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Association between hyperglycemia and the malignant transformation of oral leukoplakia in China

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Abstract

Objectives: This study aimed to examine the association between hyperglycemia and the malignant transformation of oral leukoplakia (OLK).

Patients and Methods: This retrospective case–control study involved 133 patients with the malignant transformation of OLK into oral squamous cell carcinoma (case group) and 266 patients with untransformed OLK (control group). The clinical history and follow-up data included age, gender, lesion size and location, and fasting plasma glucose. Logistic regression analysis, Kaplan–Meier survival analysis, and univariate and multivariate Cox regression analyses were used to assess the effects of risk factors on the malignant transformation of OLK.

Results: Hyperglycemia (adjusted hazard ratio [AHR] = 4.7, p = .001), non-homogenous OLK (AHR = 3.0, p < .001), location of the lesion on the ventral surface of the tongue or floor of the mouth (AHR = 3.6, p < .001), and epithelial dysplasia (AHR = 2.8, p = .005) had significant effects on the malignant transformation of OLK.

Conclusion: Hyperglycemia, non-homogenous OLK, location of the lesion on the ventral surface of the tongue or floor of the mouth, and epithelial dysplasia might be associated with malignant transformation of OLK.

KEYWORDS

diabetes mellitus, head and neck cancer, hyperglycemia, oral cancer, oral leukoplakia, squamous cell carcinoma

1 | INTRODUCTION

Oral leukoplakia (OLK) was defined in 2005 by World Health Organization (WHO) as "white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer," and classified as an oral potentially malignant disorder (OPMD; Reibel et al., 2017; Warnakulasuriya, Johnson, & van der Waal, 2007). The pooled estimated prevalence of OLK ranged from 1.5% (95% confidence interval [CI] = 1.4–1.5) to 2.6% (95% CI = 1.7–2.7; Petti, 2003).

Studies have reported the estimated mean overall malignant transformation rate of OLK is 3.5% (range = 0.1%–34.0%; Carrard & Van der Waal, 2018; Warnakulasuriya & Ariyawardana, 2016), and the annual malignant transformation rate is 2%–3% per year (Carrard & Van der Waal, 2018). Multiple risk factors, including histopathological and clinical characteristics, might contribute to malignancy development. Several studies have reached consensus about the risk factors, such as the size of the lesion, the clinical subtype of OLK, and the presence of epithelial dysplasia (Carrard & Van der Waal, 2018;

Abbreviations: 2-hr PG, 2 hr plasma glucose; AHR, adjusted hazard ratio; CI, confidence interval; FPG, fasting plasma glucose; HbA1C, glycated hemoglobin; MT, malignant transformation; OGTT, oral glucose tolerance test; OR, odds ratio; PG, plasma glucose; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; UT, untransformed.

Jin Li and Yang Liu contributed equally to this work.

Villa & Woo, 2017; Warnakulasuriya & Ariyawardana, 2016). However, research reports on the association between systemic diseases and the malignant transformation of OLK are lacking.

Diabetes mellitus (DM) is a group of diseases associated with disorders of glucose metabolism, characterized by decreased insulin secretion and decreased insulin sensitivity (insulin resistance), or both (Seino et al., 2010). Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of cases of DM and causes serious complications, such as diabetic ketoacidosis, chronic kidney disease, and damage to the eyes (Seino et al., 2010). Prediabetes refers to glucose levels that do not meet the criteria for DM but are too high to be considered normal (American Diabetes Association, 2019). In 2015, 425 million people worldwide had DM and the number was predicted to rise to 642 million by 2040 (Ogurtsova et al., 2017). A nationally representative cross-sectional survey reported the overall prevalence of DM among adults in China was 10.9%, and 35.7% for prediabetes (Wang et al., 2017), causing a substantial medical and financial burden.

Multiple studies and meta-analyses have reported an association between DM and an increased risk of developing cholangiocarcinoma, breast, colorectal, endometrial, and gallbladder cancers (Tsilidis, Kasimis, Lopez, Ntzani, & Ioannidis, 2015). Patients with T2DM have been found to have a higher risk of developing oral cancer or precancerous lesions than those without DM (Gong, Wei, Yu, & Pan, 2015), and the role of hyperglycemia in raising the risk of developing OLK has been documented in recent studies (Marta & Lopez-Jornet, 2017). However, research supporting an increased risk of malignant transformation of OLK related to DM and prediabetes is lacking. As hyperglycemia is the common characterized metabolic alteration in both DM and prediabetes, the objective of this study was to assess the association between hyperglycemia and the malignant transformation of OLK and to verify the significant effects of risk factors on malignant transformation, including the size and location of lesions and the presence of dysplasia.

2 | PATIENTS AND METHODS

A retrospective paired case–control study was conducted, using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting the methods and results (O'Connor et al., 2016).

2.1 | Ethics approval

The Peking University Institutional Review Board, China, approved this study (PKUSSIRB-201736078), and all methods were performed in accordance with the relevant guidelines and regulations.

2.2 | Study population

This study involved the retrospective assessment of the hospital archive records of 399 consecutive OLK patients in 1999–2018 at the Department of Oral Medicine of the Peking University School and Hospital of Stomatology, China. Among them, 133 patients with OLK and a malignant transformation into oral squamous cell carcinoma (OSCC) were selected for the case group and 266 patients with untransformed OLK were selected for the control group. The case and control groups were matched by sex and age (±1 year), and the ratio was 1:2.

2.3 | Inclusion criteria

The inclusion criteria for the case group, that is, the malignant transformation (MT) group were as follows: (a) patients with OSCC that developed in the same site of a previous OLK with available histopathological reports as per WHO criteria (Lester, 2005; Reibel et al., 2017), and (b) diagnosis of OLK preceded diagnosis of OSCC in all cases with a biopsy interval of >1 month.

The inclusion criteria for the control group, that is, the untransformed (UT) group were as follows: (a) patients with OLK without malignant transformation during the long-term follow-up period, (b) a follow-up period longer than 12 months, (c) the most recent follow-up time within 3 months before the end of the study (November 2017–January 2018), and (d) matched by sex and age (±1 year).

2.4 | Exclusion criteria

The exclusion criteria were as follows: (a) patients without available histopathological examinations with diagnosis of OLK or OSCC, (b) patients with a diagnosis of OLK concomitant with OSCC at the initial visit, (c) patients with a history of malignant neoplasia at any site, or (d) patients without fasting plasma glucose (FPG) data within 6 months before the end of the study (August 2017–January 2018).

2.5 | Data collection

Clinical history and follow-up data were obtained from archived files. The following patient-related information was collected and recorded: age, sex, smoking (yes/no), alcohol consumption (yes/no), history of DM (yes/no), and history of hypertension (yes/no) and cardiovascular diseases (yes/no).

The following clinical and histopathological characteristics were recorded: lesion size (cm^2), lesion location (ventral tongue, floor of the mouth, or other sites including dorsum, buccal mucosa, gingiva, lip mucosa, and palatal mucosa), clinical type of OLK, number of lesions (single or multiple), and the degree of dysplasia (none, mild, moderate, or severe). The grading criteria for epithelial dysplasia (Lester, 2005) were as follows: mild dysplasia, architectural disturbance limited to the lower third of the epithelium; moderate dysplasia, architectural disturbance extending into the middle third of the epithelium; and severe dysplasia, architectural disturbance extending beyond two-thirds of the epithelium with associated cytological atypia.

The primary exposure variable, that is, hyperglycemia, was validated using the FPG level (normal range, 3.9–6.1 mmol/L). Patients with FPG ≥ 6.1 mmol/L were considered to have hyperglycemia. Patients with FPG ≥ 7.0 mmol/L or 2-hr plasma glucose ≥ 11.1 mmol/L during a 75 g oral glucose tolerance test (OGTT) or a random PG ≥ 11.1 mmol/L were considered to have DM (American Diabetes Association, 2019). Patients with impaired fasting glucose (6.1 mmol/L ≤ FPG <7 mmol/L) and/or impaired glucose tolerance (7.8 ≤ 2-hr PG < 11.1 mmol/L) were considered to have prediabetes (Chinese Diabetes Society, 2017 criteria; Jia, 2017).

Additionally, the levels of total cholesterol (TC; normal range, 3.1–5.7 mmol/L) and triglycerides (TG; normal range, 0.5–1.7 mmol/L) were included. The serum results were measured at a single time point, while some patients had multiple measurements and some had only one result. For the final data analysis, we selected the most recent measurement result for the patients with multiple measurement results.

Data extraction and collection were completed independently by two of the authors (JL and YL). Disagreements were resolved through rechecks and discussion or consulting a third author (HH). The Kappa test was used to confirm the interrater reliability, and the Kappa coefficient was 0.8, indicating satisfactory consistency and reliability.

2.6 | Reducing bias

To reduce selection bias, we included all cases with confirmed FPG results and a random sample of FPG-confirmed controls matched by sex and age. To reduce information bias, we used the available histopathological reports and serum results to validate our primary outcome (malignant transformation) and primary exposure (hyperglycemia).

2.7 | Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 22.0 (IBM Corp). Percentages and frequencies were calculated for categorical variables, and means and standard deviations were calculated for continuous variables. Logistic regression analysis was used to estimate the odds ratios (OR) and 95% CI for the effects of relevant risk factors on malignant transformation.

Kaplan–Meier survival analysis was performed to assess the significance of differences in the generated survival curves. Univariate and multivariate Cox regression analyses were performed to determine each variable's predictive value. "Time 0" represented the date of onset according to the initial case record. The study duration ranged from the initial visit to the development of OSCC (non-censored observation) or until the end of the follow-up (censored observation) period. All *p*-values were two-tailed with a significance level of <0.05.

3 | RESULTS

3.1 | Patient characteristics

The characteristics of all the patients (*N* = 399) are presented in Table 1. The ratio of males to females in the MT group was 1:2, and the average age was 55.4 years. The mean time for the malignant transformation of OLK was 61.8 months (range = 1–480 months). The average age of the UT group was 55.4 years, and the average follow-up period was 70.1 months (range = 12–289 months).

The homogenous type of OLK was the most frequently observed type in the UT group (81.2%), and the non-homogenous type was the most common form in 69.9% of patients in the MT group, of which the ulcerative type was found in 33.8% of patients in that group. Lesions located on the ventral surface of the tongue or floor of the mouth were predominant in 74.4% of patients in the MT group, and lesions at the other sites were predominant in 74.1% of patients in the UT group. Lesions measuring 2 cm^2 or larger accounted for 69.2% of patients in the MT group and only 45.1% of patients in the UT group (Table 1).

In the UT group, 65.8% of patients presented no dysplasia. Dysplasia accounted for 72.2% of patients in the MT group, including 25.6% with mild dysplasia, 24.0% with moderate dysplasia, and 22.6% with severe dysplasia. No significant differences were found in the mean total TC and TG levels between the MT and UT groups (Table 1).

The average FPG of the MT group was significantly higher than that of the UT group. Among the 64 patients with hyperglycemia in the MT group, the average time for malignant transformation was 40.7 months, which was much shorter than the overall average of 61.8 months for the entire MT group (Table 2).

3.2 | Logistic regression analysis

Table 3 shows the results of the logistic regression analysis of the contributions of various risk factors to the malignant transformation of OLK. No significant differences were found between the MT and UT groups on the number of lesions, size of lesions, smoking, alcohol consumption, or level of TC or TG.

Hyperglycemia apparently had a significant effect on the risk of malignant transformation (OR = 15.0, 95% CI = 5.5–41.1, $p < .001$). Lesions located on the ventral surface of the tongue or floor of the mouth were a significantly higher risk of the development of OSCC than those in other locations (OR = 10.1, 95% CI = 4.2–24.2, $p < .001$). The non-homogenous type of OLK presented a higher risk of malignant transformation than the homogenous type (OR = 6.3, 95% CI = 2.3–17.7, $p < .001$). Patients with dysplasia had a significantly higher risk of malignant transformation than those without dysplasia (OR = 2.0, 95% CI = 1.3–3.1, $p = .002$).

TABLE 1 Characteristics of oral leukoplakia with malignant transformation (MT) and untransformed (UT) oral leukoplakia

Characteristic	MT	UT	Total
Cases (*n*/%)	133 (33.3)	266 (66.7)	399 (100)
Sex (*n*/%)			
Male	45 (33.8)	90 (33.8)	135 (33.8)
Female	88 (66.2)	176 (66.2)	264 (66.2)
Age (years)			
Mean ± *SD*	55.4 ± 12.2	55.4 ± 12.3	55.4 ± 12.3
Range	27–81	26–82	26–82
Clinical type (*n*/%)			
Homogeneous	40 (30.1)	216 (81.2)	256 (64.2)
Ulcerative	45 (33.8)	27 (10.2)	72 (18.0)
Erythroleukoplakia	30 (22.6)	7 (2.6)	37 (9.3)
Verrucous	18 (13.5)	16 (6.0)	34 (8.5)
Number of lesions (*n*/%)			
Single	109 (82.0)	227 (85.3)	336 (84.2)
Multiple	24 (18.0)	39 (14.7)	63 (15.8)
Location of lesion (*n*/%)			
Ventral tongue/floor of the mouth	99 (74.4)	69 (25.9)	168 (42.1)
Other locations	34 (25.6)	197 (74.1)	231 (57.9)
Size of lesion (*n*/%)			
<2 cm^2	41 (30.8)	146 (54.9)	187 (46.9)
≥2 cm^2	92 (69.2)	120 (45.1)	212 (53.1)
Dysplasia (*n*/%)			
None	37 (27.8)	175 (65.8)	212 (53.2)
Mild	34 (25.6)	63 (23.7)	97 (24.3)
Moderate	32 (24.0)	22 (8.3)	54 (13.5)
Severe	30 (22.6)	6 (2.2)	36 (9.0)
Follow-up period (months)			
Mean ± *SD*	61.8 ± 68.1	70.1 ± 51.1	67.4 ± 57.4
Range	1–480	12–289	1–480
TC (mmol/L)			
Mean ± *SD*	4.8 ± 1.0	5.1 ± 1.0	5.0 ± 1.0
Range	2.5–7.4	2.8–7.5	2.5–7.5
TG (mmol/L)			
Mean ± *SD*	2.0 ± 2.5	1.6 ± 0.8	1.8 ± 1.8
Range	0.4–19.6	0.5–4.4	0.4–19.6
Smoking (*n*/%)			
Yes	28 (21.1)	72 (27.1)	100 (25.1)
No	105 (78.9)	194 (72.9)	299 (74.9)
Alcohol consumption (*n*/%)			
Yes	23 (17.3)	75 (28.2)	98 (24.6)
No	110 (82.7)	191 (71.8)	301 (75.4)
History of DM (*n*/%)			
Yes	38 (28.6)	24 (9.0)	62 (15.5)
No	95 (71.4)	242 (91.0)	337 (84.5)

(Continues)

TABLE 1 (Continued)

Characteristic	MT	UT	Total
History of hypertension (*n*/%)			
Yes	34 (25.6)	67 (25.2)	101 (25.3)
No	99 (74.4)	199 (74.8)	298 (74.7)
History of cardiovascular diseases (*n*/%)			
Yes	10 (7.5)	15 (5.6)	25 (6.3)
No	123 (92.5)	251 (94.4)	374 (93.7)

Abbreviations: DM, diabetes mellitus; MT, malignant transformation; *SD*, standard deviation; TC, total cholesterol; TG, triglycerides; UT, untransformed.

TABLE 2 Comparison of FPG levels of oral leukoplakia with malignant transformation (MT) and untransformed (UT) oral leukoplakia

Characteristic	MT	UT	Total
FPG (mmol/L)			
<6.1	69 (51.9)	230 (86.5)	299 (74.9)
6.1~7.0	20 (15.0)	27 (10.2)	47 (11.8)
≥7.0	44 (33.1)	9 (3.3)	53 (13.3)
Mean ± *SD*	6.4 ± 1.5	5.5 ± 0.6	5.8 ± 1.1
Range	4.0–10.9	4.2–8.4	4.0–10.9
Follow-up (months)			
Mean ± *SD*	40.7 ± 36.6 (hyperglycemia) 61.8 ± 68.1 (total)	70.13 ± 51.09	67.35 ± 57.38
Range	1–165 (hyperglycemia) 1–480 (total)	12–289	1–480

Abbreviations: FPG, fasting plasma glucose; MT, malignant transformation; *SD*, standard deviation; UT, untransformed.

3.3 | Kaplan–Meier survival analysis

The results of the Kaplan–Meier survival analyses are summarized in Table 4. Consistent with the logistic regression analysis, hyperglycemia, non-homogenous OLK, location of lesions on the ventral tongue or floor of the mouth, and the presence of dysplasia were significant risks of the malignant transformation of OLK (log-rank test, $p < .001$; Table 4; Figures S1–S4). Patients with hyperglycemia were divided into two subtypes (prediabetes and DM) by setting 7.0 mmol/L as the cutoff point for FPG. The curves indicated that patients with a higher FPG level had a significantly higher risk of malignant transformation (log-rank test, $p < .001$; Table 4; Figure 1). The Kaplan–Meier curves for the non-homogenous subtypes and the presence of dysplasia corroborated the significant effects of all subtypes on the malignant transformation of OLK (log-rank test, $p < .001$; Table 4; Figures 2 and 3). The curves in Figure 3 indicated a higher severity of dysplasia was associated with a higher risk of malignant development. The Kaplan–Meier curves showed that OLK lesions of 2 cm^2 or larger were a significantly higher risk of developing OSCC than lesions smaller than 2 cm^2 (log-rank test, $p = .004$; Table 4; Figure S5).

3.4 | Univariate and multivariate Cox proportional regression analyses

Table 5 presents the results of the univariate and multivariate Cox proportional regression analyses of the independent risk factors for malignant transformation of OLK. The univariate analysis showed that hyperglycemia, non-homogenous OLK, location of lesions on the ventral surface of the tongue or floor of the mouth, lesions of 2 cm^2 or larger, and the presence of dysplasia were significantly related to the malignant development of OLK, which was consistent with the results of the Kaplan–Meier survival analysis.

A multivariate Cox regression analysis was performed on the potential risk factors identified by the univariate analysis to verify those results. No significant difference was found in the risk of malignant transformation between different sizes of lesions in the adjusted multivariate Cox regression analysis. Hyperglycemia (adjusted [A] HR = 4.7, 95% CI = 1.8–12.0, $p = .001$), non-homogenous type (AHR = 3.0, 95% CI = 1.7–5.3, $p < .001$), lesion location on the ventral surface of the tongue or floor of the mouth (AHR = 3.6, 95% CI = 2.0–6.6, $p < .001$), and the presence of dysplasia (AHR = 2.8, 95% CI = 1.4–5.7, $p = .005$) were independent risk factors for the

TABLE 3 Logistic regression analysis of the risk factors for the malignant transformation of oral leukoplakia

Risk factors	Beta	*SE*	OR	95% CI	*p*
Non-homogeneous	1.8	0.5	6.3	2.3–17.7	.000*
Number of lesions (multiple)	0.5	0.5	1.7	0.6–4.6	.284
Location (ventral tongue/floor of mouth)	2.3	0.4	10.1	4.2–24.2	<.001*
Size (≥2 cm^2)	0.5	0.5	1.7	0.7–4.1	.252
Dysplasia	0.7	0.2	2.0	1.3–3.1	.002*
Hyperglycemia	2.7	0.5	15.0	5.5–41.1	.000*
Total cholesterol (abnormal)	−1.0	0.6	0.4	0.1–1.1	.085
Triglycerides (abnormal)	−0.9	0.5	0.4	0.2–1.1	.067
Smoking	−0.3	0.7	0.8	0.2–2.8	.666
Alcohol consumption	−0.2	0.6	0.8	0.2–2.9	.776
History of hypertension	0.5	0.5	1.6	0.6–4.2	.363
History of cardiovascular diseases	−1.2	0.9	0.3	0.0–2.0	.210
Constant	−3.6	0.6	N/A	N/A	<.001*

Note: Model: $\chi^2(13) = 156.1$, $p < .001$.

Abbreviations: CI, confidence interval; N/A, not availableOR, odds ratio; *SE*, standard error.

*A significant statistical difference was observed.

malignant transformation of OLK. No significant interactive effects were found among these risk factors.

4 | DISCUSSION

In 2015, 425 million people worldwide had DM and the number was predicted to rise to 642 million by 2040 (Ogurtsova et al., 2017). As a common chronic metabolic disease, DM has serious complications, such as diabetic ketoacidosis and chronic kidney disease (Seino et al., 2010), causing a substantial disease burden. Recent studies have found that DM can increase the risk of developing breast, colorectal, and endometrial cancers (Tsilidis et al., 2015). Research has revealed an association between hyperglycemia/DM and the risk of developing OLK and OSCC (Bragg et al., 2017; Marta & Lopez-Jornet, 2017). Specific biological mechanisms have yet to be explored in terms of their relevance to chronic inflammation and impairment of the immune system caused by hyperglycemia, hyperinsulinemia, and inflammatory factors (Piątkiewicz & Czech, 2011). However, there is a lack of empirical evidence supporting the association between hyperglycemia and malignant transformation of OLK.

This study showed that compared with normal FPG levels, hyperglycemia significantly increased the risk of malignant transformation of OLK (AHR = 4.7, 95% CI = 1.8–12.0, $p = .001$). Moreover, the Kaplan–Meier analysis demonstrated that patients with higher FPG levels had a significantly higher risk of malignant transformation (log-rank test, $p < .001$). The average malignant transformation time for patients with hyperglycemia (40.7 months) was much shorter than the time of the entire MT group (61.8 months), indicating that hyperglycemia might be a strong factor for the MT of OLK patients. Therefore, good glycemic control might be a promising method of improving the prognosis of OLK and reducing the risk of malignancy in patients with OLK and hyperglycemia. It is also worth mentioning that many cases of prediabetes and DM are undiagnosed in China (Bragg et al., 2017; Xu et al., 2013). A 2017 study reported that the estimated standardized prevalence of both diagnosed and undiagnosed DM in Chinese adults was 10.9% and 6.9%, respectively (Wang et al., 2017). Thus, the FPG should be recommended as one of the routine screening tests for patients with OLK. Generally, patients with OLK should be monitored every 3 months for life (Villa & Woo, 2017), and our findings reveal the significant association between hyperglycemia and malignant transformation of patients with OLK. Accordingly, we recommend closer clinical and histopathological surveillance to detect malignant transformation early and improve the prognosis of patients with OLK and hyperglycemia. Furthermore, to achieve good glycemic control in patients with OLK and hyperglycemia, clinicians should not only strengthen self-management education on health for their patients, such as diet and lifestyle (Beck et al., 2018), but also refer patients to endocrinologists in a timely manner and provide appropriate management. These recommendations highlight the importance of interdisciplinary cooperation between oral medicine and endocrinology.

However, there is considerable potential for overlap with patients with DM also developing cancer, as both DM and cancer are common diseases worldwide (Giovannucci et al., 2010). In addition, the association between DM and cancer could be explained at least partially by the shared risk factors such as older age, obesity, poor diet, low physical activity, low socioeconomic status, and poor access to health care (Holden, 2016). Consequently, it remains unclear whether the association between hyperglycemia and malignant transformation of OLK is direct (e.g., due to WNT/β-catenin and inflammatory cytokines) or indirect due to common risk factors such as obesity (Chocarro-Calvo, García-Martínez, Ardila-González, De la Vieja, & García-Jiménez, 2013; Garcia-Jimenez, Garcia-Martinez, Chocarro-Calvo, & De la Vieja, 2013; Giovannucci et al., 2010). Our results should be interpreted with caution, and further studies are needed to confirm the impact of hyperglycemia on the malignant transformation of OLK by reducing the influence of these confounders.

The current consensus is that oral carcinogenesis is a multistep process characterized by an accumulation of both genetic mutations and epigenetic alterations sufficient for malignant transformation, such as the genetic alterations in *TP53* and the epigenetic processes, including DNA methylation (Chari et al., 2019; Gazdzicka, Golabek, Strzelczyk, & Ostrowska, 2019; Rhodus, Kerr, & Patel, 2014; Stransky et al., 2011; Vogelstein & Kinzler, 2015). This study showed that,

TABLE 4 Kaplan–Meier survival analysis for the malignant transformation of oral leukoplakia

Risk factors	OSCC	OLK	χ^2	*p*
Sex (female/male)	88/45	176/90	0.1	.763
Age (mean ± *SD*)	55.4 ± 12.2	55.4 ± 12.3	44.0	.833
Homogeneous (yes/no)	40/93	216/50	84.7	<.001*
Clinical type				
Homogeneous	40	216	102.4	<.001*
Ulcerative type	45	27		
Erythroleukoplakia	30	7		
Verrucous type	18	16		
Number of lesions (single/multiple)	109/24	227/39	0.2	.658
Location of lesion				
Ventral surface of the tongue/floor of the mouth	99	69	80.7	<.001*
Other locations	34	197		
Size				
<2 cm^2	41	146	8.2	.004*
≥2 cm^2	92	120		
Dysplasia				
None	37	175	87.7	<.001*
Mild	34	63		
Moderate	32	22		
Severe	30	6		
Hyperglycemia (yes/no)	65/68	39/227	62.1	<.001*
Total cholesterol (normal/abnormal)[a]	85/18	88/39	2.6	.104
Triglycerides (normal/abnormal)[a]	70/33	85/42	0.0	.838
Smoking (yes/no)	28/105	72/194	0.4	.540
Alcohol consumption (yes/no)	23/110	75/191	1.9	.165
History of hypertension (yes/no)	34/99	67/199	0.0	.905
History of cardiovascular diseases (yes/no)	10/122	15/251	0.2	.650

Abbreviation: *SD*, standard deviation.

[a]Data for some patients were unavailable.

*A significant statistical difference was observed.

compared with the absence of dysplasia, the presence of dysplasia had a significant effect on malignant transformation, thereby verifying this study's hypothesis. However, the efficacy of histopathological grading of dysplasia as an indicator of malignant transformation remains controversial. In our study, the Kaplan–Meier survival analysis indicated that a higher severity of dysplasia was associated with a higher risk of malignant transformation, which was consistent with most of the published studies (Gandara-Vila et al., 2018; Liu et al., 2010) and in keeping with the concept of multistep process of accumulation of mutations and epigenetic alterations. Nevertheless, other studies have found no significant association between a higher severity of dysplasia and an increased risk of malignant transformation (Dost, Cao, Ford, Ades, & Farah, 2014; Tilakaratne, Sherriff, Morgan, & Odell, 2011). The possible reason might be that more severe cases are treated more aggressively by wider excision, and therefore, the likelihood of malignant transformation is reduced (Dost et al., 2014; Tilakaratne et al., 2011). Thus, further research is needed to confirm our results. Follow-up intervals in the clinical setting should be scheduled according to the degree of dysplasia. Generally, the recommended interval for patients without dysplasia is every 6 months and that for patients with dysplasia is every 3 months (Van der Waal, 2009); for severe dysplasia, lesions should be excised with clear margins (Villa & Woo, 2017), and it is recommended that the follow-up interval be shortened to 1–3 months for life. At the same time, non-invasive detection techniques (toluidine blue staining, oral cytology, and VELscope [LED Dental]) and periodic biopsies should be used to increase the rates of early detection of malignant events (Macey et al., 2015).

As mentioned before, oral epithelial dysplasia is considered the progenitor of malignant changes, and the issue of inter-examiner

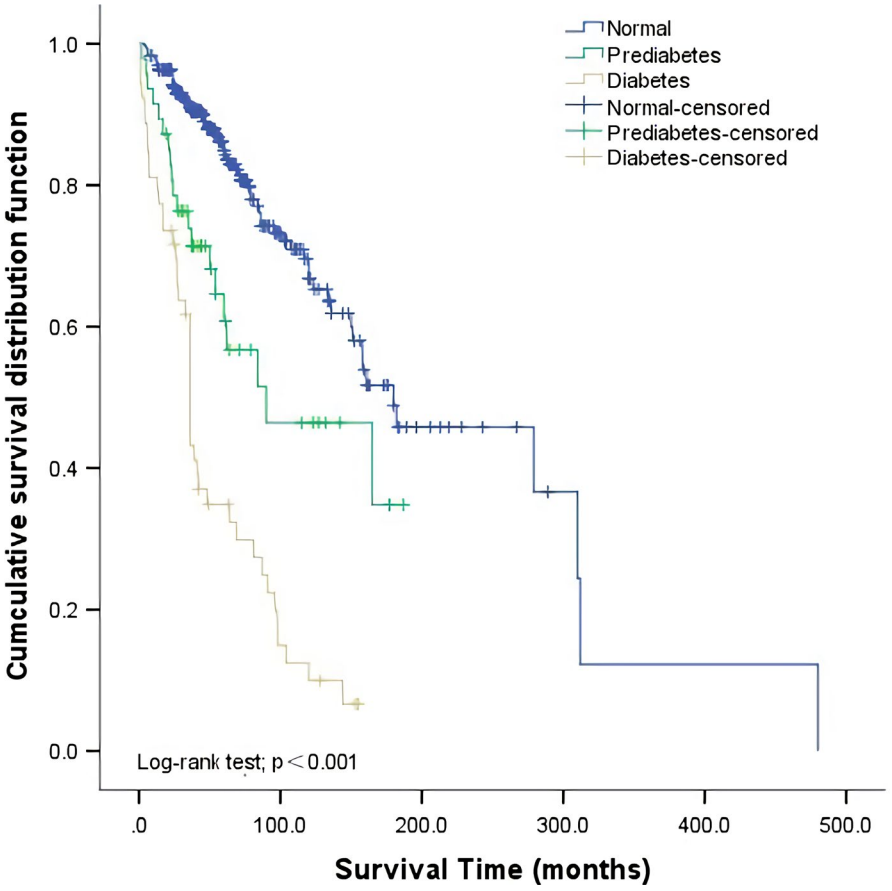

FIGURE 1 Kaplan–Meier survival curves for the malignant transformation of oral leukoplakia: comparisons of fasting plasma glucose levels

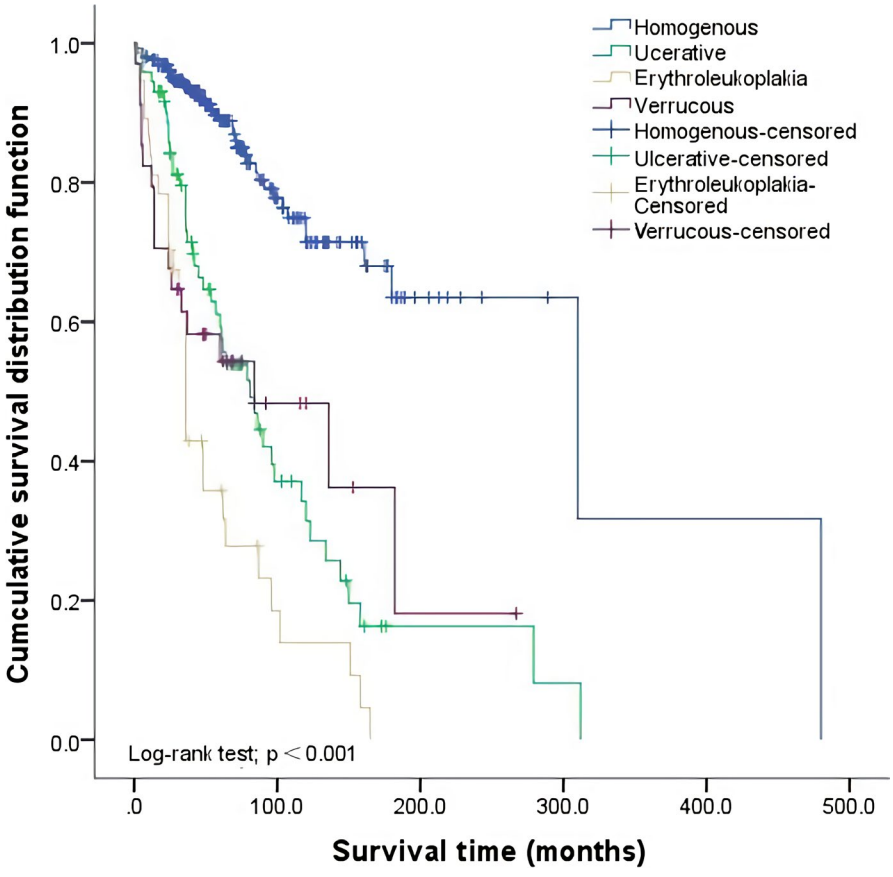

FIGURE 2 Kaplan–Meier survival curves for the malignant transformation of oral leukoplakia: comparisons of non-homogenous subtypes and homogenous subtypes

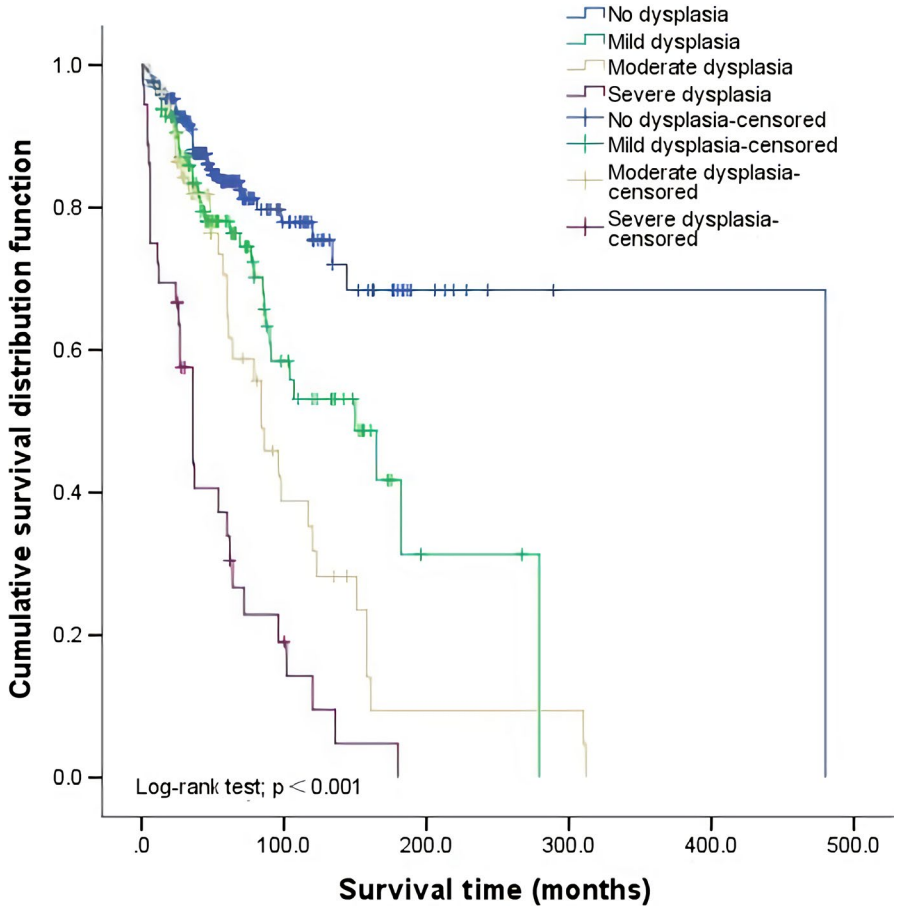

FIGURE 3 Kaplan–Meier survival curves for the malignant transformation of oral leukoplakia: comparisons of the absence of dysplasia with various degrees of dysplasia

variability remains a great challenge for pathologists when it comes to assessing the degree of dysplasia (Woo, 2019). In the present retrospective study, dysplasia was graded as mild, moderate, and severe based on the involvement of <1/3, between 1/3 and 2/3, and >2/3 (but not full thickness) of the epithelium according to WHO classification criteria (Lester, 2005; Reibel et al., 2017). A binary system was proposed subsequently, grading the lesions into either low risk or high risk based on scoring the features used by the 2005 WHO classification (Kujan et al., 2006; Warnakulasuriya, Reibel, Bouquot, & Dabelsteen, 2008). Recent studies have declared that it is difficult to use the division of the epithelium into thirds for grading lesions with bulky and verrucous architecture, and a new criteria combining architectural features (low power), organizational features (medium power), and cytological features (high power) have been proposed (Woo, 2019). Further evaluation of the reproducibility and reliability of the different classification criteria should be encouraged, and future studies should test whether the new criteria are more likely to predict malignant transformation.

It is worth mentioning that 27.8% of cases with no dysplasia, referred as keratosis of unknown significance (KUS), developed into OSCC in our study (Woo, Grammer, & Lerman, 2014). Recent studies have revealed that KUS and dysplasia share similar molecular and genomic characteristics (Villa et al., 2019). KUS is not as benign as was thought historically; it might be a very early form of dysplasia and correspond to the "first strike" of the "three strikes" in multistep carcinogenesis (Villa et al., 2019; Vogelstein & Kinzler, 2015). Therefore, all OLK lesions should be followed by observation at close intervals (3–6 months) independent of the presence or absence of dysplasia, emphasizing the need for periodic biopsies and tools for detecting malignant transformation in suspicious lesions (Holmstrup, Vedtofte, Reibel, & Stoltze, 2007; Woo, 2019).

Moreover, various other risk factors are thought to be associated with malignant transformation of OLK, such as lesion location, non-homogeneous clinical type, and lesion size (2 cm^2 or larger; Liu et al., 2012; Van der Waal, 2014; Yuri, Fumihiko, Masaru, Kei-Ichi, & Ken, 2012). Our study confirmed that the lesions located on the ventral surface of the tongue or floor of the mouth were significantly more likely to develop into OSCC than lesions in other sites, which is consistent with previous studies (Anderson & Ishak, 2015; Monica et al., 2015). An acceptable explanation for the susceptibility of carcinogenesis might be that certain anatomical sites may have the unique histological characteristic of lacking a protective keratin layer (Gandara-Vila et al., 2018; Mashberg & Meyers, 1976) and might be more readily penetrated by carcinogens, such as tobacco and alcohol (Schepman, Bezemer, van der Meij, Smeele, & van der Waal, 2001). This study also confirmed the significantly higher probability of malignant development of the non-homogenous rather than homogenous type of OLK with a hazard ratio of 3.0, suggesting the use of an optimal biopsy site and shorter follow-up interval for such high-risk

TABLE 5 Univariate and multivariate Cox proportional regression analyses of the malignant transformation of oral leukoplakia

Risk factors	HR	95% CI	*p*
Univariate analysis[a]			
Non-homogeneous	4.9	3.3–7.1	<.001*
Number of lesions (multiple)	0.9	0.6–1.4	.660
Location (ventral tongue/floor of mouth)	5.0	3.4–7.5	<.001*
Size (≥2 cm^2)	1.7	1.2–2.5	.005*
Dysplasia	3.1	2.1–4.5	<.001*
Hyperglycemia	3.7	2.6–5.2	<.001*
Total cholesterol (abnormal)	0.7	0.4–1.1	.109
Triglycerides (abnormal)	1.0	0.7–1.6	.839
Smoking	0.9	0.6–1.3	.542
Alcohol consumption	0.7	0.5–1.1	.169
History of hypertension	1.0	0.7–1.5	.906
History of cardiovascular diseases	1.2	0.6–2.2	.652
Multivariate analysis[b]			
Non-homogeneous	3.0	1.7–5.3	<.001*
Location (ventral tongue/floor of mouth)	3.6	2.0–6.6	<.001*
Size (≥2 cm^2)	1.3	0.7–2.3	.380
Dysplasia	2.8	1.3–5.7	.005*
Hyperglycemia	4.7	1.8–12.0	.001*
Hyperglycemia × dysplasia	1.0	0.4–2.4	.951
Hyperglycemia × non-homogeneous	0.9	0.4–2.0	.713
Hyperglycemia × location	0.7	0.3–1.6	.413
Hyperglycemia × size	0.9	0.4–2.1	.887

Abbreviation: HR, hazard ratio; CI, confidence interval.

[a]Univariate analysis adjusted for age and sex.

[b]Multivariate analysis adjusted for age, sex, number of lesions, total cholesterol, triglycerides, smoking, alcohol consumption, history of hypertension, and history of cardiovascular diseases.

*A significant statistical difference was observed.

[x]Interactive effects were analyzed.

patients (Holmstrup, Vedtofte, Reibel, & Stoltze, 2006). In the present study, both Kaplan–Meier survival analyses and univariate Cox proportional regression analyses showed that OLK lesions of 2 cm^2 or larger presented a significantly higher risk of developing OSCC than lesions smaller than 2 cm^2, which is consistent with previous studies (Van der Waal, 2014). However, no significant effect of lesion size (2 cm^2 or larger) was found in both logistic regression and multivariate Cox proportional regression analyses after adjusting for other risk factors. Such inconsistency in univariate and multivariate analysis is termed Simpson's paradox, which is very common in observational studies due to the effects of confounding (Wang, Wu, Kwan, Mtu, & Feng, 2018). The inconsistency indicates that the lesion size might be a confounding risk factor rather than an independent risk factor for the malignant transformation of OLK in the present study. Further studies are essential for clarifying the issue.

Additionally, two patients with OLK with poorly managed DM (FPG ≥ 7.0 mmol/L), whose initial histopathological results showed mild dysplasia, developed into OSCC after only 1 month of the present study: One was characterized as homogenous OLK and the other was non-homogenous OLK. The possible reasons were as follows: (a) The single-site biopsy taken was not representative of the whole lesion, especially for non-homogenous and multifocal OLK; (b) the reading of epithelial dysplasia was inaccurate (Holmstrup et al., 2007; Lee et al., 2007). Therefore, clinicians should be aware of possible underdiagnosis from incisional biopsy, and multiple-site biopsies and periodic biopsies should be taken when necessary.

This study has several limitations. First, the most significant limitation is the retrospective nature of the study, which limits access to clinical details. Second, FPG data represent the current glucose level and HbA1C would be more indicative of long-term glycemic control. FPG was used in this study because HbA1C has not been recommended to diagnose DM according to the current guidelines in China. However, HbA1C and FPG both should be encouraged in future studies. Finally, there is the risk of having excluded potential new cases that develop in the long term due to the limited follow-up for some patients in the control group (range, 12–289 months). The results and conclusion of the present study should be interpreted with more caution; further large-scale prospective studies are needed to confirm our conclusions.

5 | CONCLUSION

Hyperglycemia, non-homogenous type of OLK, location of lesion on the ventral surface of the tongue or floor of the mouth, and the presence of dysplasia might be associated with malignant transformation of OLK. High-risk individuals should have closer clinical and histopathological surveillance. Routine screening of FPG levels is recommended for patients with OLK to facilitate the early detection of malignant events and improve their prognosis, given that good glycemic control would help to reduce the risk of malignant transformation to some extent. Furthermore, clinicians should improve self-management education about health, such as diet and lifestyle, refer patients to endocrinologists in a timely manner, and provide appropriate management to achieve good glycemic control in patients with OLK and hyperglycemia. Large-scale prospective studies are needed to confirm this study's results and conclusions.

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CONFLICTS OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Jin Li and Yang Liu contributed to data collection and statistical analysis, and drafted the manuscript; Hua Zhang guided and assisted in the statistical analysis; and Hong Hua contributed to conception and design, and critically revised the manuscript. All authors have approved the final manuscript and agreed to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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