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Original Article

NLR, PLR, LMR and MWR as diagnostic and prognostic markers for laryngeal carcinoma

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Abstract: Objective: To evaluate whether neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR) and monocyte-to-white blood cell ratio (MWR) can be used as diagnostic and prognostic markers for laryngeal carcinoma (LC). Methods: In this retrospective study, 50 patients with LC treated in the Department of Otolaryngology, Head and Neck Surgery of Beijing Tongren Hospital from August 2014 to August 2015 were enrolled in research group. In addition, 40 healthy volunteers from the same period were selected as control group. The counts of white blood cells, neutrophils, lymphocytes, monocytes and platelets in the peripheral blood of participants were measured with a blood counting instrument (Sysmex XE-2100, Sysmex Corporation, Japan), and the NLR, PLR, LMR and MWR were calculated. After that, the survival rate of patients was observed through a 5-year follow-up. The prognostic value of the above four indexes and their combination was discussed in patients with different clinical characteristics. Results: Compared with the control group, the NLR, PLR and MWR were higher and the LMR was lower in the research group. In terms of survival, patients with higher NLR, PLR and MWR and lower LMR showed a higher 5-year mortality than those with lower NLR, PLR and MWR and higher LMR, indicating that NLR, PLR and MWR were higher and LMR was lower in the survival group than in the death group. Subsequent analysis identified that NLR, PLR, LMR and MWR were closely correlated with age, alcohol drinking, smoking, clinical staging and T-staging. Clinical staging, T-staging, NLR, PLR, LMR, and MWR were confirmed as influencing factors for LC. Conclusions: NLR, PLR, LMR, and MWR can be used as diagnostic and prognostic markers for LC and their combination has a superior diagnostic performance.

Keywords: NLR, PLR, LMR, MWR, laryngeal carcinoma, tumor

Introduction

Laryngeal carcinoma (LC), a common carcinoma with the highest incidence among head and neck cancers, accounts for 1-5% of global cancer incidence [1]. Smoking, drinking and the invasion of toxic substances can lead to the development of LC [2]. A variety of treatments can be used to treat LC, such as radiotherapy [3] and targeted specific molecular therapy [4, 5]. In recent years, the targeted therapy based on LC-related miRNAs their targets have played an essential role in improving the survival rate of patients [6, 7]. Early diagnosis and adequate preoperative evaluation can increase the possibility of cure while retaining the function. The prognosis of patients who were diagnosed in the early stage is optimistic, with an cure rate of up to 80-90% [8, 9]. In addition, the study of cancer-related prognostic markers has always been a research hotspot. In the past decade, the research on LC has shifted from traditional clinicopathological factors to new biomarkers [10, 11], so as to better describe tumor prognosis and develop targeted treatment strategies. Thus, in this study, we focused on finding diagnostic and prognostic markers for LC.

Accumulating evidences have confirmed that microenvironment inflammation plays a key role in the development and progression of malignant tumors by inhibiting apoptosis and promoting angiogenesis [12, 13]. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR) and monocyte-to-white blood cell ratio (MWR)

have been shown to play important prognostic roles in various diseases and are generally used to evaluate the severity of inflammatory reaction [14, 15]. Increased NLR, PLR and MWR indicated poor prognosis in various cancers [13], such as non-small cell lung cancer [16] and gastric cancer [17]. Feng et al. [17] studied the relationship between blood test parameters and the prognosis of patients with gastric cancer, and found that high MLR, NLR, PLR, NWR, MWR and low LWR were related to the poor prognosis. In esophageal cancer, low LMR is also found to be related to aggravated conditions of the patients [18]. However, there are few studies on the role of NLR, PLR and MWR in LC, which motivated us to figure out whether these indicators can be served as diagnostic and prognostic markers for LC. Accordingly, the innovative points and the purpose of this study were to find out the role of NLR, PLR, LMR and MWR in the diagnosis and prognosis of LC and to analyze the correlations of the four with different clinical characteristics.

Methods

General data

This study is a retrospective study. Patients diagnosed with laryngeal squamous carcinoma without preoperative chemotherapy or radiotherapy (n=50) were enrolled in research group. They were treated in the Department of Otolaryngology, Head and Neck Surgery of Beijing Tongren Hospital from August 2014 to August 2015. A total of 40 healthy volunteers from the same period were selected as the control group. Inclusion criteria: (1) All subjects were older than 18 years old; (2) All patients were diagnosed with LC by pathology and imaging; (3) Patients did not use aspirin or steroids before treatment; (4) Patients underwent routine blood test; (5) Patients did not have mental disorder and was able to accurately reflect their discomforts; (6) Patients provided complete clinical data. Exclusion criteria: (1) Patients had serious complications or died within 30 days after treatment; (2) Patients had other malignant tumors; (3) Patients did not comply with the treatment; (4) Patients did not finish the follow-up; and (5) Patients had incomplete clinical files.

Patients, family members and healthy volunteers all participated this study voluntarily and signed an informed consent form. This study was approved by the Medical Ethics Committee of Beijing Tongren Hospital.

Methods

Detection: After the diagnosis, 2 mL of fasting peripheral blood was collected from all the patients within one week before treatment. The counts of peripheral blood white blood cells, neutrophils, lymphocytes, monocytes and platelets were detected using a blood counting instrument (Sysmex XE-2100, Sysmex Corporation, Japan). Then, NLR, PLR, LMR and MWR were calculated. NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; LMR: lymphocyte to monocyte ratio; MWR: monocyte-to-white blood cell ratio. In the testing process, all the procedures were carried out in strict accordance with the operating instructions, and all the experimental reagents (Sigma, Japan) matched the instruments (Sysmex XE-2100, Sysmex Corporation, Japan).

Follow-up: All patients were followed up for at least 60 months, except for those who died during the process. Follow-ups were conducted through self-made questionnaires, telephone calls, short messages and social media. Regular follow-ups were carried out through consulting outpatient and inpatient data. The follow-up started from the first month after treatment, and the interval of review was varied depending on patients' tumor stage. Patients in stage I were reexamined once every six months in the first three years and once a year in the next two years. Patients stage II-III were reviewed every 3 months for the first 2 years and every 6 months for the following 3 years. Patients in stage IV were reexamined every 3 months. The follow-up ended in September 2020. Patient survival was analyzed through the follow-up data.

Statistical methods

SPSS 21.0 (Beijing Bizinsight Information Technology Co., Ltd) was used for data processing. The counting data were presented as n (%), and compared by the Chi-squared test or Fisher's exact test. Measurement data, recorded as (mean ± standard deviation), were analyzed by independent sample t-test between

Table 1. General clinical data of research group and control group

Group	Research group (n=50)	Control group (n=40)	F/X^2	P
Sex			0.25	0.614
Male	35 (70.00)	26 (65.00)		
Female	15 (30.00)	14 (35.00)		
Age (years old)			0.03	0.867
≤63	12 (24.00)	9 (22.50)		
>63	38 (76.00)	31 (77.50)		
Average age	61.33±13.31	61.54±12.79	0.08	0.940
BMI (kg/m^2)	23.76±1.89	24.15±1.73	1.01	0.315
Drinking			0.08	0.777
Yes	26 (52.00)	22 (55.00)		
No	24 (48.00)	18 (45.00)		
Smoking			0.10	0.749
Yes	36 (72.00)	30 (75.00)		
No	14 (28.00)	10 (25.00)		
Clinical staging			-	-
I	9 (18.00)	-		
II	24 (48.00)	-		
III	13 (26.00)	-		
IV	4 (8.00)	-		
T-staging			-	-
T1	12 (24.00)	-		
T2	22 (44.00)	-		
T3	10 (20.00)	-		
T4	6 (12.00)	-		

Note: BMI: body mass index.

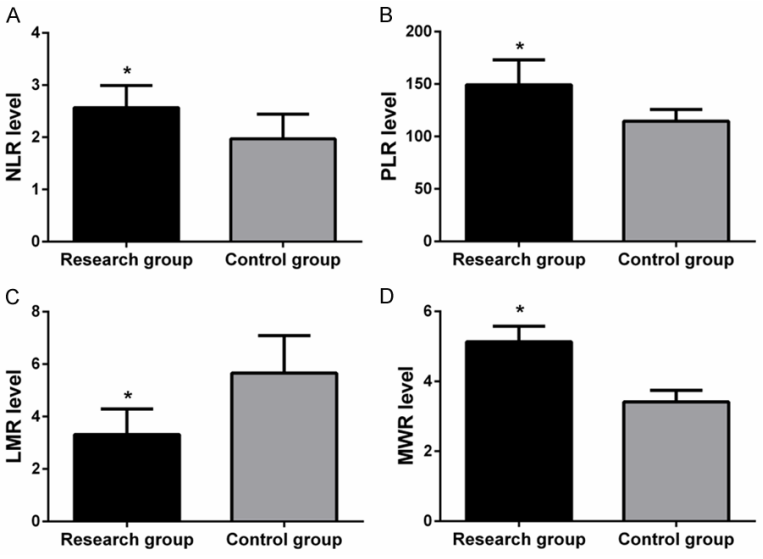

Figure 1. Comparison of NLR, PLR, LMR and MWR between the research group and the control group. (A-D) The NLR (A), PLR (B), LMR (C) and MWR (D) in the research group were higher than those in the control group. NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, LMR: lymphocyte to monocyte ratio, MWR: monocyte-to-white blood cell ratio. *P<0.05 *vs.* the control group.

two groups. Kaplan-Meier survival curves and log-rank analysis were performed to estimate the survival curves and compare the differences between them. The sensitivity and specificity of NLR, PLR, LMR and MWR in predicting the prognosis was assessed by receiver operating characteristic (ROC) curves, and the area under the ROC curve (AUC) also was calculated. The Cox proportional hazards regression model was used for multivariate analysis. The significance level was set at P<0.05.

Results

General data

There were no significant differences in general clinical data such as sex, age, body mass index (BMI), and history of drinking and smoking between the two groups (P> 0.05), indicating compatibility (**Table 1**).

Comparison of NLR, PLR, LMR, and MWR between patients and controls

Compared with the control group, the NLR, PLR and MWR were higher while the LMR was lower in the research group (P<0.05) (**Figure 1**).

Effects of NLR, PLR, LMR and MWR on the survival of patients with LC

According to value of NLR, PLR, LMR and MWR, patients were divided into high- (n=25) and low-level subgroups (n= 25) with a median of 2.47, 145.39, 3.26 and 5.09, respectively. After analyzing the survival, it was found that patients with high NLR, PLR and MWR and low LMR had an

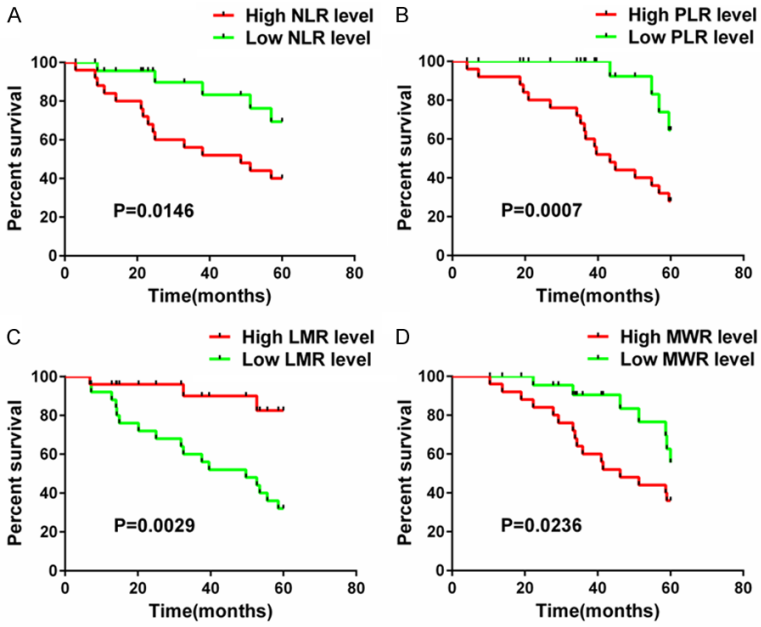

Figure 2. Effects of NLR (A), PLR (B), LMR (C) and MWR (D) on the survival rate of patients with laryngeal carcinoma. NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, LMR: lymphocyte to monocyte ratio, MWR: monocyte-to-white blood cell ratio.

evidently lower 5-year survival rate (P<0.05) (**Figure 2**).

Prognostic value of NLR, PLR, LMR and MWR for LC

Based on the prognosis, patients were divided into either the death group or the survival group, and NLR, PLR, LMR and MWR were compared between the two subgroups. We identified higher NLR, PLR, and MWR and lower LMR in the death group as compared with those in the survival group (P<0.05, **Figure 3A-D**). ROC curve analysis of NLR, PLR, LMR and MWR showed that each one of them had high predictive value for the prognosis (AUC: 0.8164 for NLR, 0.8824 for PLR, 0.8808 for LMR, 0.7955 for MWR, **Figure 3E**, **3F**). In addition, we also calculated the AUC of the combination of NLR, PLR, LMR, and MWR, which showed excellent diagnostic performance (AUC=0.9059, **Figure 3I**).

Correlation of NLR, PLR, LMR and MWR with the clinicopathological features of patients with LC

Correlation analysis of NLR, PLR, LMR and MWR with the clinicopathological features showed that NLR, PLR, LMR and MWR were not associated with the sex of patients, but was closely correlated with age, clinical staging, T-staging, and history of drinking and smoking (P<0.05) (**Figures 4-7**).

Multivariate analysis of prognosis and related factors of LC

Age, drinking, smoking, T-staging, as well as NLR, PLR, LMR, and MWR were set as independent variables and assigned, and death was used as the dependent variable for multivariate Cox regression analysis (**Table 2**). Univariate cox analysis showed that age, clinical staging, T-staging as well as NLR, PLR, LMR and MWR were the factors affecting prognosis of patients with LC (**Table 3**). Then, these indicators were subjected to multivariate analysis, and the results indicated that higher clinical staging and T-staging as well as higher NLR, PLR and MWR were the independent risk factors for poor prognosis of patients with LC, while higher LMR was the protective factor against poor prognosis of the patients (**Table 4**).

Discussion

Searching for prognostic factors has always been one of the focuses of various cancer studies [19, 20]. It has been shown that miRNAs and related lncRNAs are important prognostic factors [21]. Based on this, we will discuss whether NLR, PLR, LMR and MWR can be used as prognostic markers for LC.

The ratios of blood cells such as NLR, LMR and PLR have always been important indicators of inflammation [22]. In various diseases, especially malignancies, tests conducted on immune inflammatory cells have proved that the blood indicators can be effective predictors, and they are convenience and with low cost as part of routine laboratory analysis [23-25]. In order to understand the functions of these indicators,

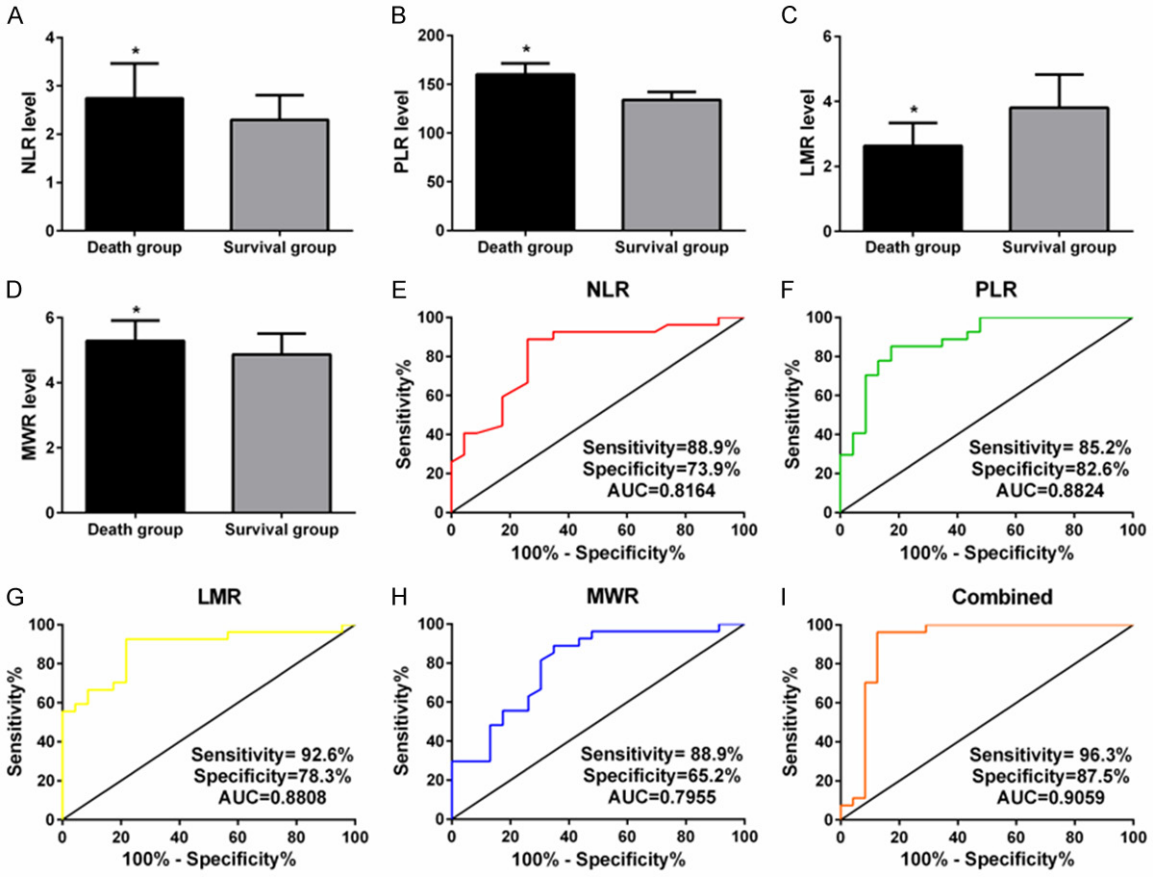

Figure 3. Predictive value of NLR, PLR, LMR and MWR for the prognosis of patients with laryngeal carcinoma. (A, B, D) The NLR (A), PLR (B) and MWR (D) in the death group were significantly higher than those in the survival group (P<0.05); (C) The LMR in the death group was significantly lower than that in the survival group (P<0.05); (E-I) The ROC of NLR (E), PLR (F), LMR (G), MWR (H) and NLR+PLR+LMR+MWR (I) for the prognosis of the patients. NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, LMR: lymphocyte to monocyte ratio, MWR: monocyte-to-white blood cell ratio, ROC: receiver operating characteristic. *P<0.05 vs. the survival group.

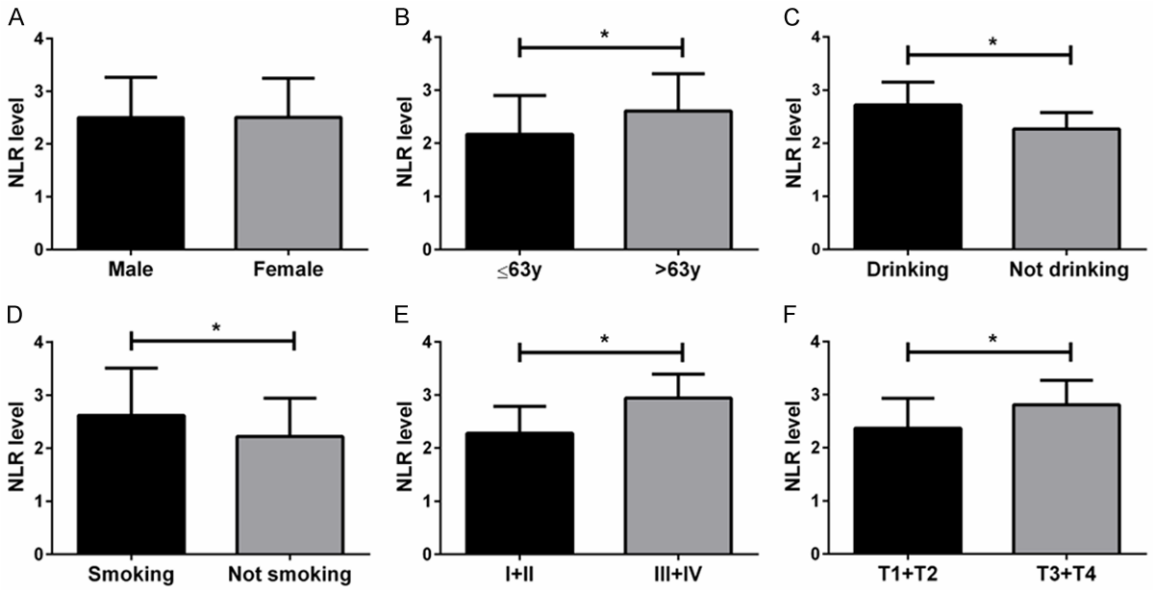

Figure 4. NLR in patients with different clinical features. A. Sex: There was no difference in the NLR between males and females (P>0.05); B. Age: the NLR in patients aged 63 or less was significantly lower than that in patients over 63 years old (P<0.05); C. Drinking: the NLR in patients with a drinking history was significantly higher than that in non-drinkers (P<0.05); D. Smoking: the NLR in patients with a smoking history was significantly higher than that in non-smokers (P<0.05); E. Clinical staging: the NLR of patients in stage I-II was significantly lower than that of patients in stage III-IV (P<0.05); F. T-staging: the NLR of patients in stage T1-T2 was significantly lower than that of patients in stage T3-T4 (P<0.05). NLR: neutrophil-to-lymphocyte ratio. *P<0.05.

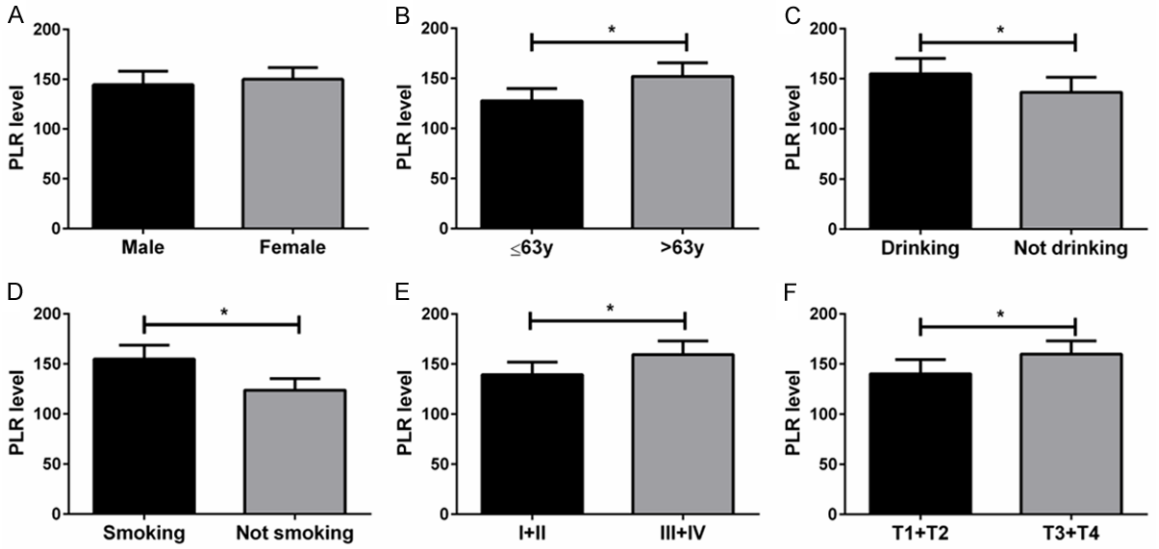

Figure 5. PLR in patients with different clinical features. A. Sex: there was no difference in the PLR between males and females (P>0.05); B. Age: the PLR in patients aged 63 or less was significantly lower than that in patients over 63 years old (P<0.05); C. Drinking: the PLR in patients with a drinking history was significantly higher than that in non-drinkers (P<0.05); D. Smoking: the PLR in patients with a smoking history was significantly higher than that in non-smokers (P<0.05); E. Clinical staging: the PLR of patients in stage I-II was significantly lower than that of patients in stage III-IV (P<0.05); F. T-staging: the PLR of patients in stage T1-T2 was significantly lower than that of patients in stage T3-T4 (P<0.05). PLR: platelet-to-lymphocyte ratio. *P<0.05.

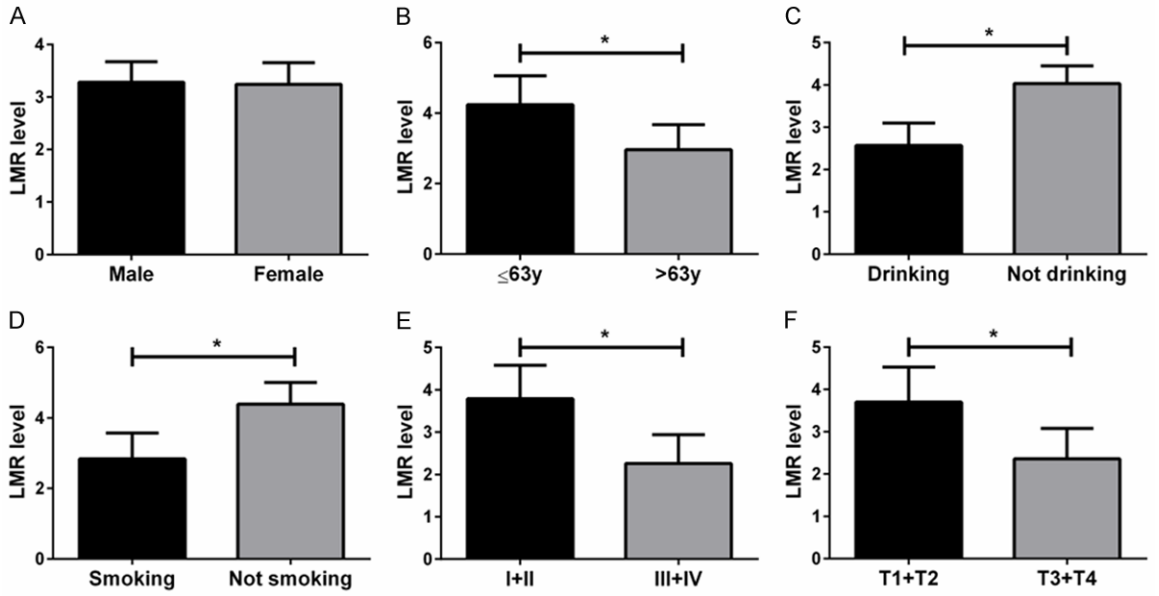

Figure 6. LMR patients with different clinical features. A. Sex: there was no difference in the LMR between males and females (P>0.05); B. Age: the LMR in patients aged 63 or less was significantly higher than that in patients

over 63 years old (P<0.05); C. Drinking: the LMR in patients with a drinking history was significantly lower than that in non-drinkers (P<0.05); D. Smoking: the LMR in patients with a smoking history was significantly lower than that in non-smokers (P<0.05); E. Clinical staging: the LMR of patients in stage I-II was significantly higher than that of patients in stage III-IV (P<0.05); F. T-staging: the LMR of patients in stage T1-T2 was significantly higher than that of patients in stage T3-T4 (P<0.05). LMR: lymphocyte to monocyte ratio. *P<0.05.

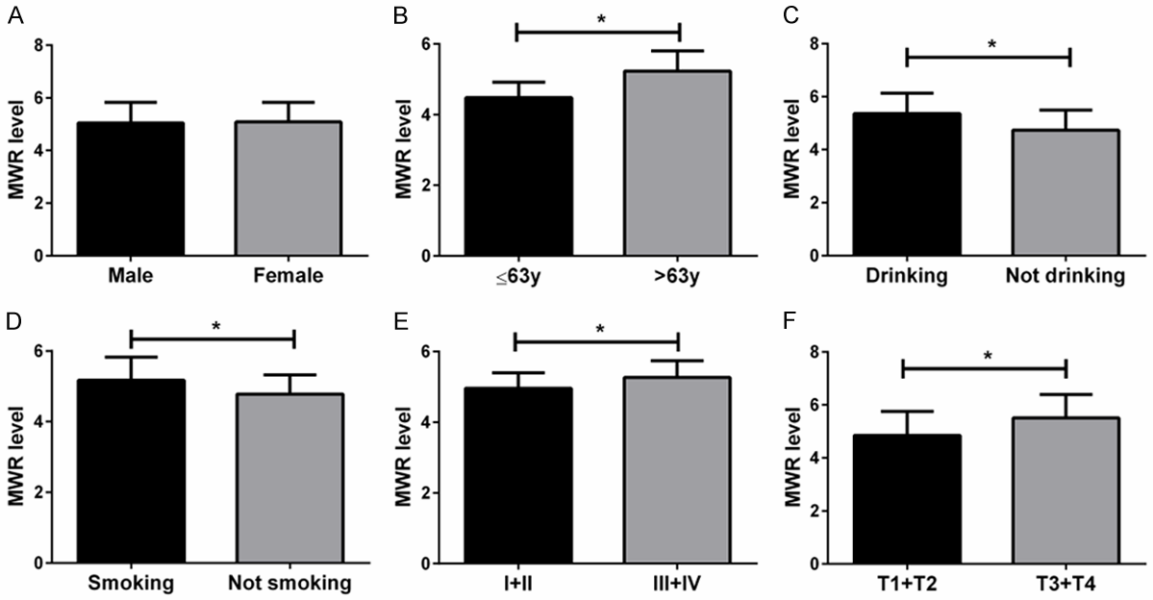

Figure 7. MWR in patients with different clinical features. A. Sex: there was no difference in the MWR between males and females (P>0.05); B. Age: the MWR in patients aged 63 or less was significantly lower than that in patients over 63 years old (P<0.05); C. Drinking: the MWR in patients with a drinking history was significantly higher than that in non-drinkers (P<0.05); D. Smoking: The MWR in patients with a smoking history was significantly higher than that in non-smokers (P<0.05); E. Clinical staging: the MWR of patients in stage I-II was significantly lower than that of patients in stage III-IV (P<0.05); F. T-staging: the MWR of patients in stage T1-T2 was significantly lower than that of patients in stage T3-T4 (P<0.05). MWR: monocyte-to-white blood cell ratio. *P<0.05.

Table 2. Assignment of factors related to the prognosis of laryngeal carcinoma

Related factors	Assignment description
Age	≤63=0, >63=0
Drinking	No=0, yes=1
Smoking	No=0, yes=1
Clinical staging	I+II=0, III+IV=1
T-staging	T1+T2=0, T3+T4=1
NLR	Continuous variable
PLR	Continuous variable
LMR	Continuous variable
MWR	Continuous variable

Note: NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, LMR: lymphocyte to monocyte ratio, MWR: monocyte-to-white blood cell ratio.

we must first figure out the specific role of the cells in these indicators [26]. Neutrophils play an important role in the progression of cancer [27]. The toxic substances produced by neutrophils, such as reactive oxygen species, neutrophil elastase and prostaglandin E2, can effectively promote cell carcinogenesis, cancer cell growth, metastasis and angiogenesis [28]. Lymphocytes are always squeezed and mutated in the process of tumor invasion, and the number is also constantly decreasing [29]. In theory, an increase in platelets means an increase in cancer invasiveness, also, cancer cells and platelets can indirectly interact with each other through secreted molecules to become more aggressive [30]. Therefore, the higher the NLR and PLR, the more serious the cancer.

LMR represents the balance between lymphocyte and monocyte levels in cancer [31]. Low LMR indicates a relative decrease in lymphocytes or an increase in monocytes, which in most cases, suggests a dominant pro-tumor

Table 3. Univariate analysis of factors related to the prognosis of laryngeal carcinoma

Variables	β	SE	Wald	P	Exp (β)	95% CI
Age	0.040	0.020	3.885	0.049	1.041	1.000-1.084
Smoking	0.291	0.422	0.474	0.491	1.337	0.584-3.061
Drinking	0.225	0.481	0.218	0.641	1.252	0.487-3.215
Clinical staging	1.773	0.554	10.249	0.001	5.886	1.989-17.423
T-staging	0.992	0.436	5.189	0.023	2.697	1.149-6.334
NLR	1.621	0.568	8.134	0.004	5.059	1.660-15.414
PLR	0.033	0.012	8.205	0.004	1.0.34	1.011-1.057
LMR	-0.511	0.257	3.945	0.047	0.600	0.363-0.993
MWR	1.626	0.590	7.604	0.006	5.081	1.600-16.135

Note: SE: standard error, CI: confidence interval, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, LMR: lymphocyte to monocyte ratio, MWR: monocyte-to-white blood cell ratio.

Table 4. Multivariate analysis of factors related to the prognosis of laryngeal carcinoma

Variables	β	SE	Wald	P	Exp (β)	95% CI
Age	0.030	0.025	1.486	0.223	1.031	0.982-1.082
Clinical staging	2.246	0.802	7.835	0.005	9.451	1.961-45.552
T-staging	1.172	0.591	3.928	0.047	3.228	1.013-10.285
NLR	1.897	0.681	7.750	0.005	6.664	1.753-25.333
PLR	0.055	0.020	7.552	0.006	1.057	1.016-1.110
LMR	-1.082	0.430	6.340	0.012	0.339	0.146-0.787
MWR	1.547	0.778	3.955	0.047	4.699	1.023-21.589

Note: SE: standard error, CI: confidence interval, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, LMR: lymphocyte to monocyte ratio, MWR: monocyte-to-white blood cell ratio.

inflammatory response, indicating a high degree of malignancy and rapid progression of cancer [32]. Monocytes plays a significant role in carcinogenesis by associating with cancer progression, enhancing angiogenesis in primary tumors and inhibiting the host anti-cancer immune response [33]. The effect of LMR on cancer is diametrically opposed to that of NLR and PLR, and a decrease in LMR means an increase risk of cancer. The decline in white blood cells, which are immune cells, is associated with an increase in monocytes, which affects the function of white blood cells as immune cells. Elevated MWR is a hallmark of the imbalance between monocytes and white blood cells, indicating further progression of cancer. From this, we can draw the conclusion that increased NLR, PLR and MWR and decreased LMR suggest further deterioration of neoplastic diseases.

In this study, we found that NLR, PLR and MWR were higher and LMR was lower in patients with LC than in controls, which preliminarily proved that the above indicators could lead to further deterioration of LC and played the same role in LC as in other cancers. Meanwhile, our research found that higher NLR, PLR and MWR and lower LMR are correlated with higher mortality. Subsequent data and survival curve analyses showed that these indicators had high prognostic value in LC. Similarly, a previous study on gastric cancer revealed that high NLR, PLR and MWR, and low LMR predicted poorer survival of patients with gastric cancer [34]. Furthermore, this study found that different cancer stages were closely related to the value of NLR, PLR, MWR and LMR. In T-staging, patients in stage T1-T2 had lower NLR, PLR and MWR and higher LMR than those in stage T3-T4. In clinical stages, patients in stage I-II had lower NLR, PLR and MWR and higher LMR those in stage III-IV. It also corresponds well with the conclusion that increased NLR, PLR and MWR, and decreased LMR indicate further deterioration of cancer. Moreover, we found that drinking and smoking history can elevate NLR, PLR and MWR and inhibit LMR. Subsequent research revealed that these four were also influencing factors of the progno-

sis of LC. Studies have also shown that drinking and smoking are inducing factors for LC, and may lead to changes in factors such as NLR and PLR [35, 36]. Another study suggested that the effects of smoking and drinking on the occurrence and development of LC cannot be underestimated [37]. Therefore, alcohol consumption and smoking, which are closely associated with the levels of NLR, PLR, MWR and LMR, are also the risk factors of the prognosis of LC.

There are still some limitations in this study. First, the sample size is relatively small, which may lead to certain bias in the research results. Second, for some of the indicators, we only analyzed the research results with previous literature. In future research, we will measure more indexes and related prognostic factors based in a larger sample-size study, so as to more accurately understand the specific role of NLR, PLR, LMR and MWR in LC.

To sum up, NLR, PLR, LMR and MWR can be used as diagnostic and prognostic markers in LC even in early stages. Moreover, the combination of NLR, PLR, LMR and MWR has a superior diagnostic performance.

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Disclosure of conflict of interest

None.

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