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LARYNGOLOGY

Elevated peripheral inflammatory markers are related with the recurrence and canceration of vocal fold leukoplakia

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Abstract

Objective To evaluate the predictive value of preoperative peripheral inflammatory markers in patients with vocal fold leukoplakia.

Methods A retrospective study was performed of the patients diagnosed with vocal fold leukoplakia and who accepted carbon dioxide (CO_2) laser resection in our center in the last 10 years. We calculated the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) after collecting and analyzing the clinical, histopathological and laboratory data. The potential relation between blood indexes and clinical events as recurrence or canceration was evaluated.

Results A total of 589 patients were involved, including 300 cases without recurrence (group A), 198 with recurrence but not canceration (group B) and 91 transformed into squamous cancer (group C). Baseline analysis of NLR, PLR, and MLR showed no difference among the three groups before the first surgery. But all the indexes significantly elevated in groups B ($P < 0.001, < 0.001$, 0.023, respectively) and C ($P = 0.009$, 0.004, 0.007, respectively) in the last operation. The receiver-operating curve (ROC) analysis showed NLR as a potential marker of canceration of leukoplakia (AUC = 0.837) and the cutoff value was 2.505. When regrouping with pathological outcomes, severe dysplasia and squamous cell carcinoma (SCC) groups both revealed a higher level of NLR, PLR, and MLR comparing to the no dysplasia, mild dysplasia, and moderate dysplasia groups. NLR, PLR, and MLR in high-risk group (moderate, severe dysplasia and carcinoma) also elevated comparing to low-risk group (no dysplasia, mild dysplasia) ($P = 0.039$, 0.011, 0.007, respectively).

Conclusions The peripheral inflammatory markers NLR, PLR, and MLR are closely connected with the development of vocal fold leukoplakia. NLR may be a potential marker to predict the poor outcomes (recurrence or canceration) of patients in first surgery.

Keywords Vocal fold leukoplakia · Neutrophil · Lymphocyte · Platelet · Monocyte · Recurrence · Canceration

Introduction

Vocal fold leukoplakia is a white mucosa lesion with squamous cell keratosis or dyskeratosis, accompanied by non-dysplasia, dysplasia or carcinoma, and cannot be diagnosed as any other disease [1]. With the morbidity rate of 1–6%, vocal fold leukoplakia acquires otolaryngologist's attention for its canceration tendency [2]. There is a consensus management of vocal fold leukoplakia, and surgical resection, especially with carbon dioxide (CO_2) laser, is the most popular strategy in clinic [3]. However, the recurrence and canceration still contribute to the failure of treatment. Published data suggest that the recurrence rates of vocal fold leukoplakia after CO_2 laser surgery vary from 16.0 to 22.7%

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[2, 4, 5], while preoperative markers to predict potential outcomes are still lacking.

Recent studies revealed the close interaction between systemic inflammation and local tumor [6]. As tumor or its microenvironment produced cytokines to recruit response immune cells, the latter were stimulated and the distribution of neutrophil, monocyte, platelet in the peripheral circulating system rises up [7]. Increase of neutrophil and monocyte was thought to be related with the suppression of lymphokine-activated killer cells [8], and platelet stimulated the angiogenic factors in tumor microenvironment [9]. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) were reported to be validated markers of systemic inflammation, also with diagnostic and prognostic values in several tumors, including laryngeal squamous cell carcinomas (LSCC) [10–12]. However, few researches with large cohort discussed the inflammatory markers of the laryngeal premalignant lesions.

The aim of this study was to investigate the prognostic value of peripheral inflammatory markers (NLR, PLR, and MLR) in recurrence and canceration of vocal fold leukoplakia after CO_2 laser treatment. Therefore, we performed a retrospective review of 589 patients with vocal fold leukoplakia.

Materials and methods

The project was approved by the ethics committee of the Eye, Ear, Nose, and Throat Hospital of Fudan University, Shanghai, China.

Patients

The patients diagnosed with vocal fold leukoplakia and who accepted CO_2 laser treatment in the Eye, Ear, Nose, and Throat Hospital of Fudan University from January 2008 to December 2018 were enrolled in our research. The retrospective study was performed according to the following criteria: (1) the preoperational office-based laryngoscopy located white mucosa lesion on vocal fold; (2) the postsurgical histopathological report revealed squamous cell keratosis or dyskeratosis with non-dysplasia, dysplasia or carcinoma. (3) Patients with the presence of fever and other acute or chronic inflammatory status, cardiovascular diseases, autoimmune diseases, hematologic disease, osteoporosis, and other malignant tumors were excluded from the research. And the following laryngeal white lesions were not included: (1) vocal cord pseudomembrane caused by fever and coughing; (2) vocal cord fungal mass after the long-term use of hormone spray to treat asthma; (3) vocal cord non-keratinized lesion such as laryngeal tuberculosis.

The no-recurrence group (as group A below) contained patients with single surgical experience, and confirmed without recurrence by office-based laryngoscopy in the outpatient of our center, or through telephone contacting to the patients who accepted postsurgical laryngoscopy examination in local hospitals and confirmed without recurrence. The recurrence group (group B) included patients with multi-operations in our center and no pathological report of carcinoma. The canceration group (group C) enrolled the patients diagnosed primarily as leukoplakia and progressed into LSCC after several times of surgeries. All the patients accepted related western medicine and Chinese medicine treatment in outpatient and received no positive effect, therefore, were suggested with surgical treatment.

Clinical data

The baseline characteristics of patients included age, gender, smoking history, alcohol-consuming habit, site of lesion, size of lesion, anterior commissure involved situation and postoperative pathological reports.

Patients who consumed 20 or more cigarettes, 80 mg or more pure alcohol per day and quitting less than 1 year were defined as current smokers and drinkers, respectively [13]. Two observers reviewed the preoperative office-based laryngoscope image and defined the records as following: the site of lesion was $< 50\%$ (the sum of all leukoplakia is less than half length of one entire vocal cord) or $> 50\%$ (the sum of all leukoplakia is more than half length of one entire vocal cord) [14]; the size of lesion was unilateral or bilateral; the anterior commissure was involved or not. The pathological report was defined as keratosis or dyskeratosis, with no dysplasia, mild dysplasia, moderate dysplasia, severe dysplasia, and carcinoma according to the World Health Organization (WHO) 2005 classification [15]. And a two-tier classification system divided non-, mild dysplasia group into "low risk" and moderate dysplasia, severe dysplasia, carcinoma into "high risk" group, as introduced in the WHO 2017 Blue Book [16].

The preoperative complete blood counting examinations were accomplished 2 weeks before receiving treatment and obtained from the electronic medical records. We excluded the cases without laboratory data or pathological diagnosis of leukoplakia. The neutrophil, lymphocyte, monocytes and platelet counting were extracted and NLR was calculated as a division of the absolute neutrophil to the absolute lymphocyte count, PLR and MLR followed as the same.

Statistical analysis

SPSS version 22.0 software (IBM Corporation, Chicago, USA) was used to perform the statistical analysis. The descriptive data were shown as percentage, and potential

clinical factors were examined by Pearson Chi square test. The differences among the three or more groups were calculated by the Kruskal Wallis test. And Mann–Whitney *U* test was employed to make comparison between the two groups, as the data were shown in abnormal distribution. The receiver-operating curve (ROC) analysis was performed to acquire the Youden index (sensitivity + specificity − 1), and the optimal cutoff values of NLR, PLR, and MLR were further calculated. Statistically significance was defined as two-sided *P* values < 0.05.

Results

A total of 589 patients with vocal fold leukoplakia signed their informed consents and accepted CO_2 laser surgery. There were totally 84 cases with missing data, including 35 cases without complete laboratory testing, 41 cases without laryngoscope image, and 8 cases without finding of pathological reports in the retrospective system. The non-recurrence group (group A) contained 287 males and 13 females, the recurrence group (group B) consisted of 183 males and 15 females, while the canceration group (group C) included 89 males and 2 females.

The mean age of group A was 59.62 ± 10.76 years, 59.32 ± 13.59 years in group B and 64.29 ± 8.93 years in group C. The distributed situations of smoking, alcohol consuming, site of lesion, size of lesion, anterior commissure involvement are listed in Table 1. The percentages of smoker ($P = 0.013$, R × *C* Pearson Chi square test), bilateral vocal cord infected ($P < 0.001$, $R \times C$ Pearson Chi square test), anterior commissure involvement ($P < 0.001$, $R \times C$ Pearson Chi square test) showed gradient rise from group A to B to C.

The mean NLR, PLR, and MLR in group A were 2.02 ± 0.91, 104.68 ± 39.26, and 0.22 ± 0.08. The mean NLR, PLR, and MLR of the first treatment in group B were 2.13 ± 0.99, 108.49 ± 42.52, and 0.23 ± 0.10, and the ratios in last surgery were 2.58 ± 1.76, 121.54 ± 54.74, and 0.26 ± 0.14. The mean NLR, PLR, and MLR of the first treatment in group C were 2.02 ± 0.91, 111.11 ± 45.56, and 0.25 ± 0.11, while the values in the treatment with pathological diagnosis of carcinoma were 2.62 ± 0.71, 139.71 ± 69.92, and 0.30 ± 0.14. As baseline analysis using Kruskal–Wallis *H* test, there was no difference of NLR ($P = 0.285$), PLR ($P = 0.496$), MLR ($P = 0.222$) between the three groups in the first surgery. Mann–Whitney test showed that NLR, PLR, and MLR significantly elevated with the course of recurrence ($P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively) and canceration ($P < 0.001$, $P = 0.062$, and $P < 0.001$, respectively) except the PLR in latter. And there were also statistically differences of NLR, PLR, and MLR between the canceration group and recurrence group ($P = 0.034$, $P = 0.004$, and $P = 0.005$, respectively) (Fig. 1).

Table 1 Baseline characteristics of patients

Variable	Data (%)		
	No recur	Recur	Cancerate
Age (years)			
< 60	141 (47.0%)	105 (53.0%)	24 (26.4%)
≥ 60	159 (53.0%)	93 (47.0%)	67 (73.6%)
Gender			
Male	287 (95.7%)	183 (92.4%)	89 (97.8%)
Female	13 (4.3%)	15 (7.6%)	2 (2.2%)
Smoking			
Yes	140 (46.7%)	107 (54.0%)	58 (63.7%)
Alcohol consuming			
Yes	133 (44.3%)	85 (42.9%)	44 (48.4%)
Site of lesion			
Unilateral vocal cord	203 (67.7%)	120 (60.6%)	40 (44.0%)
Bilateral vocal cords	97 (32.3%)	78 (39.4%)	51 (56.0%)
Size of lesion			
≥ 50%	95 (31.7%)	105 (53.0%)	45 (49.5%)
Anterior commissure involved			
Yes	47 (15.7%)	75 (37.9%)	46 (50.5%)
Sum	300	198	91

The ROC analysis was used and the area under curve (AUC) of NLR, PLR, and MLR was 0.837, 0.661, and 0.680, with the 95% confidence interval varying from 0.789 to 0.886, 0.593–0.729, and 0.618–0.743, and $P < 0.001$, < 0.001, and < 0.001, respectively. The cutoff values were calculated between the canceration group and non-recurrence group. The optimal cutoff value was 2.505 for NLR, 101.785 for PLR, and 0.235 for MLR, respectively. There was no significant difference between the recurrence and non-recurrence group, canceration and recurrence group.

Regrouping the data according to the WHO 2005 classification, there were five pathological levels as non-, mild, moderate, severe dysplasia and carcinoma. And WHO 2017 Blue Book divided the pathologic records into two tiers as low risk and high risk. The distribution of data within two classification standards is listed in Table 2.

In the pathological classification system, the NLR (2.26 ± 1.13), PLR (112.40 ± 44.49), and MLR (0.24 ± 0.11) of severe dysplasia were higher than the non-dysplasia group (2.09 ± 1.06, $P = 0.024$; 104.29 ± 40.35, $P = 0.044$; 0.22 ± 0.10, $P = 0.015$, Mann–Whitney test). In addition, the data in carcinoma group (2.84 ± 1.84, 135.82 ± 56.05, 0.32 ± 0.15) were much higher than the non-dysplasia group ($P = 0.007$, 0.001, < 0.001, respectively, Mann–Whitney test), and significantly than the severe dysplasia group ($P = 0.043$, 0.011, 0.001, respectively, Mann–Whitney test) (Fig. 3).

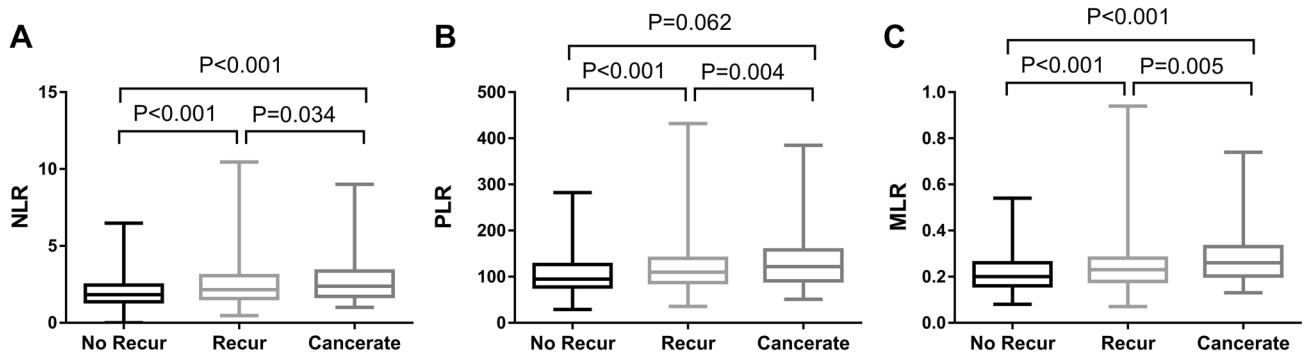

Fig. 1 Comparison of NLR (**a**), PLR (**b**), and MLR (**c**) in non-recurrence, recurrence, and canceration group. *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio

Table 2 Pathological grade and two-tier risk classification of patients

Variable	Data (%)				
	No recur	Recur		Cancerate	
		First	Last	First	Last
Histopathology					
Non-dysplasia	124 (41.3%)	48 (24.2%)	17 (8.6%)	7 (7.7%)	0 (0%)
Mild dysplasia	64 (21.3%)	54 (27.2%)	53 (26.8%)	10 (11.0%)	0 (0%)
Moderate dysplasia	35 (11.7%)	34 (17.2%)	50 (25.3%)	31 (34.1%)	0 (0%)
Severe dysplasia	72 (24.0%)	62 (31.4%)	78 (39.3%)	43 (47.2%)	0 (0%)
Carcinoma	5 (1.7%)	0 (0%)	0 (0%)	0 (0%)	91 (100%)
Risk grade					
Low risk	188 (62.6%)	102 (51.4%)	70 (35.4%)	17 (18.7%)	0 (0%)
High risk	112 (37.4%)	96 (48.6%)	128 (64.6%)	74 (81.3%)	91 (100%)
Sum	300	198	198	91	91

In the two-tier risk classification system, the NLR (2.29 ± 1.20), PLR (113.46 ± 44.79), and MLR (0.25 ± 0.11) in high-risk group elevated comparing to the low-risk group (2.10 ± 0.99, $P = 0.039$; 105.04 ± 38.30, $P = 0.011$; 0.23 ± 0.10, $P = 0.007$, Mann–Whitney test) (Fig. 4).

Discussion

Vocal fold leukoplakia is a complicate precancerous lesion with varied incidences of malignant transformation [17, 18]. Although there is consensus statement of diagnosis and management of this laryngeal dysplasia [3, 19], reliable prediction of clinical outcome still challenges the clinicians worldwide. The WHO has published the detailed pathological classification of vocal fold leukoplakia in 2006 and simplifies the standard to a two-tier system in 2018, enlightening the value of histopathologic records. As for preoperational markers, Chen et al. described a morphological classification based on laryngoscopy report, which divided as flat and smooth leukoplakia, elevated and smooth leukoplakia and rough leukoplakia, and proved the need for positive surgical involvement for rough type [20]. The narrow-band imaging (NBI) endoscopy focused on its vascularization, could improve the identification of laryngeal lesions and provided indicative information for the biopsy and operative margins [21]. In our study, we investigated the role of circulating inflammatory markers before the treatment and verified their connection with the recurrence and canceration of vocal fold leukoplakia.

Inflammation can be a response to infection, tissue injury, immune disorder, benignant and malignant neoplasm and detected by circulating blood cell counting. Recent studies recognized inflammation as a hallmark of cancer that substantially facilitated the tumorigenesis and development of local malignancies [22]. In several cancers, the close relationship between inflammation and cancer had been revealed, which demonstrated the infiltration of inflammatory cells in tumor microenvironment and their multifactorial process to facilitate the growth, migration and metastasis of cancer [23, 24].

As for head and neck cancer, especially the laryngeal malignance, inflammatory status can be predictable and reasonable. First, the vast majority of patients are in the middle ages, as mean age of 61 years in our study, whose immune system tends to be imbalanced and performed poorly to inflammatory challenge [25]. Second, there is obvious trend of smoking and alcohol-consuming habits of male patients included (shown in Table 1). The nicotine included and alcohol can both disrupt and damage the gene stability of normal tissue [26, 27], tripper the inflammation in larynx [28] and contribute to partial hypoxia, which directly activates angiogenesis on vocal cord [29]. Third, as a bacterial environment, the microbiome, helicobacter pylori for instance, can destroy epithelial mucosa and cause chronic inflammatory injury resulting in larynx pathology [30]. The possible link between helicobacter pylori and benign, malignant laryngeal lesions had also been fully demonstrated recently [31].

To evaluate the inflammatory status, several peripheral circulating indexes had been targeted and proven of positive connections with cancer. Neutrophil was previously known as rapid aggressors with poor regulatory functions. However, neutrophil was found to be recruited and influence the tumor microenvironment in multiple mechanisms, as inducing genetic damage, produce signaling in pre-tumoral cells to promote tumorigenesis [32] and activate the angiogenesis pathway and other tumor-supporting factors [9]. Lymphocytes, especially the CD4+ helper lymphocytes and CD8+ cytotoxic lymphocytes, play an important role in the immune response to tumor and other pathologies. The decrease of lymphocytes was observed in many types of cancers [33], and lymphocytopenia has been commonly considered as a state of system immunodepression. Platelets are the main cells working in the traditional hemostasis process, meanwhile, it also produce MMP9 and participate in the tumor angiogenesis, which promote the microvascular permeability and extravasation of tumor cells, as a synergistic effect with neutrophil [34].

Palumbo et al. described the immune-escaping function of platelet in tumor microenvironment and peripheral circulating blood as a "cloak" to cover the tumor cells and protects it from immune surveillance [35]. Monocytes are known as the precursor of macrophages, and the latter infiltrates into the cancer and forms the main component of tumor microenvironment. The tumor-associated macrophages (TAMs) are phenotypically and functionally different from the normal macrophages, and involved in the tumor migration, metastasis and angiogenesis [36]. Therefore, the peripheral circulating neutrophils, lymphocytes, platelets and monocytes may indirectly reflect the inflammatory status of local solid tumor and distinguish the malignant neoplasms from benignant lesions.

Notably, the circulating inflammatory indexes reflect the systematic status of infection and inflammation, such as acute inflammation, immune disease, hematologic disease and also other benignant or malignant tumors. Therefore, the statistical results can be affected by many potential clinical biases and are often doubt with certain difficulty to specifically reflect the local lesions in common clinical practice. In our research, we purposefully excluded the patients with such disease above to minimize the potential bias and our research outcomes may reflect the objective connection between inflammatory markers and vocal fold leukoplakia.

The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio (MLR) had been validated as markers with prognostic significance of several tumors, including the head and neck squamous cell carcinomas (HNSCC) [10, 37, 38]. Yasumatsu et al. analyzed 41 patients with HNSCC who accepted nivolumab monotherapy. And they found NLR may help to indicate the earlier confirmation of treatment failure [39]. Chen et al. reported the elevated preoperative NLR, PLR, and MLR connected with worse survival and cancer progression [38]. However, in all the aforementioned researches, patients with precancerous lesions were not counted and the significance of NLR, MLR, and PLR were not fully discussed. To our knowledge, Rauf Oguzhan Kum et al. first investigated the possible relationship of NLR in LSCC patients comparing to the benign and precancerous laryngeal lesions [12]. The subgroups were divided as mild dysplasia, moderate dysplasia and severe dysplasia/CIS groups, and no significance was found in this research. While in our study, the NLR, MLR, and PLR in pathological classification and two-tier risk classification system all showed a significant difference in subgroup comparison (shown in Figs. 2, 3). And we found the NLR, MLR, and PLR were lowest in the patients without recurrence, higher in recurrence group and highest in canceration group. As shown in Fig. 4, the cutoff values were 2.505 for NLR, 101.785 for PLR, and 0.235 for MLR in our analysis, in line with the existing data released by Chen et al. [38]. With ideal AUC value, NLR can serve as a potential quantized marker in clinical practice. The different statistic results might derive from the sample size, as we gathered the available data of the last decade in our center, with 589 patients included in the analysis.

The strength of this research was the large sample size of patients with vocal fold leukoplakia, including plenty cohort of patients with recurrence and canceration. The research also had limitations. It focused on the analysis and comparison of patients who accepted CO2 laser surgery, however, the characteristics and outcome of patients not treated with CO2 laser or only accepted medicine treatment in outpatient were missing. In addition, the results had difficulty in relating with other current well-known factors of vocal fold leukoplakia, which required further multi-factor analysis of the reliable markers in origin and progression of vocal fold leukoplakia.

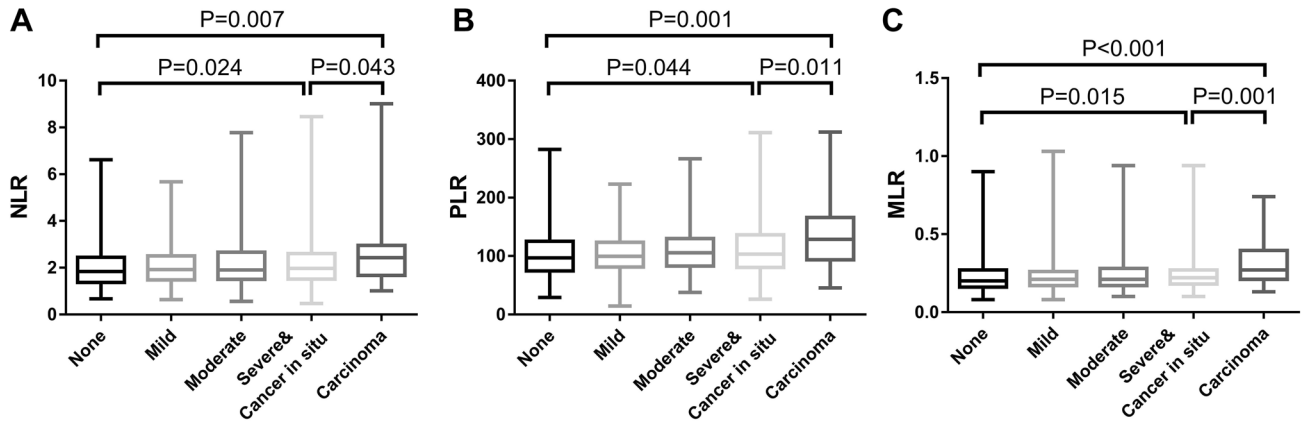

Fig. 2 Comparison of NLR (**a**), PLR (**b**), and MLR (**c**) among the pathological grade of vocal cord leukoplakia. *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio

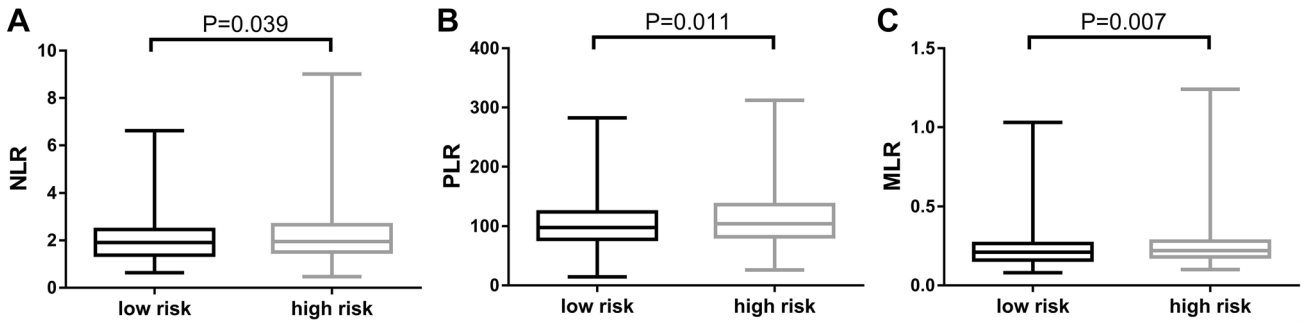

Fig. 3 Comparison of NLR (**a**), PLR (**b**), and MLR (**c**) among the two-tier risk classification of vocal cord leukoplakia. *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio

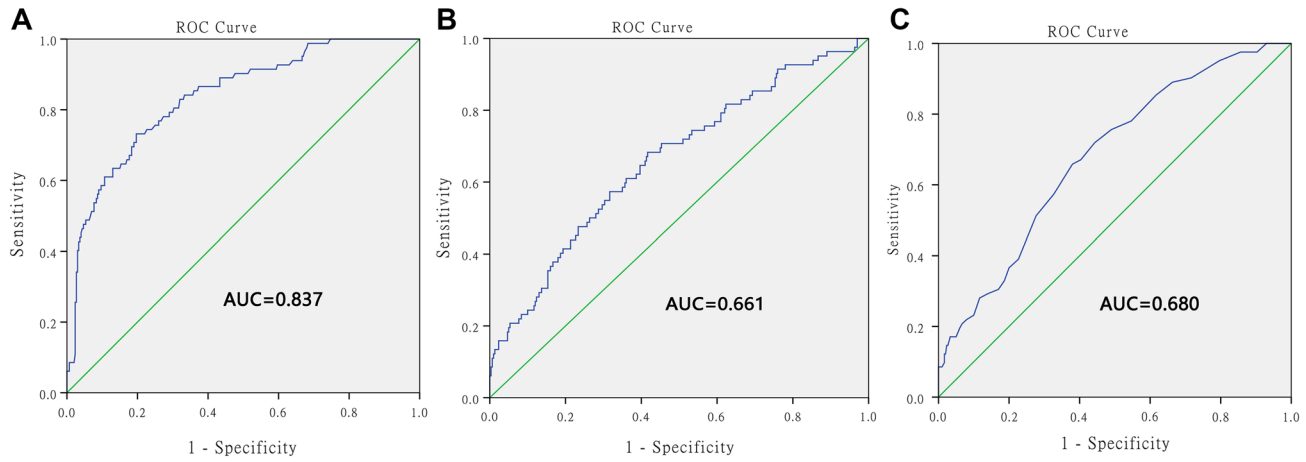

Fig. 4 The receiver-operating characteristic (ROC) curve and the area under curve (AUC) to identify optimal cutoff value of NLR (**a**), PLR (**b**), and MLR (**c**). *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio

Conclusion

Above all, the peripheral inflammatory markers NLR, PLR, and MLR are closely connected with the development of vocal fold leukoplakia. NLR may be a potential marker to predict the poor outcomes of patients in the first surgery.

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Compliance with ethical standards

Conflict of interest There is no financial relationship and conflict of interest.

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