 2017 WHO system, a modification of the 2005 WHO system, hyperplasia and carcinoma in situ were merged with the mild and severe classes, respectively, to reduce the number of grading categories.[17] One of the main reasons for developing the Binary system, despite the widespread use of the WHO system, was to minimize discrepancies among pathologists in their slide evaluations.[16] In the present study, for pathologist A, 47.6% of moderate cases in the WHO system were low-risk in the binary system, and 52.4% were high-risk. For pathologist B, 59.1% of moderate cases in the WHO system were low-risk in the binary system, and 40.9% were high-risk. This division indicates differing prognoses and treatment plans. The two groups, low-risk and high-risk, have different treatment plans, so the new binary grading system can help clinicians make more appropriate treatment decisions for OED, aligning with Kujan et al.'s opinion. [15] This result was not achieved in the WHO 2017 edition as the issue with the moderate group persisted, leading to subjective decision-making for lesions in this group. From a research perspective, adopting a standardized system for classifying lesions among all pathologists and ensuring uniformity in reporting the severity of dysplasia internationally would enhance the speed and accuracy of many systematic studies.[1]

In a systematic review conducted by Gupta et al., ease of use is highlighted as an advantage of the 2017 WHO system over other systems.[17] According to the present study, the Binary

system is relatively time-consuming as it involves counting cellular and structural features and conducting further analyses to classify lesions into one of two grades. Based on Tilakaratne et al.'s opinion [5], an effective OED grading system should be: 1. Clinically relevant; It should aid in case management by distinguishing lesions that require treatment, whether surgical or nonsurgical, from those that can be monitored. 2. Reproducible; It should minimize intra- and inter-examiner disagreements. 3. Biologically significant; It should effectively identify lesions with a high likelihood of malignant transformation. To develop more precise guidelines and accurately assess the significance of each feature, several steps can be taken: calibrating pathologists' opinions regarding the definitions of structural and cellular features, ensuring a large and homogeneous sample population with the same type of dysplasia in the same mouth location, and monitoring patients over several years for malignancy. Alternatively, a retrospective study with a diverse range of lesions may be designed to examine the correlation between each dysplastic feature and the likelihood of malignant transformation.

Conclusion

Compared to the WHO system, the Binary classification system provides more consistent and reproducible results due to the reduced number of grades. However, the Binary system's reliance on detailed numerical classification and additional estimations makes it more time-consuming and challenging to use, which is why the WHO system remains more widely adopted among pathologists.

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Conflict of Interest: No Conflict of Interest Declared ■

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