Research Square

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Prognostic role of an inflammation scoring system in radical resection of oral squamous cell carcinoma

Meng Wu
Huaian First People's Hospital
Pu Ye
Huaian First People's Hospital
Wei Zhang
Huaian First People's Hospital
Hong Zhu
Huaian First People's Hospital
Huiming Yu (yhm2277544083@163.com)
Huaian First People's Hospital

Research Article

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Abstract

Background

Inflammatory markers can influence postoperative prognosis and outcome of malignant tumors. However, prognostic factors for surgical treatment of oral squamous cell carcinoma (OSCC) are still debatable. The primary objective of this investigation has been to detect the preoperative blood fibrinogen and neutrophil-lymphocyte ratio (NLR) in OSCC patients, and to determine the predictive validity of F-NLRs (the combined fibrinogen and NLR score).

Methods

A total of 421 patients with oral cancer after surgery were separated into three classes: F-NLRs of 2, with hyperfibrinogenemia (> 400 mg/dL) and high NLR (> 2.5); F-NLRs of 1, with only one higher index; and F-NLRs of 0, with no higher indices. Univariate and multivariate analyses were used to identify risk factors for demographic and clinical characteristics of patients with three group F-NLRs. Kaplan-Meier survival analysis was used to assess the prognosis.

Results

The preoperative F-NLRs showed relatively better predictive role in oral cancer prognosis than fibrinogen and NLR alone. Multivariate analysis revealed that the F-NLRs has the potential to be an independent predictor for OSCC outcome ($P = 0.030$). Patients with high scores have a relatively poor prognosis relative to those with low scores ($P < 0.01$).

Conclusions

Our findings indicate that the blood F-NLRs may serve as an independent prognostic factor in OSCC patients.

Background

The most common cancer in the oral cavity is oral squamous cell carcinoma (OSCC) [1]. OSCC is a highly metastatic tumor, and even patients in early stages have a high rate of recurrence and metastasis. Surgery, radiation, targeted therapy, and chemotherapy are the predominant treatment options for oral cancer, depending on the kind and severity of the disease [2]. Although there have been steady advancements in treatment, OSCC has a poor prognosis when compared to those other head and neck cancers. The most likely reason is a combination of variables, including tumor depth, local invasion, nodal involvement, and perineural invasion [3]. Regretfully, these parameters are only known after

surgical excision and histological investigation. Accordingly, it is critical to determine whether blood indicators can predict OSCC prognosis during the initial clinical evaluation.

Multiple studies have been conducted for years to correlate blood inflammatory factors to predict survival in patients with OSCC. Cancer cell adhesion is facilitated by systemic inflammation, which is signaled by the increase of circulating neutrophils at the front line of defense [4–6]. Lymphocytes, particularly cytotoxic lymphocytes, on the other hand, influences cancer progression and influence cancer treatment by eliminating tumor cells[7, 8]. These available evidences suggest that increased pretreatment neutrophil and lymphocyte numbers are correlated to a poor cancer outcome [9–11].

Fibrinogen is a protein that promotes inflammation, which is produced in the liver by a result of interleukin-6 and IL-1b activation [12, 13]. Fibrinogen is converted to fibrin by activated thrombin in the coagulation cascade and can regulate the development of malignant tumors [14]. Recent research has confirmed that plasma fibrinogen levels play an oncogenic function in a variety of human cancers [15–18]. Approximately, NLR has become a prognostic indicator for many malignant tumors, and high NLR often shortens the survival of patients [19–21]. The generation of inflammatory cytokines/chemokines by neutrophils facilitate the occurrence and development of tumors by creating a suitable tumor microenvironment [22]. Currently, there are no data on analyzing the combined effect of plasma fibrinogen and NLR in the preoperative environment to assist in OSCC therapy planning.

The objectives of this research are to determine the prognostic significance of F-NLRs (the combined fibrinogen and NLR score) in patients with OSCC. This work will generate fresh insight into the clinical efficacy of a composite score based on F-NLRs as a predictor of OSCC.

Methods

Materials and Methods

A total of 421 individuals were enrolled in this retrospective analysis who had OSCC and were treated with radical resection at the Department of Oral and Maxillofacial Surgery, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, from February 2014 and November 2019. The eligibility criteria included patients who had (1) confirmed pathological diagnosis of OSCC; (2) no history of cancers; (3) no distant metastasis; (4) standard surgical approach: including primary tumor resection and neck dissection; (5) clinical data and follow-up data were collected; (6) no other conditions that cause the blood values to change; and (7) without adjuvant radiotherapy and chemotherapy preoperatively. Patients with missing or partial data were also ruled out of the research. Preoperative medical and blood tests, as well as other necessary examinations, were performed on these patients, which contributed in the proper planning of surgery.

Blood assessment for determination of fibrinogen and NLR

One week before to the start of treatment, blood samples were taken. Neutrophils and lymphocytes were measured using SYSMEX Analyzer CS5100, Japan. Plasma fibrinogen concentrations were detected by SYSMEX analyzer XN-9000, Japan.

Calculation of prognostic scores

The cutoff threshold widely accepted for fibrinogen was 400 g/L[23-25]. Similarly, the threshold of NLR and FLR adopts the previously reported[26-29]. F-NLRs of 2, with hyperfibrinogenemia (>400 mg/dL) and high NLR (>2.5); F-NLRs of 1, with only one higher index; and F-NLRs of 0, with no higher indices.

Follow up

Follow-up is performed monthly for the first 6 months, then every 6 months telephone follow-up or clinical follow-up. There was no mention of any other illness but OSCC as a cause of death. From the time of surgery to death, the duration of disease-free survival (DFS) was recorded.

Statistical analysis

Univariable and multivariable analysis were used to evaluate clinical factors for unplanned reoperation. Categorical data were analyzed by Chi-square test or Fisher's exact test. Continuous data were compared with the Mann–Whitney U test. A multivariate Cox regression analysis and Kaplan–Meier analysis were utilized to assess recurrence-free and overall survival of UR. All data analyses were performed with the SPSS (IBM SPSS 22.0, SPSS Inc). Statistical tests were two sided and considered significant with a *P*-value□0.05.

Results

Demographic data

A total of 421 patients who were eligible to participate were included in this study. The age of treatment ranged from 17 to 96 years, with males averaging 64 years and females averaging 63 years. 227 (53%) of the patients were females, whereas 194 (47%) were males. Tumor size ≤ 4 cm (87.9%) and no lymph node metastases(82.2%)was the most common (Table 1).

ROC Analysis

We identified the survival prediction value of fibrinogen, NLR and F-NLR using ROC curve analysis. Figure 1 shows the ROC curves and AUC results: the curve of fibrinogen (AUC = 0.688, 95%CI = 0.627 - 0.749, and Youden index = 0.46; the curve of NLR (AUC = 0.704, 95%CI = 0.64 - 0.76, and Youden index = 0.33; the curve of F-NLR (AUC = 0.759, 95%CI = 0.700 - 0.818, and Youden index = 0.50). The preoperative F-NLRs showed relatively better predictive role in oral cancer prognosis than fibrinogen and NLR alone (Figure 1).

Fibrinogen and NLR correlation with Clinicopathologic characteristics

Patients were divided into three groups according to F-NLRs (0, n=280; 1, n=125; 2, n=16). The clinicopathological characteristics of patients with three group scores are listed in Table 2. Higher F-NLRs were associated with tumor size (*P*=0.0019), cervical node metastasis (*P*=0.0059) and tumor site (*P*=0.003).

Risk factors for Prognosis of OSCC

10 clinicopathological parameters were included in univariate and multivariate analysis (Table 3). Multivariate analysis showed F-NLRs was an independent prognostic factor for cancer-specific survival (HR for F-NLRs 1 and F-NLRs 2: 4.086 and 3.477; 95% CI: 1.145-14.586 and 1.096-11.035; *P*=0.030 and *P*=0.034, respectively). Patients with a high F-NLRs portend a poor prognosis (Figure 2).

In a stratified analysis based on tumor size and lymph node metastasis, the results showed that the prognostic value of F-NLRs maintained for T1-T2 (*P*=0.0052, Figure 3A), T3-T4 (*P*=0.0105, Figure 3B), N(-) (*P*=0.0355, Figure 3C) and N(+) (*P*=0.0007, Figure 3D).

Discussion

Oral cancer is the world's 11th most prevalent cancer[30]. Diagnosis at the early stage is thus critical for improving patient survival rates. When identified early, the survival probability is roughly 80–90 percent[31]. Therefore, it is critical to assess patients' prognostic variables before surgery. Plasma biomarkers have a great potentiality for predicting tumor recurrence because they can help surgeons make more individualized treatment plans[32]. Furthermore, these markers can be collected through standard blood testing prior to surgery, which is both cost effective and convenient.

Patients with cancer frequently have a better prognosis when there is no inflammation. The detection of circulating cell components is the most common method for measuring the degree of activation of the systemic inflammatory response [33]. For several common peripheral blood-derived inflammation scores, neutrophils play an active role in promoting tumor progression [34]. Conversely, lymphocytes can significantly inhibit the proliferation of tumor [35]. Therefore, the neutrophil-lymphocyte ratio can provide a more reliable tumor prediction effect. Numerous studies have confirmed that NLR is a prognostic factor for a variety of benign and malignant tumors, and as a representative indicator of tumor-associated inflammation, and NLR has been shown to have predictive value for oral cancer[36–39]. Activation of the coagulation cascade has substantial effect in the development of cancer and fibrinogen has been shown to be one of the regulators of systemic inflammation and tumour progression[40, 41]. These studies have laid a solid foundation for the next step to explore the role of inflammatory factors in the prognostic of oral cancer. In this study, patients with advanced tumors tend to have high fibrinogen and NLR levels. In addition, high fibrinogen and high NLR are important indicators for predicting the clinical outcome in this study ($P = 0.027$ and $P = 0.014$). The mechanism of action could be as follows: Fibrinogen may function by forming a protective framework that facilitates tumor migration, invasion, and angiogenesis. Tumor cells then create and release fibrinogen, increasing the inflammatory response throughout the body.

The new scoring system (F-NLRs) is a good predictor for prognosis of a variety of malignancies. Wang et al. proved that F-NLRs can independently predict the prognosis of patients with non-small cell lung cancer [42]. Data from Felice's studies showed the F-NLRs is substantially related to worse survival results in individuals with anal canal cancer[43]. The above research has established that the F-NLRs is a reliable scoring system for assessing malignant tumors. There has been no detailed investigation of the application prospects of the F-NLR scoring system in oral cancer. Therefore, the retrospective study was set out to find the F-NLRs associated with prognosis after radical resection of oral cancer.

For predictive analysis following radical excision of oral cancer, we separated the patients with different F-NLRs into three independent groups. The results suggested the F-NLRs, as predicted, can identify more individuals with a worse prognosis than fibrinogen or NLR alone. This demonstrates that F-NLRs may be more reliable than individual scores. In this study, the number of T3-T4 patients with F-NLRs of 0, 1, 2 was 88 (31.42%), 62 (49.6%) and 7 (43.75%) (Table 2). These data show the F-NLRs is connected to tumor development and aggressiveness. The median survival time was 46 months (scores of 0) and 38 months (scores of 1–2), respectively. Patients with the high F-NLRs had a substantially poorer prognosis than those with low score. In our subgroup analyses, the F-NLRs was good prognosis factor, such as in patients with different tumor sizes and lymph node metastases, the F-NLR scoring system has shown a good prognostic effect.

This study has some limitations. Firstly, a single-center retrospective study may lead to selection bias. Secondly, the short follow-up period was not sufficient to further assess the survival of patients. Consequently, a more comprehensive multicenter prospective study is needed to confirm that the F-NLRs does independently predict prognosis in patients with OSCC.

According to the findings of this study, the F-NLRs has clinical promise as a prognostic diagnosis in patients with OSCC. The F-NLRs might be used as a low-cost biomarker to help guide treatment decisions for patients with OSCC.

Conclusion

This study suggests that the F-NLRs is an independent evaluation system for the survival rate after radical resection of oral cancer. The F-NLRs might be used as a low-cost biomarker to help guide treatment decisions for patients with OSCC.

Abbreviations

OSCC: oral squamous cell carcinoma; F-NLRs: the combined fibrinogen and NLR score; NLR: Neutrophil-to-lymphocyte ratio; AUC: Area under the receiver operating characteristic curve; CI: Confidence interval; ROC: Receiver operating characteristic; DFS: disease-free survival.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

HY conceived the study, carried out the design and coordination, wrote the manuscript, and gave the final approval of the version to be submitted. MW and HZ critically revised the manuscript for important intellectual content. WZ and PY collected the clinical data and drafted the article. All authors read and approved the final manuscript.

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Availability of data and materials

The raw data are confidential and cannot readily be shared. Researchers need to obtain permission from the Institutional Review Board and apply for access to the data from The Ethics Committee of The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University.

Ethics approval and consent to participate

All participants gave written informed consent. This study was conducted according to the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Affiliated Huaian No.1 People's Hospital of Nanjing Medical University

Consent to publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Comparison of clinical characteristics of the enrolled subjects (n = 421).

Variables	Patients (n, %)
Gender	
male	227 (65.8)
female	194 (34.2)
Age	
<60	133 (31.6)
≥60	288 (68.4)
Smoking	
No	318 (89.6)
Yes	37 (10.4)
Alcohol	
No	377 (89.5)
Yes	44 (10.5)
NLR	
≤2.5	378 (89.8)
2.5	43 (10.2)
Fibrinogen (mg/dl)	
≤400	304 (72.2)
400	117 (27.8)
F-NLRs	
0	280 (66.5)
1	125 (29.7)
2	16 (3.8)
MPV (fl)	
10	357 (84.8)
≥10	64 (15.2)
Tumor size	
T1-T2	370 (87.9)
T3-T4	51 (12.1)

Cervical node metastasis	
N0	346 (82.2)
N1	46 (10.9)
N2	29 (6.9)
Cancer subsites	
Oral cavity	365 (86.7)
Oropharynx	13 (3.1)
Larynx	7 (1.7)
Salivary Gland	36 (8.5)

F-NLRs the combined fibrinogen and NLR score, *NLR* Neutrophil-to-lymphocyte ratio

Table 2 The clinicopathological characteristics stratified by the F-NLR score

Characteristics	F-NLRs 0 (n=280)	F-NLRs 1 (n=125)	F-NLRs 2 (n=16)	P-value
Age				0.5126
<60	91	39	3	
≥60	189	86	13	
Gender				0.7137
male	128	60	6	
female	152	65	10	
Smoking				0.3065
No	178	84	13	
Yes	102	41	3	
Alcohol				0.7862
No	166	66	9	
Yes	128	59	7	
MPV (fl)				0.5739
10	204	87	10	
≥10	76	38	6	
Tumor size				**0.0019**
T1-T2	192	63	9	
T3-T4	88	62	7	
Cervical node metastasis				**0.0059**
N0	144	88	8	
N1	96	22	6	
N2	40	15	2	
Cancer subsites				**0.0045**
Oral cavity	201	89	8	
Oropharynx	32	5	2	
Larynx	2	0	1	
Salivary Gland	45	31	5	

F-NLRs the combined fibrinogen and NLR score, *NLR* Neutrophil-to-lymphocyte ratio

Table 3. Univariate and multivariate analyses of prognostic factors in 421 patients with oral cancer

Variable	Univariate survival analysis			Multivariate survival analysis		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	p-value
Gender	0.987	0.633-1.541	0.955			
Smoking	0.927	0.446-1.927	0.838			
Alcohol use	0.950	0.413-2.186	0.904			
Age	2.312	1.297-4.123	**0.005**	2.236	1.241-4.030	**0.007**
Tumor size	2.074	1.257-3.421	**0.004**	1.944	1.172-3.222	**0.010**
Cervical nodal metastasis						
N0	Ref					
N1	4.878	2.873-8.264	**<0.001**	3.654	2.036-6.559	**<0.001**
N2	2.667	1.300-5.464	**0.007**	1.862	0.864-4.012	0.112
NLR	2.257	1.345-3.787	**0.002**	2.400	1.190-4.481	**0.014**
Fibrinogen (mg/dL)	1.829	1.169-2.863	**0.008**	3.561	1.155-10.974	**0.027**
MPV	2.693	1.583-4.582	**<0.001**	2.335	1.353-4.030	**0.002**
F-NLRs						
0						
1	3.796	2.093-6.881	**<0.001**	4.086	1.145-14.586	**0.030**
2	3.033	1.581-5.819	**0.001**	3.477	1.096-11.035	**0.034**

F-NLRs the combined fibrinogen and NLR score, *NLR* Neutrophil-to-lymphocyte ratio

Figures

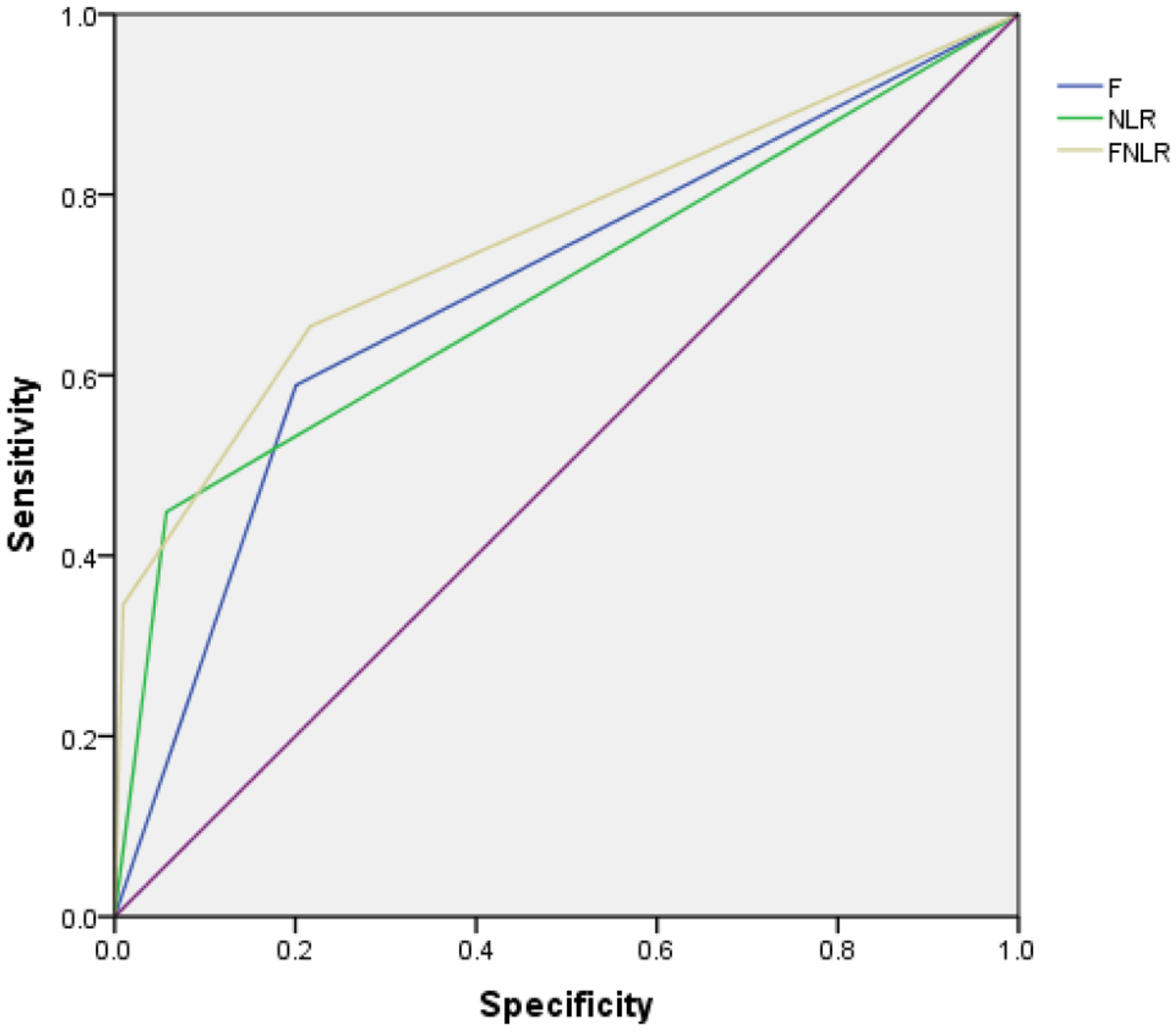

Figure 1

ROC curve for the fibrinogen, NLR and F-NLRs in OSCC patients.

Fibrinogen, NLR, F-NLRs and DFS were used as the test and state variables, respectively. The area under the curve is 0.688, 0.704 and 0.759 respectively.

Abbreviations: ROC, receiver operating characteristic; F-NLRs, the combined fibrinogen and NLR score; NLR, Neutrophil-to-lymphocyte ratio; DFS, disease-free survival; OSCC: oral squamous cell carcinoma.

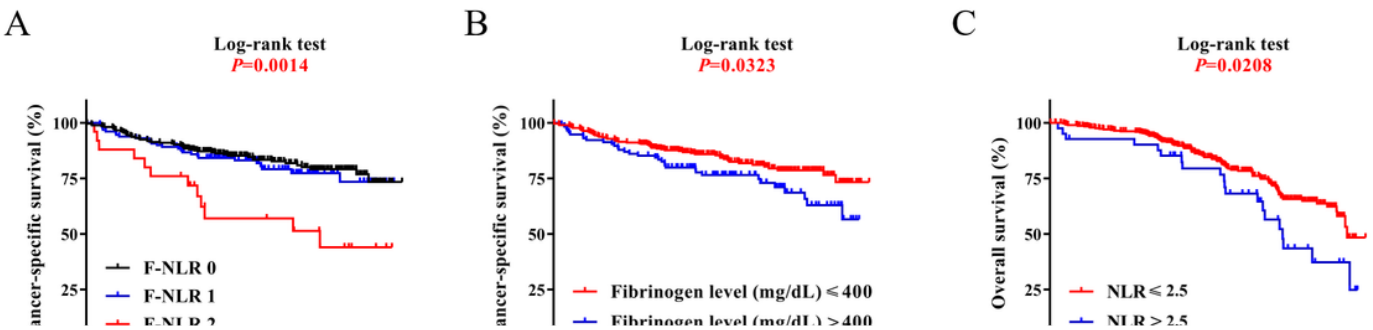

Figure 2

Kaplan-Meier curves for DFS according to the the F-NLRs (A), fibrinogen (B), and NLR (C) in OSCC patients.

Abbreviations: F-NLRs, the combined fibrinogen and NLR score; NLR, Neutrophil-to-lymphocyte ratio; DFS, disease-free survival, OSCC: oral squamous cell carcinoma.

Figure 3

DFS based on the F-NLRs in OSCC patients with T1-T2 (A), patients with T3-T4 (B), patients with lymphatic metastasis (C) and patients without lymphatic metastasis (D).

The DFS was significantly worse in patients with a higher F-NLRs than those with a lower F-NLRs.

Abbreviations: F-NLRs, the combined fibrinogen and NLR score; NLR, Neutrophil-to-lymphocyte ratio; DFS, disease-free survival, OSCC: oral squamous cell carcinoma.