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Posted Date: 4 July 2024

doi: 10.20944/preprints202407.0387.v1

Keywords: dNLR; Oral cancer; Prognosis; TPF; induction chemotherapy



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Article

Derived Neutrophils to Lymphocyte Ratio Predicts Survival Benefit from TPF Induction Chemotherapy in Local Advanced Oral Squamous Cellular Carcinoma

Fangxing Zhu ^{1,†}, Xinyu Zhou ^{1,†}, Yiyi Zhang ^{1,†}, Zhihang Zhou ¹, Yingying Huang ¹,
Zhong Laiping ^{2,3,*}, Tongchao Zhao ^{2,3,*} and Wenjun Yang ^{1,*}

¹ Department of Oral & Maxillofacial-Head & Neck Oncology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. No. 639, Zhizaoju Road, Shanghai, China; College of Stomatology, Shanghai Jiao Tong University. No. 639, Zhizaoju Road, Shanghai, China; National Center for Stomatology; National Clinical Research Center for Oral Diseases. No. 639, Zhizaoju Road, Shanghai, China; Shanghai Key Laboratory of Stomatology; Shanghai Research Institute of Stomatology. No. 639, Zhizaoju Road, Shanghai, China

² Department of Stomatology, Huashan Hospital, Fudan University, Shanghai 200040, China

³ Huangpu Branch, Shanghai Ninth People's Hospital Shanghai Jiao Tong University School of Medicine, No.58, Pu Yu Dong Road, Shanghai 200011, China

* Correspondence: zhonglaiping9th@163.com (Z.L.); zhaotongchao@Gmail.com (T.Z.); yangwenjun@163.com (W.Y.)

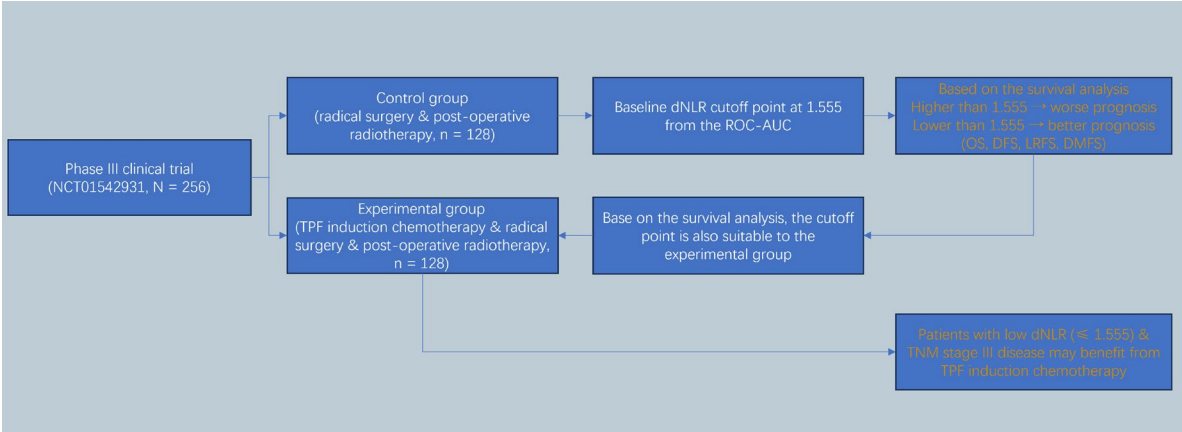
† These authors contributed equally to this work.

Simple Summary: This study aimed at evaluating derived neutrophil to lymphocyte ratio in predicting the prognosis of patients with locally advanced oral squamous cell carcinoma, and the survival benefits from docetaxel, cisplatin, and 5-F induction chemotherapy. derived neutrophil to lymphocyte ratio is an independent negative predictive factor for the disease and patients with a cTNM stage III disease and low derived neutrophil to lymphocyte ratio may benefit from the induction chemotherapy.

Abstract: Background: To evaluate derived neutrophil to lymphocyte ratio (dNLR) in predicting the prognosis of patients with locally advanced oral squamous cell carcinoma (LAOSCC), and the survival benefits from docetaxel, cisplatin, and 5-FU (TPF) induction chemotherapy (IC); Methods: Patients from a phase III trial involving TPF IC in stage III/IVA OSCC patients (NCT01542931) were enrolled. Receiver operating characteristic curves were built and area under the curve was computed to determine dNLR cutoff points. Kaplan-Meier estimates of survival and Cox proportional hazards models were used for longitudinal analysis; (3) Results: 224 patients were identified (median age, 55.4 yr; range, 26 to 75 yr; median follow-up, 90 months; range, 3.2 to 93 months); Cutoff points for dNLR was 1.555. Multivariate analysis showed dNLR was an independent negative predictive factor for survival (overall survival (OS): hazard ratio (HR) = 1.154, 95% confidence interval (CI): 1.018-1.309, P = 0.025, disease-free survival (DFS): HR = 1.123, 95% CI: 0.260-1.000, P = 0.050, local recurrence-free survival (LRFS): HR = 1.134, 95% CI: 1.002-1.283, P = 0.047, distant metastasis-free survival (DMFS): HR = 1.146, 95% CI: 1.010-1.300, P = 0.035). Low dNLR combining cTNM stage III disease predicts benefit from TPF IC for the patients [OS ($\chi^2 = 4.674$, P = 0.031), DFS ($\chi^2 = 7.134$, P = 0.008), LRFS ($\chi^2 = 5.937$, P = 0.015) and DMFS ($\chi^2 = 4.832$, P = 0.028)]; (4) Conclusions: dNLR is an independent negative predictive factor in LAOSCC patients. Patients of cTNM stage III and low dNLR can benefit from TPF IC.

Keywords: dNLR; oral cancer; prognosis; TPF; induction chemotherapy

Graphical Abstract



1. Introduction

Oral squamous cell carcinoma (OSCC) is the most common tumor among oral and maxillofacial region¹. It accounts for the most part of the head and neck cancer and it is the sixth most common malignancy in the world^{2,3}, the annual estimated incidence is around 275,000 for oral cancer in 20022 and developed to 500,550 incident cases in 20184. According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines Version 1.20225, the mainstream management is still radical surgery-based combining with sequential therapy, which brings harm to the patients in sacrificing quality of life for survival due to the expanded excision and neck dissection and the following postoperative radiation. It destroys the functions of oral and maxillofacial region, e.g., eating, drinking, swallowing and speaking, as well as the appearance, and more importantly, it puts threats to the life of patient. For most countries, five-year survival rates for cancers of the tongue, oral cavity and oropharynx are around 50%² and the total number of deaths from cancer of the lip and oral cavity was 177384 (67% of deaths in males) in 20181. Thus, it is urgent to find out the exact and appropriate treatment strategy for the appropriate patients. Although a variety of neoadjuvant therapies with its clinical trials were reported and challenging the traditional standard therapy strategy (radical surgery and postoperative radiation), but yet, no one specific treatment strategy can benefit all the patients. In our last phase III clinical trial, docetaxel, cisplatin, and 5-FU (TPF) were involved as induction chemotherapy in patients with locally advanced oral squamous cell carcinoma (LAOSCC) (registration ID, NCT01542931). However, only a portion of pathologic responders benefited from it⁶ and in other phase III clinical trials, the survival benefit from the additional TPF induction chemotherapy varies from each other⁷⁻⁹. In NCT00095875, the additional TPF induction chemotherapy did not show extra survival benefit in addition to concurrent chemoradiotherapy in locally advanced head and neck cancer⁷. In NCT01245959, addition of TPF induction chemotherapy to concurrent chemoradiotherapy significantly improved failure-free survival in locoregionally advanced nasopharyngeal carcinoma with acceptable toxicity⁸. In NCT01086826, it was shown that adding TPF induction chemotherapy to concomitant treatment significantly improves radiological complete responses, progression-free survival and overall survival without compromising compliance to the concomitant platinum-based chemoradiotherapy in locally advanced head and neck squamous-cell carcinoma⁹. The aforementioned phenomenon gives us a hint about the value of neoadjuvant therapy. For only a small part of patients can benefit from the TPF induction chemotherapy⁶, it implies us about the personalized treatment strategy on how to screen out the specific part of patients. Nowadays, a variety of clinical trials of different treatment strategies were performed because of the personalized medicine which was proposed years ago and an increasing status of biomarkers in personalized medicine to screen out the appropriate patients for appropriate treatment strategy. In our previous studies, growth differentiation factor 15 (GDF15) was found to be a potential predictive biomarker and patients with cN- and high expression GDF15 can benefit from TPF induction chemotherapy in LAOSCC patients¹⁰ and normal body mass index (BMI) was found

to predict the survival benefits from TPF induction chemotherapy with stage IVA cancer in the same cohort¹¹.

Derived neutrophil lymphocyte ratio (dNLR) is an index, easily obtained from the whole blood routine test (blood RT). It is calculated as neutrophils/ (leukocytes minus neutrophils) and reflecting the relative quantity of tumor-immune-related cells in leukocytes, the smaller dNLR, the more tumor-immune-related cells infiltration¹². The prognostic value of dNLR has demonstrated its importance in metastatic non-small cell lung cancer¹³, advanced or metastatic melanoma^{14,15}, metastatic prostate cancer^{16,17}, metastatic renal cell carcinoma¹⁸, advanced or metastatic colorectal cancer^{19,20}, upper tract urothelial carcinoma²¹, etc. While in the field of head and neck squamous cellular carcinoma, there is no clear evidence reported about dNLR being a prognostic biomarker^{22,23}. However, it pointed out that the slightly decreased prognostic value was due to the smaller area under the curve-receiver operating characteristic curves (AUC-ROC) for the prediction of overall survival (OS) presented²². Also, no literature has reported the relationship of survival benefit from dNLR in TPF induction chemotherapy. However, TPF induction chemotherapy did show benefit to patients from the previous trials^{6,8,9}(NCT01542931, NCT01245959, NCT01086826). Thus, it is urgent to find out the exact patient population for TPF induction chemotherapy. Taken together, this study aimed at demonstrating our findings on dNLR in predicting survival benefit from TPF induction chemotherapy for LAOSCC patients.

2. Patients and Methods

Patients

OSCC patients diagnosed as TNM clinical stage III or IVA, treated in Department of Oral & Maxillofacial-Head & Neck Oncology, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, were enrolled in this study. The cohort was enrolled in a prospective, randomized, phase III trial (NCT01542931) in investigating the potential benefit from TPF induction chemotherapy⁶. Patients were allocated into experimental group (TPF induction chemotherapy, surgery and postoperative radiotherapy) or control group (surgery and postoperative radiotherapy) randomly. Clinical data from the control group was used to evaluate the prognostic value of dNLR.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Shanghai Ninth People's Hospital institutional review board. Signed informed consent forms were obtained from all patients.

Baseline Characteristics

All clinical baseline characteristics and data were measured and recorded when patients first referred to our department. The information was then extracted from electronic medical records, independently recorded and checked by the researchers. dNLR was calculated from the baseline blood RT, defined as the absolute neutrophil count / (white cell count – absolute neutrophil count). Positive alcohol use and smoking status were previously defined⁶.

TPF Induction Chemotherapy and Standard Treatment

The treatment strategy was reported previously⁶. In brief, the palpable edges of the primary lesion (both longest and shortest axes) were marked before induction chemotherapy, 0.5 cm away from the lesion. chemotherapy consisted of docetaxel 75 mg/m² intravenously on day 1, followed by cisplatin 75 mg/m² intravenously on day 1, followed by fluorouracil 750 mg/m² per day as a 120-hour continuous intravenous infusion on days 1 through 5. TPF Induction chemotherapy was administered every 3 weeks for two cycles, unless there was disease progression or unacceptable toxicity. For the surgery part, radical resection of the primary lesion and full neck dissection (functional or radical) with appropriate reconstruction (pedicle or free flap) was performed.

Radiotherapy was initiated 4 to 6 weeks after surgery. Standard conformal or intensity-modulated radiotherapy was allowed at a dose of 1.8 to 2 Gy per day, 5 days per week, for 6 weeks (54 to 60 Gy in total). No concurrent chemotherapy with postoperative radiotherapy was applied.

Follow-up Visit and Clinical End-Point Assessment

Patients were followed every three months for the first two years, every six months for the next three to five years, and once a year until death or data censoring. The primary outcome in this study was overall survival (OS), calculated from the day of random assignment to death. The secondary outcomes included disease-free survival (DFS), locoregional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS), which calculated from the day of random assignment to cancer recurrence, locoregional recurrence and distant metastasis, or death resulting from any cause.

Statistical Analysis

Continuous variables are demonstrated as mean $\pm$ SD. For comparing the clinical and histologic data, χ^2 , student or Mann-Whitney U test were used for categorical or continuous variables. ROC curves were built and AUC were computed and the Youden index was used to determine the optimal cutoff points for dNLR. A prognostic multivariate model was built using Cox regression analysis to investigate the hazard ratio (HR). The variables selected into the multivariate model were determined by univariate Cox regression analysis and clinical evaluation. The Kaplan-Meier method and log-rank test were used for survival analysis. Two-sided at a significance level of 0.05 were adopted in all hypothesis-generating tests. Data were analyzed with IBM SPSS Statistics 25 (IBM Corporation, Armonk, NY, USA).

3. Results

Patients

There were 256 patients [179 (69.9%) males and 77 (30.1%) females, average age at 55.4 years, range 26 to 75 years, and 168 (66.4%) patients were older than 60] enrolled in the previous trial and there were 224 patients finally completed the treatment, 29 patients did not complete the treatment and 3 patients declined any treatment. Patients who completed the treatment were allocated into experimental group (TPF induction chemotherapy, surgery and postoperative radiotherapy [109 patients]) and the control group (surgery and postoperative radiotherapy [115 patients, including 2 patients who declined TPF induction chemotherapy]). The median follow-up time was 80 months (range, 3.2-93 months).

In terms of dNLR, in the control group, the mean value was 1.89 ± 1.45 and for its counterpart in the TPF chemotherapy induction group, the mean value was 1.81 ± 1.59 . No statistical significance ($U=7411$, $p=0.187$) was found between the two groups in baseline dNLR. The most common primary site of the tumor was tongue (113 [44.1%]), followed by buccal mucosa (45 [17.6%]), gingiva (39 [15.6%]), floor of oral cavity (30 [11.7%]), palate (18 [7.0%]) and the retro-molar trigone (10 [3.9%]). The clinical TNM stages were distributed as follows: III (177 [69.1%]) and IVA (79 [30.9%]). Detailed clinical characteristics and treatments could be seen in the table (Table 1).

Table 1. Demographic and clinical data of the OSCC patients.

		total		Control group						TPF chemotherapy induction					
				dNLR≤1.555		dNLR>1.555		t/χ²/Fisher		dNLR≤1.555		dNLR>1.555		t/χ²/Fisher	
		N	%	N	%	N	%	exact test	p	N	%	N	%	exact test	p
Gender	Age(years)														
	Average	55.4		54.8		56.1				56		56.2			
	Range	26, 75		26, 75		29, 74				32, 73		29, 74			
	<60	168	66	45	73	40	61	2.055	0.152	49	67	34	62	0.387	0.534
	≥60	88	34	17	27	26	39			24	33	21	38		
	Female	77	30	20	32	20	30	0.057	0.812	21	29	16	29	0.002	0.968
	Male	179	70	42	68	46	70			52	71	39	71		
	Smoking status														
	Negative	126	49	39	63	32	48	2.691	0.101	36	49	23	42	0.710	0.400
	Positive	130	51	23	37	34	52			37	51	32	58		
	Alcohol Status														
	Negative	98	38	42	68	40	61	0.707	0.400	45	62	31	56	0.363	0.547
	Positive	158	62	20	32	26	39			28	38	24	44		
	Tumor site														
	Tongue	113	44	31	50	29	44	2.568	0.766	34	47	19	35	4.352	0.500
Buccal	45	18	9	15	11	17			13	18	12	22			
Gingiva	40	16	9	15	10	15			12	16	9	16			
Floor of mouth	30	12	6	10	12	18			6	8	6	11			
Palate	18	7	3	5	3	5			5	7	7	13			
Retromolar triangle	10	4	4	6	1	2			3	4	2	4			
BMI															
Underweight	20	8	5	8	6	9	1.137	0.258	5	7	4	8	0.501	0.617	
Normal	132	52	34	55	39	59			35	49	24	45			
Overweight	72	28	16	26	17	26			24	33	15	28			

cT stage	Obese	29	11	7	11	4	6			8	11	10	19		
	T1	9	4	0	0	2	3	1.637	0.749	4	5	3	5	0.911	0.937
	T2	57	22	12	19	13	20			20	27	12	22		
	T3	149	58	40	65	40	61			38	52	31	56		
	T4	41	16	10	16	11	17			11	15	9	16		
cN stage															
	N0	110	43	31	50	30	45	3.516	0.172	29	40	20	36	0.397	0.820
	N1	94	37	23	37	19	29			30	41	22	40		
	N2	52	20	8	13	17	26			14	19	13	24		
TNM clinical stage															
	III	177	69	50	81	43	65	3.863	0.049	49	67	35	64	0.169	0.681
	IVa	79	31	12	19	23	35			24	33	20	36		

OSCC: oral squamous cell carcinoma; TPF: docetaxel, cisplatin, and 5-FU; dNLR: derived neutrophil to lymphocyte ratio; BMI: **body mass index**.

dNLR Predicts Survival Outcomes in LAOSCC Patients Treated by Surgery and Postoperative Radiation

According to the baseline blood RT, the continuous variable dNLR, with an average value of 1.89, ranged from 0.20 to 10.75 and its cutoff points at 1.555 could predict OS, calculated on the basis of receiver operating characteristic curves (ROC curves) ($P < .001$, and area under the curve (AUC) = 0.681, Figure 1). The same cutoff points were confirmed in DFS, LRFS and DMFS. Subsequently, the two groups of patients (control group, experimental group) were allocated into the high dNLR group (dNLR > 1.555) and low dNLR group (≤ 1.555), respectively. In the control group, 66 patients were allocated into the high dNLR group and 62 into the low dNLR (≤ 1.555 , $n = 62$) group. In the experimental group, 73 patients were allocated into the high dNLR group and 55 into the low dNLR group. It was found that in the control group, there is a statistical correlation in clinical stage and dNLR, in which stage IVA disease is concomitant of high dNLR instead of low ($\chi^2 = 3.863$, $P = 0.049$, Table 1).

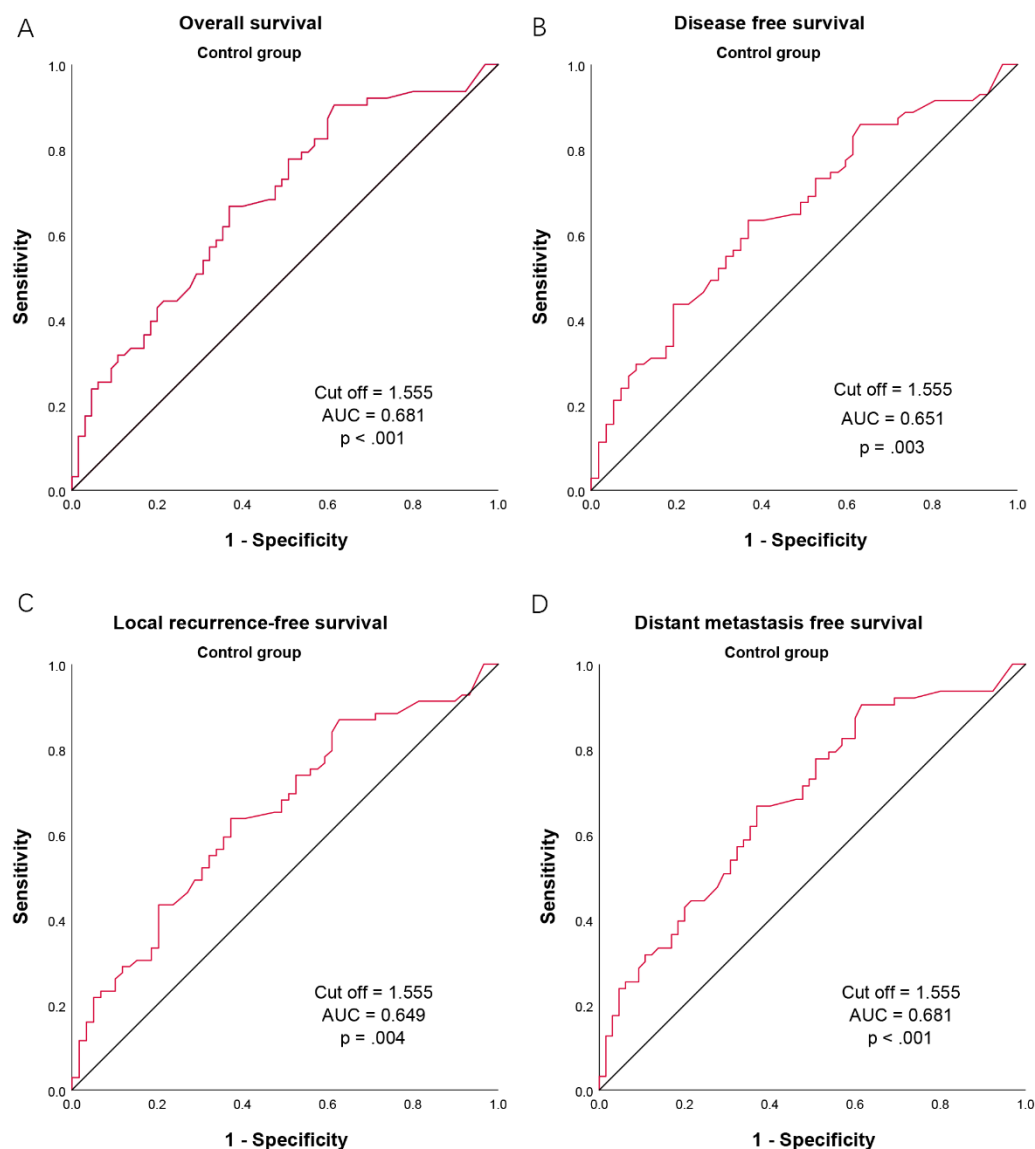


Figure 1. Receiver operating characteristic curve for (A) overall survival (B) disease-free survival (C) locoregional recurrence-free survival (D) and distant metastasis-free survival. AUC, area under the curve.

To further verify whether the cutoff points of $dNLR \leq 1.555$ was effective in predicting a good prognosis in control group, survival analysis between the patients with high dNLR and low dNLR were performed and the Kaplan Meier analysis showed patients with low dNLR had longer OS, DFS, LRFS, and DMFS than patients with high dNLR, with statistically significance. According to the log-rank test, a longer OS ($\chi^2=12.791$, $p<.001$), DFS ($\chi^2=12.067$, $p=.001$), LRFS ($\chi^2=11.598$, $p=.001$) and DMFS ($\chi^2=12.394$, $p<.001$) were seen in patients with low dNLR than its counterpart, high dNLR, in control group (Figure 2). In control group, patients with high dNLR have lower 5-year survival rate. Their OS, DFS, LRFS and DMFS were 40.4%, 34.4%, 35.9% and 40.4%, while it is 69.4%, 59.7%, 62.9% and 67.7% in patients with low dNLR (Table 2).

Table 2. 5-year survival outcomes of the patients with different treatments and different baseline dNLR level.

	Standard treatment group (N = 115)		TPF induction chemotherapy group (N = 109)	
	Low dNLR (n = 56)	High dNLR (n = 59)	Low dNLR (n = 63)	High dNLR (n = 46)
Overall survival	69.4%	40.4%	77.4%	35.7%
Disease-free survival	57.8%	30.4%	74.0%	28.1%
Locoregional recurrence-free survival	62.9%	35.9%	74.0%	32.1%
Distant metastasis-free survival	67.7%	40.4%	80.8%	35.7%

TPF: docetaxel, cisplatin, and 5-FU; dNLR: derived neutrophil to lymphocyte ratio.

Then, univariate Cox model analyses was used in the control group. BMI at diagnosis, cTNM (vs. stage III) and dNLR were found to have a significant correlation with OS, DFS, LRFS and DMFS (Table 3). The underweight group had worse survival outcomes (vs. normoweight group, OS: HR = 2.145, 95% confidence interval [CI]: 1.065-4.321, $P = 0.033$; LRFS: HR = 2.106, 95% CI: 1.053-4.210, $P = 0.035$; DMFS: HR = 2.067, 95% CI: 1.027-4.162, $P = 0.042$). The overweight and obese group had better clinical survival outcomes than the normoweight group but it did not show any statistical significance. Also, cTNM stage showed a statistical significance with the survival outcomes (stage IVA vs. III, OS: HR = 1.993, 95% CI: 1.184-3.354, $P = 0.009$, DFS: HR = 1.792, 95% CI: 1.088-2.952, $P = 0.022$, LRFS: HR = 1.939, 95% CI: 1.173-3.207, $P = 0.010$, DMFS: HR = 1.603, 95% CI: 1.127-3.190, $P = 0.016$). In terms of dNLR, statistically significances were found in survival outcomes (OS: HR = 1.227, 95% CI: 1.099-1.369, $P < 0.001$, DFS: HR = 1.186, 95% CI: 1.063-1.324, $P = 0.002$, LRFS: HR = 1.200, 95% CI: 1.073-1.341, $P = 0.001$ and DMFS: HR = 1.218, 95% CI: 1.091-1.361, $P < 0.001$).

To investigate the applicability of the aforementioned prognostic factors, the multivariate analysis was adjusted for potentially confounding clinical variables. cTNM (stage IVA vs. III, OS: HR = 2.026, 95% CI: 1.196-3.434, $P = 0.009$, DFS: HR = 1.765, 95% CI: 1.068-2.916, $P = 0.027$, LRFS: HR = 1.917, 95% CI: 1.155-3.184, $P = 0.012$, DMFS: HR = 1.910, 95% CI: 1.128-3.235, $P = 0.016$) and dNLR (OS: HR = 1.154, 95% CI: 1.018-1.309, $P = 0.025$, DFS: HR = 1.123, 95% CI: 0.260-1.000, $P = 0.050$, LRFS: HR = 1.134, 95% CI: 1.002-1.283, $P = 0.047$, DMFS: HR = 1.146, 95% CI: 1.010-1.300, $P = 0.035$) were found to be the two independent predictive factors in the control group (Table 4).

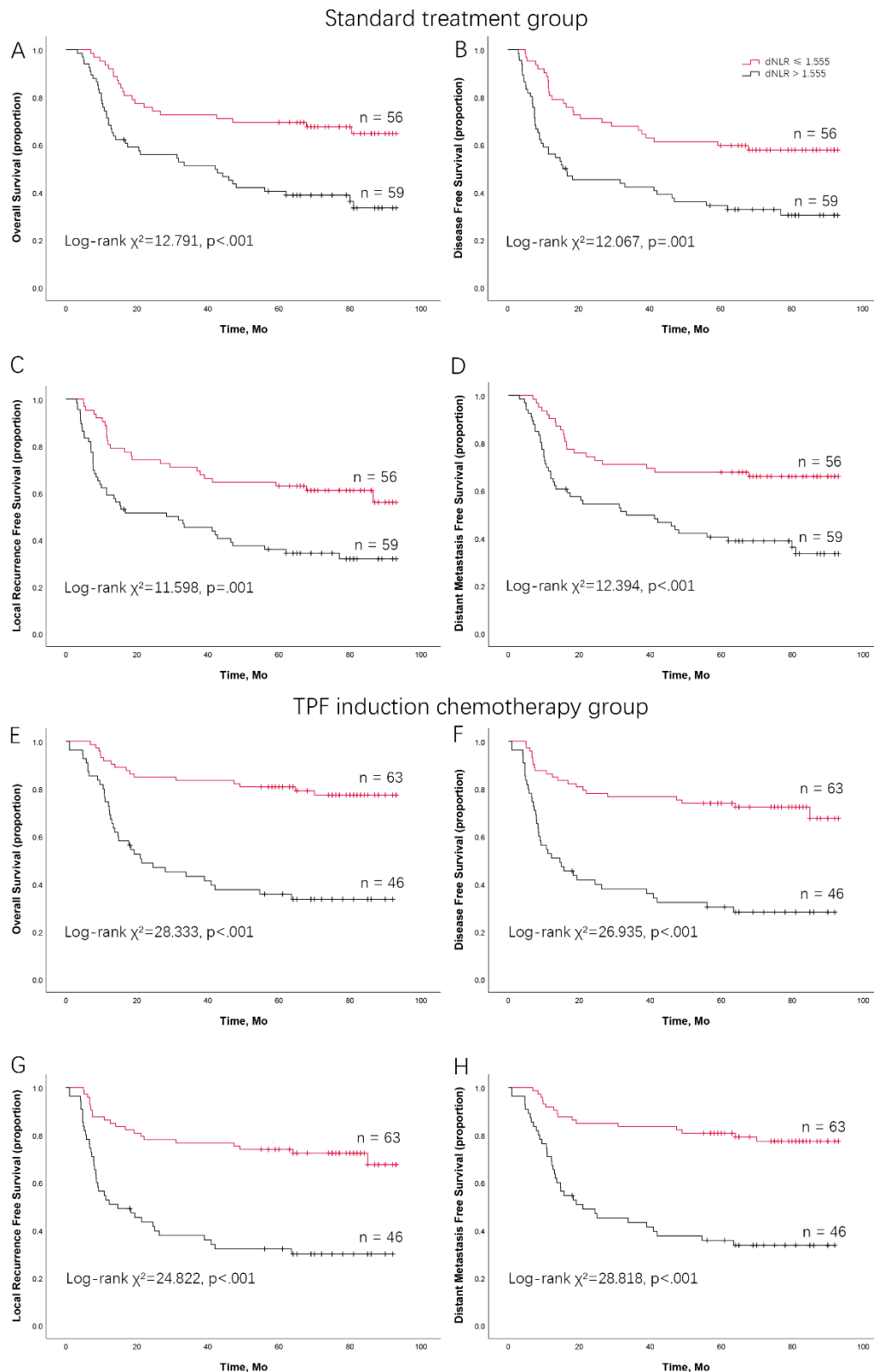


Figure 2. Survival analysis between patients with low derived neutrophils to lymphocyte ratio and high derived neutrophils to lymphocyte ratio in standard treatment group and TPF induction chemotherapy group, respectively. (A) overall survival (B) disease-free survival (C) locoregional recurrence-free survival (D) and distant metastasis-free survival (E) overall survival (F) disease-free survival (G) locoregional recurrence-free survival (H) and distant metastasis-free survival. dNLR, derived neutrophils to lymphocyte ratio. TPF, docetaxel, cisplatin, and 5-FU;.

Table 3. Univariate analysis of clinical prognostic factors for clinical outcomes in the control group.

Variable	OS			DFS			LRF			DMFS		
	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p
Sex (vs. Female)	0.96	0.568-1.642	0.89	0.73	0.452-1.199	0.21	0.74	0.453-1.222	0.24	0.985	0.580-1.676	0.95
Age (vs. <60 years)	1.19	0.716-2.009	0.49	1.06	0.654-1.738	0.79	1.07	0.654-1.768	0.77	1.166	0.697-1.952	0.55
Smoking status (vs. non-smoker)	1.21	0.743-2.000	0.43	1.02	0.639-1.630	0.93	1.01	0.630-1.630	0.95	1.225	0.747-2.009	0.42
Alcohol status (vs. non-alcohol abuser.)	1.38	0.807-2.376	0.23	1.44	0.867-2.394	0.15	1.33	0.799-2.245	0.28	1.432	0.834-2.456	0.19
BMI at diagnosis			0.00			0.00			0.00			0.00
Normal	Ref.		5	Ref.		9	Ref.		7	Ref.		8
Underweight	2.14	1.065-4.321	0.03	1.91	0.961-3.814	0.06	2.10	1.053-4.210	0.03	2.067	1.027-4.162	0.04
Overweight	0.52	0.270-1.029	0.06	0.58	0.319-1.062	0.07	0.11	0.334-1.122	0.61	0.538	0.276-1.051	0.07
Obese	0.39	0.123-1.287	0.12	0.33	0.103-1.069	0.06	0.34	0.107-1.114	0.07	0.399	0.123-1.292	0.12
cTNM (vs. III)	1.99	1.184-3.354	0.00	1.79	1.088-2.952	0.02	1.93	1.173-3.207	0.01	1.603	1.127-3.190	0.01
dNLR	1.22	1.099-1.369	<0.0	1.18	1.063-1.324	0.00	1.20	1.073-1.341	0.00	1.218	1.091-1.361	<0.0

OS: overall survival; DFS: disease-free survival; LRFs: locoregional recurrence-free survival; DMFS: distant metastasis-free survival; HR: hazard ratio; BMI: body mass index; dNLR: derived neutrophil to lymphocyte ratio.

Table 4. Multivariate analysis of clinical prognostic factors for clinical outcomes in the control group.

Variable	OS			DFS			LRF			DMF		
	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p
Alcohol status (vs. non-alcohol abuser)	1.28	0.761-2.181	0.34	1.25	0.771-2.048	0.35	1.18	0.722-1.944	0.50	1.305	0.770-2.212	0.32
BMI at diagnosis			0.06			0.06			0.06			0.08
Normal	Ref.		7	Ref.		3	Ref.		2	Ref.		3
Underweight	1.55	0.708-3.425	0.27	1.49	0.700-3.191	0.29	1.66	0.777-3.554	0.19	1.515	0.689-3.335	0.30
Overweight	0.51	0.995-1.268	0.06	0.57	0.313-1.050	0.07	0.60	0.329-1.111	0.10	0.523	0.267-1.024	0.05
Obese	0.47	0.146-1.557	0.22	0.38	0.118-1.250	0.11	0.40	0.123-1.301	0.12	0.475	0.146-1.552	0.21
cTNM (vs. III)	2.02	1.196-3.434	0.00	1.76	1.068-2.916	0.02	1.91	1.155-3.184	0.01	1.910	1.128-3.235	0.01
dNLR	1.15	1.018-1.309	0.02	1.12	0.260-1.000	0.05	1.13	1.002-1.283	0.04	1.146	1.010-1.300	0.03

OS: overall survival; DFS: disease-free survival; LRFs: locoregional recurrence-free survival; DMFS: distant metastasis-free survival; HR: hazard ratio; BMI: body mass index; dNLR: derived neutrophil to lymphocyte ratio.

dNLR Predicts Survival Outcomes in LAOSCC Patients Treated by TPF Induction Chemotherapy, Surgery and Postoperative Radiation

In experimental group, patients also were further allocated into two subgroups according to their baseline dNLR and the cutoff points from the control group (1.555). The five-year OS, DFS, LRFS and DMFS were 35.7%, 30.3%, 32.1% and 35.7% in patient with high dNLR and in the counterpart, the low dNLR group, it is 80.8%, 74.0%, 74.0% and 80.8% (Table 2). According to the log-rank test, patients in low dNLR group have a longer OS ($\chi^2=28.333$, $p<.001$), DFS ($\chi^2=26.935$, $p<.001$), LRFS ($\chi^2=24.822$, $p<.001$) and DMFS ($\chi^2=28.818$, $p<.001$).

Then, univariate Cox model analyses was used, cTNM stage (stage IVA vs. III, DFS: HR = 1.926, 95% CI: 1.154-3.215, P = 0.012, LRFS: HR = 1.991, 95% CI: 1.188-3.337, P = 0.009) and dNLR (OS: HR = 1.154, 95% CI: 1.035-1.285, P = 0.010, DFS: HR = 1.141, 95% CI: 1.029-1.266, P = 0.013, LRFS: HR = 1.139, 95% CI: 1.024-1.268, P = 0.016, HR = 1.152, 95% CI: 1.034-1.282, P = 0.010) were found to have statistical significant correlations with the survival outcomes (Table 5).

Table 5. Univariate analysis of clinical prognostic factors for clinical outcomes in the TPF induction chemotherapy group.

Variable	OS			DFS			LRFS			DMFS		
	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p
Sex (vs. Female)	1.21	0.657-2.237	0.53	1.21	0.687-2.160	0.49	1.18	0.670-2.111	0.55	1.207	0.654-2.228	0.54
Age (vs. <60 years)	1.19	0.682-2.087	0.53	1.18	0.704-1.996	0.52	1.21	0.719-2.047	0.47	1.183	0.676-2.068	0.55
Smoking status (vs. non-smoker)	1.36	0.785-2.378	0.27	1.26	0.757-2.116	0.36	1.22	0.728-2.048	0.44	1.374	0.789-2.393	0.26
Alcohol status (vs. non-alcohol abuser)	1.14	0.661-1.978	0.63	1.17	0.706-1.955	0.53	1.12	0.672-1.880	0.65	1.135	0.656-1.963	0.65
BMI at diagnosis			0.55			0.50			0.51			0.56
Normal	Ref.			Ref.			Ref.			Ref.		
Underweight	1.54	0.593-4.051	0.37	1.25	0.488-3.236	0.63	1.31	0.509-3.393	0.57	1.564	0.598-4.088	0.36
Overweight	0.74	0.380-1.453	0.38	0.65	0.351-1.240	0.19	0.67	0.358-1.276	0.22	0.757	0.387-1.480	0.41
Obese	1.06	0.480-2.361	0.87	1.01	0.485-2.140	0.96	1.05	0.500-2.220	0.89	1.065	0.480-2.362	0.87
cTNM (vs. III)	1.58	0.915-2.755	0.10	1.92	1.154-3.215	0.01	1.99	1.188-3.337	0.00	1.603	0.924-2.782	0.09
dNLR	1.15	1.035-1.285	0.01	1.14	1.029-1.266	0.01	1.13	1.024-1.268	0.01	1.152	1.034-1.282	0.01

TPF: docetaxel, cisplatin, and 5-FU; OS: overall survival; DFS: disease-free survival; LRFS: locoregional recurrence-free survival; DMFS: distant metastasis-free survival; HR: hazard ratio; BMI: body mass index; dNLR: derived neutrophil to lymphocyte ratio.

cTNM stage and dNLR were further verified in the multivariate Cox model analysis. It was found that cTNM stage had an independent predictive ability for part of the survival outcomes included in the study (DFS: HR = 1.857, 95% CI: 1.107-3.112, P = 0.019, LRFS: HR = 1.931, 95% CI: 1.148-3.248, P = 0.013) and dNLR had an independent predictive ability for the survival outcomes (OS: HR = 1.147, 95% CI: 1.031-1.276, P = 0.011, DFS: HR = 1.128, 95% CI: 1.019-1.250, P = 0.021, LRFS: HR = 1.125, 95% CI: 1.014-1.249, P = 0.027, DMFS: HR = 1.145, 95% CI: 1.030-1.272, P = 0.012, Table 6).

Table 6. Multivariate analysis of clinical prognostic factors for clinical outcomes in the TPF chemotherapy induction group.

Variable	OS			DFS			LRF			DMF		
	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p	HR	95%CI	p
Alcohol status (vs. non-alcohol abuser)	1.12	0.648, 1.939	0.68	1.15	0.692, 1.927	0.58	1.10	0.656, 1.845	0.71	1.111	0.642, 1.923	0.70
cTNM (vs. III)	1.55	0.896, 2.709	0.11	1.85	1.107, 3.112	0.01	1.93	1.148, 3.248	0.01	1.570	0.903, 2.731	0.11
dNLR	1.14	1.031, 1.276	0.01	1.12	1.019, 1.250	0.02	1.12	1.014, 1.249	0.02	1.145	1.030, 1.272	0.01

TPF: docetaxel, cisplatin, and 5-FU; OS: overall survival; DFS: disease-free survival; LRF: locoregional recurrence-free survival; DMF: distant metastasis-free survival; HR: hazard ratio; BMI: body mass index; dNLR: derived neutrophil to lymphocyte ratio.

Combining cTNM Stage and dNLR Predicting the Benefit from TPF Induction Chemotherapy for LAOSCC Patients

After grouping with the management methods (control group or experimental group), in order to screen out the certain patient population who benefit from TPF induction chemotherapy, combining with the independent predicting factors previously verified, different subgroups were made, based on the cTNM stage and the dNLR level of the patients and the Kaplan-Meier method and log-rank test were used for survival analysis (Figure 3).

When comparing the survival rate of experimental group and control group, as our previous publicated results, no statistical significance was found between the two treatment groups (Supplement **Figure S1**). To our surprise, in patient group of cTNM stage III disease and low dNLR (dNLR ≤ 1.555), according to the log-rank test, patients in the experimental group showed a statistically significant longer OS ($\chi^2 = 4.674$, $P = 0.031$), DFS ($\chi^2 = 7.134$, $P = 0.008$), LRF ($\chi^2 = 5.937$, $P = 0.015$) and DMF ($\chi^2 = 4.832$, $P = 0.028$) than the control group (Figure 3). That is to say patients of cTNM stage III disease and low dNLR level (dNLR ≤ 1.555) can benefit from the TPF induction chemotherapy. In other subgroups that divided by cTNM stage only or dNLR level only, it appeared no statistically significant survival can the patients benefit from TPF induction chemotherapy (Supplement **Figures S2** and **S3**).

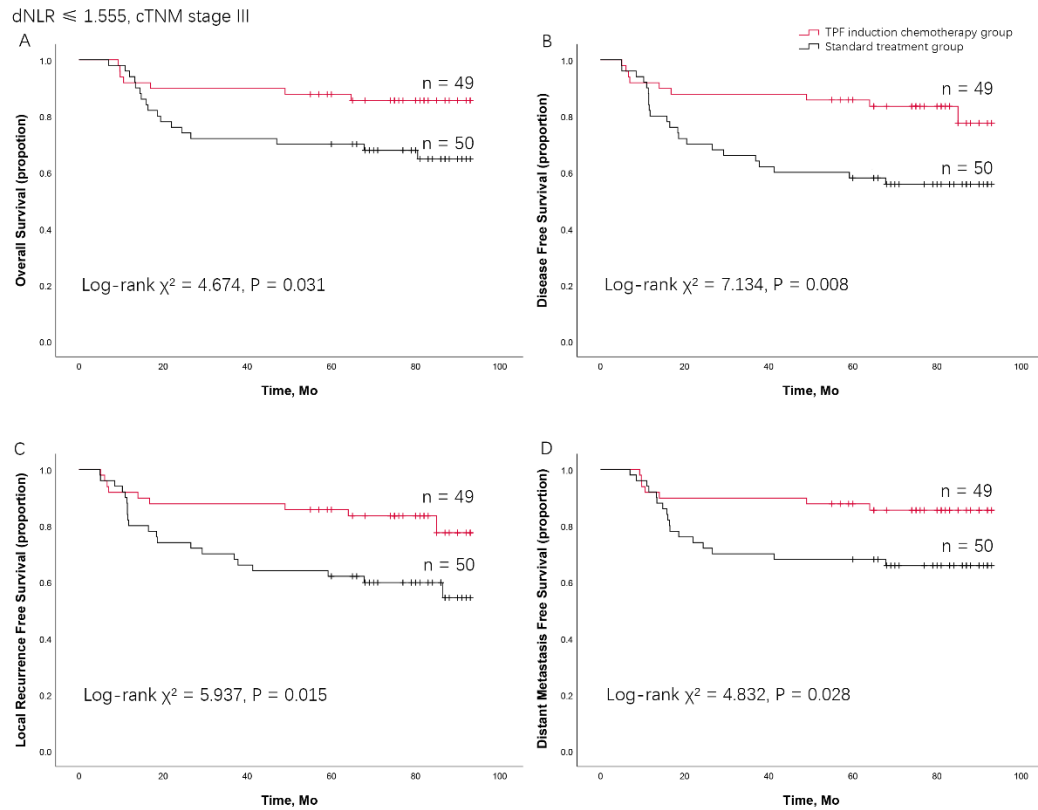


Figure 3. Survival analysis in the patients group of low dNLR combining cTNM stage III disease between TPF induction chemotherapy group and standard treatment group. (A) overall survival (B) disease-free survival (C) locoregional recurrence-free survival (D) and distant metastasis-free survival. dNLR, derived neutrophils to lymphocyte ratio. TPF, docetaxel, cisplatin, and 5-FU;.

4. Discussion

In this study, baseline blood RT, clinical characters and the survival outcomes of the LAOSCC patients were retrospectively studied. In the control group, through the univariate and multivariate Cox model analyses, baseline dNLR (continuous variable) was confirmed as an independent prognostic factor for the survival outcomes (Tables 3 and 4). Through ROC curve and Youden's index (Figure 1), dNLR at 1.555 was confirmed as the cutoff point for all the survival outcomes (OS, DFS, LRFS and DMFS), according to which, patients were further allocated into two subgroups, low dNLR and high dNLR. Patients with a low baseline dNLR had better survival outcomes (Figure 2) and this could equally be applied to patients in the experimental group (Tables 5 and 6). By the meantime, cTNM stage (categorical variable) was confirmed as an independent prognostic factor for survival outcomes. Combining the two variables together, cTNM stage III disease and low dNLR (dNLR $\leq$ 1.555), this patient population can benefit from TPF induction chemotherapy (Figure 3).

In recent years, many immune biomarkers easily acquired from blood RT have been introduced into the field of tumor therapy as prognostic factors, such as neutrophil-to-lymphocyte ratio (NLR)²⁴⁻²⁶, dNLR^{12,13,16,27}, platelet-to-lymphocyte ratio (PLR)²⁸⁻³⁰, and lymphocyte-to-monocyte ratio (LMR)^{18,31}. In OSCC, NLR was reported to be a significant independent disease specific survival (DSS) predictor^{32,33} and significantly correlated with stromal infiltration of CD8⁺, CD4⁺, and CD20⁺ lymphocytes³⁴. dNLR was reported to be correlated with the occurrence of complication³⁵. PLR was reported to be more strongly associated with disease-specific survival (DSS), and progression-free survival (PFS) in patients who were male, had stage III/IV OSCC, or had lymph node metastasis³⁶. NLR and dNLR look identical and have similar effects on cancer-specific mortality³⁷ and a positive correlation between dNLR and NLR was found³⁸. However, from the calculation method of dNLR, it is obvious that it consists of not only lymphocytes but also monocyte and other subtypes of immune-related cells and thus dNLR was chosen in this study.

To our knowledge, it is the first time that dNLR was confirmed as an independent prognostic factor from the multivariate analysis for the survival of OSCC patients, treated with either surgery and postoperative radiation or with TPF induction chemotherapy, surgery and postoperative radiation. And it is the first time to confirm dNLR level and cTNM stage as grouping conditions in screening out the patient population who can benefit from TPF induction chemotherapy (Figure 3). In our previous phase III clinical trial (registration ID, NCT01542931), TPF induction chemotherapy did not improve survival comparing with up-front surgery⁶. But in patients with cN2 disease, who seemed to have improved OS (HR, 0.418; 95% CI, 0.179 to 0.974; $P = .043$) and DMFS (HR, 0.418; 95% CI, 0.179 to 0.974; $P = .043$) when treated with TPF induction chemotherapy than those not⁶. Thus, efforts were made to find out clinical-valuable biomarkers to screen the appropriated OSCC patient population for TPF induction chemotherapy. Lymph node ratio (LNR), the ratio of pathological confirmed positive lymph node and the total surgical number of lymph nodes, was found to have a connection with the prognosis and can be an independent prognostic factor. OSCC patients with high-risk LNR ($> 7.6\%$), or positive extranodal extension (ENE) had significantly worse clinical outcomes than patients with low-risk LNR ($\leq 7.6\%$) or negative ENE³⁹. In another our previous study, BMI was found to be an independent prognostic factor as well. Compared to normoweight patients, overweight and obese patients had better clinical outcomes while underweight status was associated with poor survival¹¹. Furthermore, normoweight patients with cTNM stage IVA disease benefited from TPF induction chemotherapy followed by surgery and postoperative radiation compared with surgery and postoperative radiation only, on OS and DMFS¹¹. In this study, dNLR was found to be an independent prognostic factor of assessing the survival of OSCC patients, even so adjustment was done for other important variables. This is in accordance with many other clinical trials that reported a low dNLR value has a significant relationship with good prognosis or good clinical or pathological responses^{12,13,16,27,37,40,41}.

In the present study, for inflammation biomarkers may be influenced by TPF induction chemotherapy, hematology and the survival data from the control group was adopted to form the ROC and calculate AUC for the dNLR cutoff point. All the four survival rates pointed to a same dNLR cutoff points at 1.555. Meanwhile, it demonstrated that dNLR can be an independent prognostic factor for the survival of OSCC patients from the multivariate analysis. There were some other dNLR cutoff points (no more than 3) reported in other types of tumors. A dNLR cutoff points at 1.775 was found in predicting metastatic disease of testicular germ-cell tumors⁴¹. Another study on breast cancer reported that a baseline dNLR cutoff points smaller than 1.715 in predicting pathological complete response⁴⁰. In immune checkpoint blocker pembrolizumab in non-small cell lung cancer, patients with dNLR cutoff < 2.6 was reported to have a significantly higher objective response rate (ORR), significantly longer median progression-free survival and significantly higher numbers of tumor-associated CD8⁺, FOXP3⁺, PD-1⁺ immune cells, and PD-1⁺CD8⁺T cells¹². In lung immune prognostic index (LIPI), dNLR cutoff points was defined as 3 to determine the prognosis of the non-small cellular carcinoma¹³. There are many reasons leading to the differences between cutoff points, like tumor type, TNM stage, systematic inflammation condition and population and this may point to the more malignancy biology behavior of OSCC than other type of tumors.

It was reported that the lower level of baseline dNLR, the more tumor-associated immune cells¹². In this study, a statistically significant correlation between dNLR and cTNM stage (Table 1) was found in the control group. This could be a mutual effect that cTNM stage IVA disease often is concomitant of high dNLR. Similar results were reported that TNM stage is positively related to dNLR in colorectal cancer, renal cell carcinoma and gastric cancer⁴²⁻⁴⁴. Low dNLR is associated with significantly increased tumor-associated CD8⁺, FOXP3⁺, PD-1⁺ immune cells and favorable outcomes¹².

High baseline dNLR level means more neutrophils relatively. Neutrophils showed diversity or heterogeneity and plasticity in cancer⁴⁵⁻⁴⁷. It was reported neutrophils have different subgroups, leading to different biological process, respectively^{46,48}. In mouse and human lung cancer model, there were seven populations of neutrophils found and CD40 agonist antibody treatment can increase immune response by causing a greater than 10-fold increase in the abundance of both N1a (Sellhi

Ngphi) and N2 (Sellhi Cxcl10hi) neutrophil populations, which characterized by high expression of interferon-stimulated genes (ISGs)⁴⁸. This gives us a hint that individuals with high dNLR level at baseline may have no extra space for neutrophils differentiation into the ISGs high expression subtypes, which cause an unfavorable prognosis. Also, in tumor immune microenvironment, tumors have systemic effects that modulate neutrophil extracellular traps (NETosis), causing NET-associated complications in cancer, like thrombosis. NETosis formation, capturing tumor, promoting its growth, and the subsequent metastasis⁴⁹. In breast cancer, tumor-secreted protease cathepsin C promotes breast-to-lung metastasis by regulating recruitment of neutrophils and formation of neutrophil extracellular traps⁵⁰.

The low level of leukocytes except neutrophils, or low lymphocytes level mainly, also can cause high baseline dNLR level. Lymphocytes is the main killer cells in tumor immune. However, it cannot be ignored that the states of T lymphocytes play a decisive role in tumor immune. The dysfunction of T cells in human cancer is associated with a change in T cell functionality rather than inactivity⁵¹. Although in this study, low dNLR level predicts a better prognosis, it still requires attention to the states of lymphocytes.

Yet there were some limitations in the study. Usually, patients with LAOSCC diagnosed as cTNM stage IVA disease have worse survival outcomes and this could lead to the potential bias. Luckily, this was not seen in TPF induction chemotherapy group. This can be improved by another clinical trial including more samples and further verifying if there is any possible connection between TNM stage and baseline dNLR in LAOSCC. Furthermore, since the retrospective nature of the study, it may include any unnecessary confounding factors and it should be further confirmed by another clinical trial to determine whether the dNLR cutoff points is a suitable boundary for other survival rates or other OSCC patients with different systematic conditions or TNM stages

5. Conclusions

dNLR can be considered as an independent negative prognostic factor for OSCC patients. Patients with baseline dNLR ≤ 1.555 have better prognosis. Patients with stage III disease and dNLR ≤ 1.555 can benefit from TPF induction chemotherapy but further studies are needed to explain the biological association.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: Conceptualization, LP.Z., TC.Z. and WJ.Y.; methodology, FX.Z. and XY.Z.; software, XY.Z.; writing—original draft preparation, FX.Z.; writing—review and editing, YY.Z.; visualization, ZH.Z.; supervision, YY.H.; project administration, TC.Z.; funding acquisition, LP.Z., TC.Z. and WJ.Y.. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Shanghai Sailing Program, grant number 22YF1421700, National Natural Science Foundation of China, grant number: 81972525, 82172734, project of Shanghai Huangpu District Science and Technology Commission, grant number: HLQ202304 and The Biobank Project of Shanghai Ninth People's Hospital, grant number: YBKB202214.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (SH9H-2021-TK558-1).

Informed Consent Statement: Written informed consent has been obtained from the patients to publish this paper.

Acknowledgments: We are extremely grateful to all of our study participants for allowing their (anonymized) data to be published

Conflicts of Interest: The authors declare no conflicts of interest.

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