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Original Article

Endoscopic features of esophageal high-grade intraepithelial neoplasia dominated by cytological atypia

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Abstract: Little is known about esophageal high-grade intraepithelial neoplasia dominated by cytological atypia (HGINc). We aimed to elucidate the endoscopic features of HGINc compared with esophageal high-grade intraepithelial neoplasia dominated by architectural atypia (HGINa). All patients pathologically diagnosed as esophageal high-grade intraepithelial neoplasia after endoscopic submucosal dissection at our center between January 2018 and December 2019 were included in this study. According to the pathological diagnosis, the patients were divided into two groups: HGINa group and HGINc group. Basic characteristics and endoscopic information were collected in detail. Data were analyzed statistically. Binary logistic regression was performed and a predictive model for HGINc was established. Then we evaluated its predictive value and built a nomogram for clinical application. A total of 175 patients were included in this study (126 with HGINa and 49 with HGINc). Among 228 lesions found in all patients, there were 148 HGINa and 80 HGINc. The independent relevant factors for HGINc were tobacco and alcohol usage, color, and gross type. To predict risk of HGINc, a three-factor model (TFM) was established with a highest area under curve (AUC) as 0.869 (95% CI, 0.852, 0.939). When the cut-off value was set as 0.3569184, the diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value for HGINc was 81.14%, 88.75%, 77.03%, 67.62%, and 92.68%, respectively. HGINc differs greatly in endoscopic features from HGINa in our study. It's important to reduce misdiagnosis that our model was established with good predictive value for clinical application.

Keywords: Architectural atypia, cytological atypia, endoscopic diagnosis, esophageal squamous cell carcinoma, high-grade intraepithelial neoplasia

Introduction

Esophageal squamous cell carcinoma (ESCC) is responsible for over 70% of esophageal cancer cases globally [1], which is the sixth most common cause of cancer-related death in the world [2]. The five-year survival rate of esophageal high-grade intraepithelial neoplasia (HGIN) can be improved to 90% [3], in contrast to less than 30% in patients diagnosed as invasive carcinoma.

Until 2019, the pathological diagnosis was mainly based on the fourth edition of World Health Organization (WHO) classification, the most widely used diagnostic criteria [4]. However, the definition of HGIN is broadened with the publication of the 5th edition classification of digestive system tumours in 2019 [5]. By this definition, HGINs are classified into two categories. In this study, we refer to a class of HGINs as esophageal high-grade intraepithelial neoplasia dominated by cytological atypia (HGINc) when severe cytological atypia is present (regardless of the extent of epithelial involvement). The other HGINs are called as esophageal high-grade intraepithelial neoplasia dominated by architectural atypia (HGINa) when more than half of the epithelium is involved by dysplasia, and this type of HGIN has been elaborated in the fourth edition of WHO classification. HGINa lesions have been well studied and

effectively screened by the combined application of various means, particularly endoscopy [6]. These technologies include white light endoscopy (WLE), magnifying endoscopy with narrowband imaging (ME-NBI), and chromoendoscopy. Suspected lesions will be biopsied and confirmed by pathology. Yet the ratio and features of HGINc remain a mystery, and a study is clearly needed to resolve this question.

HGINc is characterized by severe cytological atypia, and current studies suggest that cytological atypia is associated with a poor prognosis in multiple tumors [7-10]. Thus, HGINc may be likely to develop into invasive squamous cell carcinoma at an early stage of the disease and need early diagnosis. However, inadequate recognition leads to missed or delayed diagnosis. Therefore, to reduce the miss rate, prevent complications and increase 5-year survival rate by timely advice and treatment for individuals affected by HGINc, the features of HGINc are necessary to clarify, especially compared with HGINa.

In this study, we clarified the features of HGINc, including its ratio and endoscopic findings. We further developed a predictive model for HGINc according to the risk factors, and its value for the clinical application was evaluated.

Methods

Patients

From January 2018 to December 2019, all patients, who were diagnosed preoperatively as HGIN by biopsy and met the indications of endoscopic submucosal dissection (ESD) [11], followed the standard procedure. The patients, still diagnosed postoperatively as HGIN, were included in this study. If the endoscopic pictures were blurred or the clinical data was incomplete, the case would be excluded. Written informed consent was taken from all patients. This study was approved by the Institutional Review Board of Xinqiao Hospital, Army Medical University in China (No. 2019-100-01).

Endoscopic procedure

All patients were examined with ME-NBI (GIF-H260Z, Olympus Medical Systems, Tokyo, Japan). Image enhancement model was set as A5 and Ce 0 for WLE, A8 and Cm 1 for NBI. The concentration of Lugol's solution was 1.2%. ESD procedures were performed principally using a therapeutic endoscope with a water jet function (GIF-Q260J, Olympus Medical Systems, Tokyo, Japan), electrosurgical workstation (200D, ERBE Elektromedizin, Tübingen, Germany). The patients diagnosed preoperatively as HGIN by biopsy performed standard ESD procedure. A mucosal incision or submucosal dissection was performed using Dual Knife 650D (Olympus Medical Systems, Tokyo, Japan). Traction clip with tire was used as needed. The specimens were fixed in 20% formalin for 24 to 48 hours, and then incisions were made at intervals of 2.0~3.0 mm.

Histopathological diagnosis

The histopathological diagnosis was based on the 5th edition classification of digestive system tumours [6]. When characterized with severe nuclear atypia such as enlargement, pleomorphism, hyperchromasia, loss of polarity, and overlapping, regardless of the extent of epithelial involvement, the lesion was diagnosed as HGINc. When esophageal dysplasia was involved more than half of the epithelium without severe cytological atypia, it was diagnosed as HGINa. When normal mucosa was found between the adjacent lesions on pathological sections, the lesions should be regarded as independent lesions and information should be record respectively. In cases of disagreement, the two pathologists discussed together until an agreement was reached.

Data collection and classification

The endoscopic images and clinical data of all patients included were collected carefully. According to the histopathological diagnosis, patients were divided into two groups: HGINc group and HGINa group. If a patient had different type of lesions at the same time, the patient would be counted in each group. The general characteristics (such as age, sex, tobacco and alcohol usage, number of lesions, etc.) were recorded in detail. According to the main body of lesion, endoscopic information was reviewed and carefully recorded, including location, length, gross type, color, type of intra-epithelial capillary loop (IPCL) [12], and positive pink-color sign (PCS) [13]. In the process, the endo-

Table 1. Basic characteristics of HGINa group and HGINc group (n=175)

		Total	HGINa (n=126)		HGINc (n=49)		*P* value
			n	%	n	%	
Sex	Female	46 (26.29)	37	29.37	9	18.37	0.138
	Male	129 (73.71)	89	70.63	40	81.63	
Age	Mean ± SD		63.89±8.02		63.90±6.76		0.946
Tobacco and alcohol usage	Neither	88 (50.29)	71	56.34	17	34.69	0.031
	Only smoking	14 (8.00)	11	8.73	3	6.12	
	Only drinking	13 (7.43)	7	5.56	6	12.24	
	Both	60 (34.29)	37	29.37	23	46.94	
Multiple lesions	Yes	50 (28.57)	27	21.43	23	46.94	0.001
	No	125 (71.43)	99	70.57	26	53.06	
Number of lesions	1	126 (72.00)	100	79.37	26	53.06	<0.001
	2	34 (19.43)	22	17.45	13	26.53	
	3	10 (5.71)	2	1.59	8	16.32	
	4+	4 (2.29)	2	1.59	2	4.08	

scopic findings were evaluated respectively by two experienced endoscopic experts blinded with the pathological results. If there was any discrepancy, a discussion followed.

Statistical analysis

Data was managed and evaluated with SPSS Ver23.0 and illustrated with MATLAB 2019b. Mean and standard deviation was used to express measurement data of normal distribution, and median and interquartile range (IQR) were used to represent the measurement data of non-normal distribution. A two-sample t test or Mann-Whitney test was performed for comparison between the two groups. The counting data was described as the number of cases (%). The two groups were compared with Chi square test or Fisher exact probability method. Binary logistic regression was performed to establish HGINc predictive model, and area under receiver operating characteristic (ROC) curve to determine the predictive boundary value. Diagnostic indexes such as sensitivity, specificity, accuracy, positive predictive values (PPV) and negative predictive values (NPV) were calculated to evaluate the clinical value of the model. The inspection level is α=0.05.

Results

Basic characteristics of the patients

A total of 175 patients were involved, and there were 49 (28.00%) in HGINc group and 126 (72.00%) in HGINa group. No patient presented simultaneously two types of HGIN. Basic characteristics were showed in **Table 1**, and the typical cases of HGINc and HGINa were showed in **Figures 1** and **2**, respectively. Patients with tobacco and alcohol usage in HGINc group (65.31%) were more than HGINa group, and there was a statistically significant difference (P=0.031). 46.94% of patients (23/49) was found with multiple lesions in HGINc group, which was higher than that of HGINa group (27 patients, 21.43%, P=0.001). Sex and age did not differ significantly between the two groups.

Endoscopic features of HGINa and HGINc lesions

A total of 228 lesions were found in all patients. Eighty (35.09%) of these lesions were identified as HGINc and 148 (64.91%) as HGINa. Findings of WLE, Lugol's chromoendoscopy and ME-NBI endoscopy between HGINc and HGINa were carefully compared (**Table 2**).

Gross type observed with WLE was significantly different between the two groups (P<0.001). More than half of HGINc lesions (51.25%, 41/80) were 0-IIa, while most of HGINa lesions (62.16%, 92/148) were 0-IIb. Most of HGINc lesions (87.50%, 70/80) were whitish, but the majority of HGINa lesions (77.03%, 114/148) were reddish.

With ME-NBI, background color was seen in 12.50% lesions (10/80) in HGINc, which was

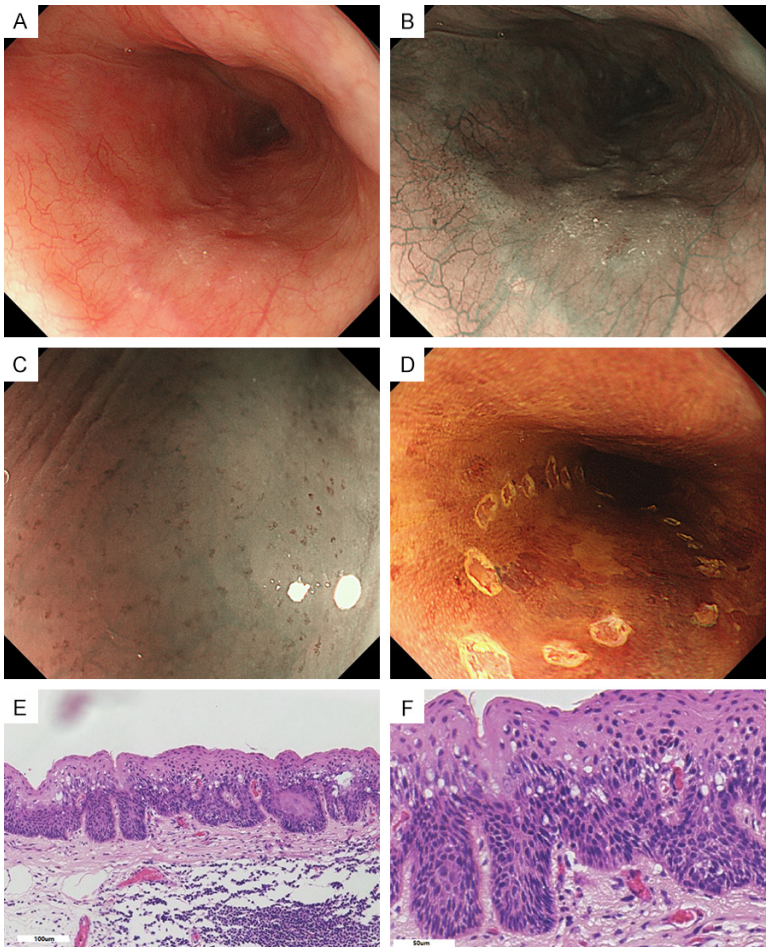

Figure 1. A typical case of HGINc. A. A lesion showed a whitish appearance with WLE. B. The lesion showed a clear demarcation without background color with ME-NBI. C. Type A vessels with loop-like formation were observed in whitish background consistent with surrounding mucosa. D. An irregular iodine unstaining area with negative pink-color sign was demonstrated. E. Histopathology showed that atypia cells were mostly confined to the lower half of the epithelium (10× magnification). F. High degree of architectural disarray and loss of polarity and cellular atypia was observed (40× magnification).

lower than that of HGINa (76.35%, 113/148, P<0.001). Type of IPCL of the two groups was also significantly different (P<0.001). Type A was seen in most lesions (87.50%, 70/80) in HGINc, while 74.32% of HGINa (110/148) was found with type B1.

After spraying with 1.2% Lugol's solution, all HGINc and HGINa lesions appeared as iodine unstaining areas. As to positive of PCS, the rate of HGINc lesions was significantly lower than that of HGINa lesions (8.75% vs 56.76%, P<0.001). No statistical difference was found in location and length in the cohort.

Analysis of relevant factors for HGINc

The diagnosis of HGINc was chosen as the dependent variable, and the factors in **Tables 1** and **2**, the corresponding variables (relevant factor). The independent relevant factors for HGINc were tobacco and alcohol usage, whitish appearance, and gross type (**Table 3**). Number of lesions, background color, IPCL and PCS were not independent relevant factors for HGINc.

Predictive model for HGINc and its diagnostic value

Development of the predictive model for HGINc: To evaluate the predictive value of relevant factors in different combinations, area under curve (AUC) was calculated. AUC value was ranged from 0.5 to 1.0. The combination of tobacco and alcohol usage, whitish appearance, and gross type showed the highest AUC as 0.869 (95% CI, 0.852, 0.939) (**Figure 3**). The results suggested that this kind of combination of relevant factors had the highest diagnostic accuracy for HGINc. According to the logistic regression results, a predictive model for HGINc (we called it as three-factor model, TFM) was established as follows:

Logit(P)=-4.248+0.690× *Only smoking* (Yes=1, no=0)+1.041× *Only drinking* (Yes=1, no=0)+2.389× *Both smoking and drinking* (Yes=1, no=0)+3.946× *Whitish appearance* (Yes=1, no=0)+0.110× *0-IIa* (Yes=1, no=0)+1.928× *0-IIc*.

Diagnostic value of TFM: According TFM for HGINc, the predictive value of each object was tested and the Youden index (YI) was taken. When the cut-off value was set as 0.3569184 (corresponding to the maximum of YI), the diag-

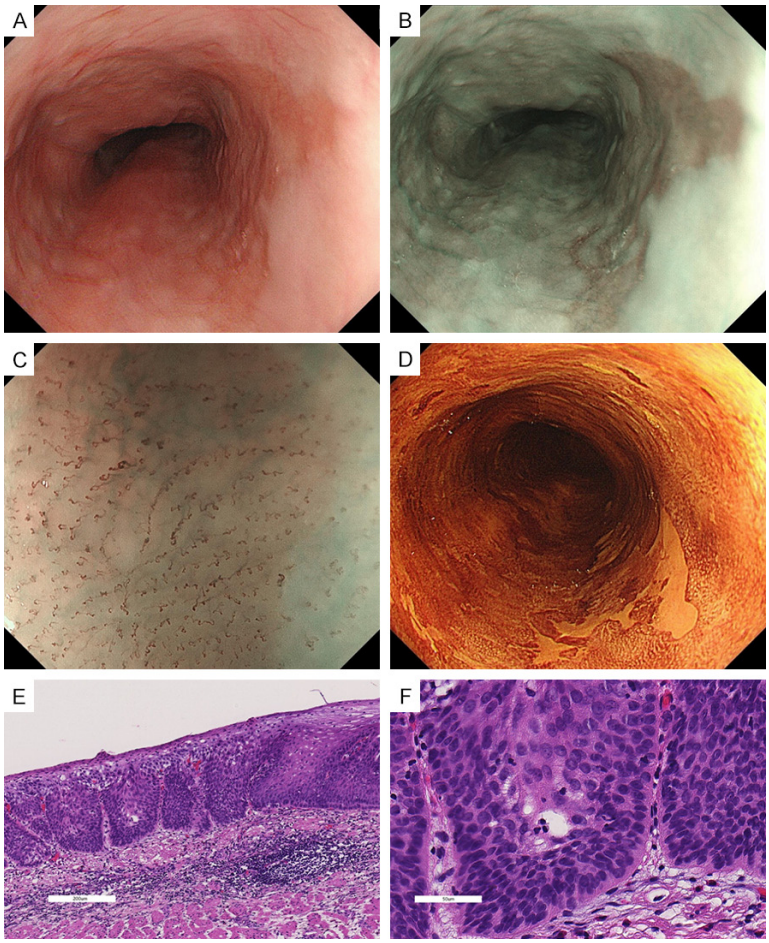

Figure 2. A typical case of HGINa. A. A lesion showed a reddish flat appearance with WLE. B. The lesion showed a clear demarcation with brownish background with ME-NBI. C. Type B1 vessels with loop-like formation were observed. D. An irregular iodine unstaining area with positive pink-color sign was demonstrated. E. Histopathology showed that the full thickness of the epithelium was involved (10× magnification). F. Oval and relatively regular nucleuses were observed (40× magnification).

nostic accuracy for HGINc was 81.14%, with a sensitivity as 88.75%, a specificity as 77.03%, a positive predictive value as 67.62% and a negative predictive value as 92.68% (**Table 4**).

To increase the clinical applicability, we transformed the TFM into a nomogram (**Figure 4**). At the same time, the correction curve was drawn according to the predictive probability and the actual probability (**Figure 5**). The predictive calibration curve was almost parallel to the diagonal line that would represent perfectly reliable prediction.

Discussion

HGIN is a precancerous lesion for ESCC, and elucidation of its features is extremely important for improving current therapeutic outcome. Firstly, we confirmed the ratio of HGINc in total HGIN in this study, indicating HGINc is a common disease. Secondly, we furtherly clarified the major differences in tobacco and alcohol usage, and endoscopic features between HGINc and HGINa. According to three independent relevant factors, the first predictive model was established and evaluated, which showed positive value for endoscopic diagnosis of HGINc. Our results are helpful in identifying the suspicious lesions and have good clinical application value. To our knowledge, this is the first report to discuss endoscopic diagnosis of HGINc in detail.

The differences about HGIN between Japanese and Western diagnostic criteria are narrowing, and one such sample is the update of the WHO standard definition of HGIN. The update illustrates that the importance of cytological atypia in tumorigenesis has been well established. As described previously, severe cytological atypia is the hallmark of HGINc. Therefore, we have reasons to believe that patients with HGINc have a higher risk of invasion than patients with HGINa. Moreover, there is a higher ratio in our cohort (28.00%, 49/175). It isn't consistent with conventional beliefs that HGINc is a rare disease. We postulate that the higher incidence is as a result of a high index of suspicion for HGINc in our center, leading to more aggressive biopsies for the suspicious lesions. It is also possible that it was diagnosed as low-grade neoplasia or HGINa according to previous histopathological criteria. Certainly, our results can not represent the incidence of HGINc, because only patients undergoing ESD were included in this study. However, it is obvious that HGINc, which accounts for about one third of HGIN in our study, is not a rare disease. Due to a high risk of invasion and a high ratio in

Table 2. Endoscopic characteristics of HGINa lesions and HGINc lesions (n=228)

		Total	HGINa (n=148)		HGINc (n=80)		*P* value
			n	%	n	%	
Location	Upper	22 (9.65)	16	10.81	6	7.50	0.550
	Middle	159 (69.74)	104	70.27	55	68.75	
	Lower	47 (20.61)	28	18.92	19	23.75	
Color	Reddish	124 (54.39)	114	77.03	10	12.50	<0.001
	Whitish	104 (45.61)	34	22.97	70	87.50	
Gross type	0-IIa	64 (28.07)	23	15.54	41	51.25	<0.001
	0-IIb	120 (52.63)	92	62.16	28	35.00	
	0-IIc	44 (19.30)	33	22.30	11	13.75	
Background color	Yes	123 (53.94)	113	76.35	10	12.50	<0.001
	No	105 (46.06)	35	23.65	70	87.50	
Intra-epithelial papillary capillary loop	A	107 (46.93)	37	25.00	70	87.50	<0.001
	B1	121 (53.07)	110	74.32	10	12.50	
	B2	1 (0.00)	1	0.68	0	0.00	
Idione unstaining area	Yes	228 (100.00)	144	100.00	84	100.00	-
	No	0 (0.00)	0	0.00	0	0.00	
Pink-color sign	Yes	91 (39.91)	84	56.76	7	8.75	<0.001
	No	137 (60.09)	64	43.24	73	91.25	
Length	Mean ± SD		3.20±1.87		3.20±1.49		0.545

-, not applicable.

Table 3. Multiple logistic regression analysis of related factors of HGINc

	B	S.E	Wals	Sig (*p*)	OR	95% CI of OR	
						Lower	Upper
neither smoking nor drinking					ref		
Only smoking	1.041	0.746	1.947	0.163	2.833	0.656	12.228
Only drinking	2.389	0.793	9.067	0.003	10.905	2.303	51.643
Both smoking and drinking	1.654	0.424	40.020	0.000	5.230	2.278	12.007
Reddish appearance					ref		
Whitish appearance	3.946	0.624	40.020	0.000	51.708	15.229	175.570
Gross type IIa	0.110	0.466	0.056	0.814	1.116	0.448	2.781
Gross type IIb					ref		
Gross type IIc	1.928	0.656	8.638	0.003	6.878	1.901	24.887
constant	-4.358	0.635	47.021	0.000	0.013		

R^2=0.415; B: partial regression coefficient; S.E: standard error; Sig: significance; OR: odds ratio; CI: confidence interval.

HGIN, methods for early diagnosis are urgently needed. However, until the current study was completed nothing was known about the features of HGINc. Lacking of knowledge of its endoscopic performances, some endoscopists may mistake such lesions for non-cancerous ones, and then do few or no biopsies. Treatment may be delay and a huge financial burden may be imposed in the end.

In our study, we found some different endoscopic features of HGINc, compared with HGINa. As we know, endoscopic findings are important to predict HGIN and decide for endoscopic resection. However, most of studies about early diagnosis have focus on HGINa for decades, little is known about HGINc. In agreement with previous studies, the common endoscopic findings of HGINa in our cohort are generally characterized by a reddish flat lesion with WLE, brownish area and Type B vessels with loop-like formation with ME-NBI, and a well-demarcated unstained area with positive PCS while Lugol's iodine staining. In contrast, the

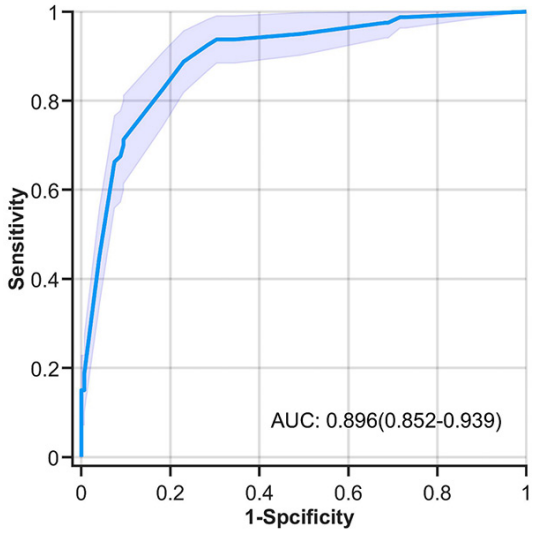

Figure 3. Receiver operating characteristic (ROC) curves for various independent relevant factors and TFM.

endoscopic features of HGINc differ greatly from HGINa. In our study, HGINc lesions often present as whitish elevated and multiple lesions simultaneously with WLE. Because of overlying hyperorthokeratosis, all of background color and IPCL and PCS are far more difficult to observe with ME-NBI and chromoendoscopy. Yet, a well-demarcated iodine-unstained area is similar between HGINc and HGINa. These results imply that a lesion without characteristics of HGINa should not be dismissed, because it may be a HGINc and need early treatment, too.

Among these different endoscopic features, whitish appearance and gross type are the independent relevant factors for HGINc. Whitish appearance is observed with WLE in multiple esophageal diseases. Glycogenic acanthosis, esophageal papilloma and eosinophilic esophagitis are easily differentiated according to the clinical symptoms and endoscopic examination [14]. HGINc lesions with whitish appearance are usually characterized pathologically by overlying hyperorthokeratosis in the squamous mucosa, similar to epidermoid metaplasia [15]. The pronounced granular layer often make lesion elevated in epidermoid metaplasia [16]. Similarly, gross type of most of HGINc lesions in our study is 0-IIa. Moreover, patients with epidermoid metaplasia or HGINc had a long-term history of smoking and drinking. And then, the most obvious one point of difference is that dysplastic cell is visible in the basal layer of HGINc. These relations suggest that HGINc may be an intermediate state between epidermoid metaplasia and ESCC. It is consistent with that esophageal epidermoid metaplasia is a precursor to in situ and invasive esophageal squamous neoplasia [17].

Tobacco and alcohol usage is found to be a crucial risk factor for HGINc in our study. Likewise, it is also recognized as a key risk factor for ESCC and the risk is significantly related to exposure intensity and duration. A recent study [18] has suggested that in physiologically normal esophageal epithelia, the progressive age-related expansion of clones that carry mutations in driver genes, which is substantially accelerated by alcohol consumption and by smoking. Moreover, multiple independent clones are present within the ESCC-bearing esophagus. And the same conclusion was confirmed in multiple studies [19-21]. In our study, HGINc has a closer relationship to tobacco and alcohol usage and presents more frequently with multiple lesions compared to HGINa. It is reasonable to speculate that more mutations in driver genes appear in HGINc. Therefore, HGINc is more susceptible to infiltration and requires special attention.

For the convenience of clinical application, we combined the independent relevant factors and successfully developed the first predictive model with good predictive values for HGINc, followed by building a nomogram. The nomogram showed that whitish appearance had the greatest contribution to prognosis, followed by tobacco and alcohol usage, gross type. The point would be given on the point scale axis, and we could get the predictive probability of individual patients through the total points, easily calculated by adding each point. As far as known, most of esophageal leukoplakia are benign lesions, and the confirmatory diagnosis depends on biopsy. However, biopsies are invasive examinations that place a burden on the patients. Thus, if there are sufficient endoscopic features, it may become unnecessary to perform a biopsy for every patient. Our study may help solve this problem, and the model can be used to predict a patient's HGINc risk. Patients with a higher predictive probability should be more carefully observed and more targeted

Table 4. Diagnostic test results of the three-factor model (TFM)*

Predictive diagnosis	Final diagnosis		Diagnostic index of							
	HGINc	HGINa	Sen	Spe	+PV	-PV	+LR	-LR	YI	Acc
HGINc	71	34	88.75% (79.77%-94.18%)	77.03% (69.58%-83.10%)	67.62%	92.68%	3.863	0.146	0.658	81.14% (75.54%-85.71%)
HGINa	9	114								

*: The cut-off value of TFM in this diagnostic test was set as 0.3569184 corresponding to the maximum of YI. Sen: Sensitivity; Spe: Specificity; +PV: Positive predictive value; -PV: Negative predictive value; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; YI: Youden index; Acc: Accuracy.

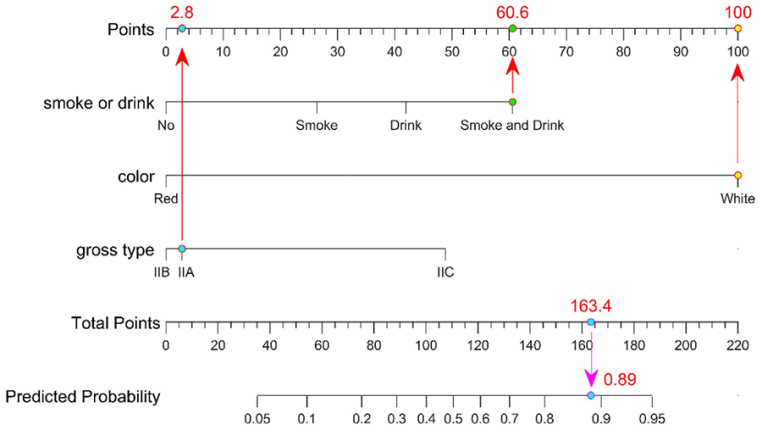

Figure 4. Nomogram for TFM. For example, if endoscopy detects the presence of whitish appearance and cross type 0-IIa in a patient with tobacco and alcohol abuse, the total points will be 163.4, so we can predict that the probability of BLSCC is 0.89.

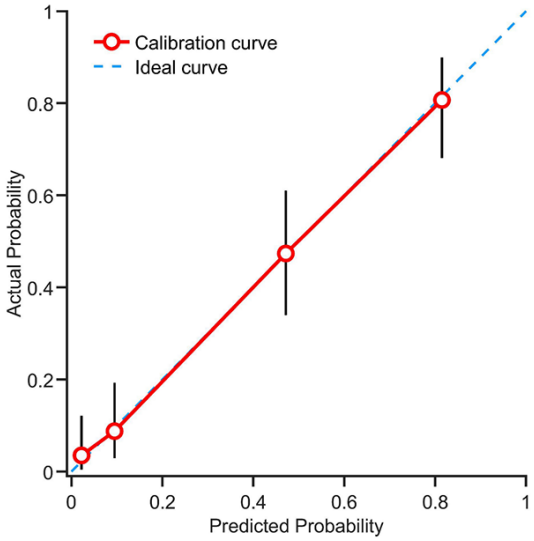

Figure 5. Calibration plots for TFM. The predictive calibration curve is almost parallel to the diagonal line which represents FFM provide a reliable prediction.

biopsies should be done. Then, the possibility of misdiagnoses and delays may be reduced. To summarize, our model and nomogram provides a feasible predictive method and it is helpful to make a more accurate diagnosis for HGINc.

Limitations of our study should also be addressed. First, sample size including in this study is not large enough. In order to obtain more clinicopathological features, more cases are needed for further prospective study. Second, our predictive model was developed using retrospectively collected data from a cohort of patients from a single endoscopic center, and further research is needed to validate the performance of the model in a larger external validation cohort. In addition, to diagnose HGINc more accurately, features of various levels, such as genome and protein expression level should be discussed in detail in further study.

In conclusion, our results clarified the ratio, and endoscopic features of HGINc. The findings can help to predict the presence of HGINc and have implications for future clinical practice.

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Disclosure of conflict of interest

None.

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