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Fibrinogen and Neutrophil-to-lymphocyte Ratio Predicts Survival in Patients with Advanced Hypopharyngeal Squamous Cell Carcinoma

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Abstract. *Background/Aim: The purpose of this study is to investigate the prognostic significance of the pretreatment F-NLR score, which is based on fibrinogen (F) and neutrophil-to-lymphocyte ratio (NLR) in patients with advanced hypopharyngeal carcinoma (HPC). Materials and Methods: A total of 111 advanced HPC patients treated with radiotherapy, chemoradiotherapy, or bioradiotherapy were classified into three groups: F-NLR score of 2 (fibrinogen ≥341 mg/dl and NLR≥3.59), score of 1 (fibrinogen ≥341 mg/dl or NLR≥3.59), and score of 0 (fibrinogen <341 mg/dl and NLR<3.59). Results: F-NLR score of 2 was an independent prognostic factor for overall (OS) and progression-free survival (PFS) in patients with advanced HPC in the multivariate analysis. Both OS and PFS were significantly lower in patients with an F-NLR score of 2 than in those with an F-NLR score of 0. Conclusion: F-NLR score was useful to stratify patients to extract poor prognostic characteristics in patients with advanced HPC.*

Hypopharyngeal carcinomas (HPC) consist mostly of squamous cell carcinoma and is known to have the worst prognosis among head and neck cancers (HNC). This is mainly because HPC can be asymptomatic in the early stages, tend to spread submucosally, and frequently have nodal and distant metastases (1). Recently, the treatment of HPC has been changing due to the development of treatment modalities including chemoradiotherapy (CRT) (2-4), cetuximab-based bioradiotherapy (BRT) (5, 6) and function-preserving surgery such as transoral surgery including transoral videolaryngoscopic surgery, endoscopic laryngopharyngeal surgery and transoral robotic surgery (7-10) for the purpose of larynx preservation. However, many patients with advanced HPC still require pharyngectomy with total laryngectomy, resulting in loss of natural voice, and also has a negative physical and psychosocial effect due to permanent tracheostomy. A goal in the management of HPC is thus to achieve compatibility between curing disease and maximizing laryngeal function. Despite such multidisciplinary treatments, the survival rate for patients with advanced HPC remains unsatisfactory because of its high recurrence and metastasis rate (11, 12). Therefore, adequate biomarkers assessing the cancer status that can help decision-making of treatment plan are necessary to make an appropriate treatment choice and improve survival.

In recent years, systemic inflammation has been reported to participate in cancer initiation and progression by promoting cell proliferation, angiogenesis and gene repair (13, 14). In fact, the relationship between inflammatory cells in the peripheral blood and the prognosis has been reported in various malignancies (15-21). Now the prognostic impact of pretreatment inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) have been reported in various malignancies (22-25), including HNC (26-29). The prognostic nutritional index (30) (PNI), originally proposed to examine the perioperative immuno-nutritional status and surgical risk in malnourished patients undergoing gastrointestinal surgery, has also been shown to be a prognostic marker for various malignancies including HPC (31).

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Key Words: Pretreatment biomarker, hypopharyngeal squamous cell carcinoma, neutrophil-to-lymphocyte ratio, F-NLR score, radiotherapy.

Kijima *et al*. (32) showed that the combined score determined by plasma fibrinogen level and the NLR (F-NLR score) is useful as a prognostic biomarker in patients with advanced esophageal squamous cell carcinoma (ESCC). Since ESCC and HPC have close anatomical, histological, and biological relationship, and risk factors in common, we hypothesized if the combination of plasma fibrinogen level and NLR ratio could predict survival in patients with advanced HPC. In the present study, we retrospectively reviewed the institutional records to assess the relationship between pretreatment inflammatory markers including F-NLR score, LMR, PLR, or PNI and prognosis in patients with advanced HPC treated with definitive RT, BRT or CRT.

Patients and Methods

Patients. A retrospective chart review of 154 patients with HPC treated at Yokohama City University Hospital between December 2005 and December 2015 was conducted. Patients were included in this study if they 1) were 20 years or older; 2) had previously untreated HPC; 3) had histologically proven squamous cell carcinoma; 4) had stage III or IV disease based on the 7th edition of the Union for International Cancer Control (UICC) TNM classification; 5) underwent with curative intent concurrent CRT, BRT, or RT. The exclusion criterion for this study was unavailability of pretreatment hematologic parameters. This study was approved by Institutional Review Board of Yokohama City University Hospital (Approval No.; B180100016) and requirement of patient consent was waived due to the retrospective nature of this study.

Treatment. Overall, 108 of 111 patients received BRT or CRT, and 3 patients received RT because of their poor performance status. The anticancer drugs concurrently combined with RT were as follows; 1) docetaxel, cisplatin and 5-fluorouracil (n=45), 2) docetaxel, cisplatin and cetuximab (n=4), 3) cisplatin, 5-fluorouracil, methotrexate and leucovorin (n=12), 4) carboplatin (n=1), 5) carboplatin and tegafur/uracil (n=7), 6) docetaxel (n=8), 7) tegafur/uracil (n=4), 8) tegafur/gimeracil/oteracil (n=17), 9) cetuximab (n=10).

The total dose of concurrent radiation ranged 39.6-70.2 Gy (median 70.2 Gy). All patients received conventional external radiotherapy to the primary site and regional lymphatic area. The treatment was planned using a CT simulator and a 3D dose-calculation computer.

Data collection and grading system for F-NLR score. Blood samples were obtained within 2 weeks before treatment initiation. NLR, LMR, and PLR were calculated by division of the absolute values of the corresponding hematological parameters. PNI was calculated as 10× serum albumin (g/dl) + 0.005 × total lymphocyte count (per mm^3) as described previously (30). A receiver operating characteristic (ROC) curve for progression-free survival (PFS) was plotted, and the cutoff values of NLR, fibrinogen, albumin, LMR, PLR, and PNI were determined using the Youden-index of the ROC curve. F-NLR score was classified into three groups based on each cutoff value of plasma fibrinogen and NLR.

Statistical analysis. Fisher's exact test was used to evaluate differences in the relationship between clinicopathological features and NLR or fibrinogen. The PFS was defined as the time to the first relapse of the disease or death from any reason. Kaplan–Meier analysis was used and compared by the log-rank test to determine any significance of F-NLR score on overall survival (OS) and PFS. Prognostic factors were assessed using univariate and multivariate analyses with Cox proportional hazards regression model. Multivariable analysis included age, sex, and all variables with p-value<0.10 in univariable analysis. p-Value <0.05 was considered to be statistically significant. All statistical analyses were performed with JMP software version 11.2.0 (SAS Institute Inc., Cary, NC, USA) and EZR version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R commander (version 2.1-2) designed to add statistical functions used frequently in biostatistics.

Results

Patient characteristics. Of 114 patients who met the inclusion criteria, 3 patients were later excluded from this study since the value of fibrinogen was not available. Therefore, data from 111 patients were analyzed in this study. Patient characteristics are summarized in Table I. The median age was 67 years (range=47-83 years) and most patients were male (91.9%). The median follow-up period was 38 months (range=2-101 months). Ninety-six patients (86.5%) had smoking history and 95 (85.6%) had drinking history. The primary site of HPC was the pyriform sinus in 76.6%, post cricoid in 4.5%, and posterior wall in 18.9%. The stage of HPC was III in 20.7%, and IV in 79.3%. The T category of HPC was T1 in 10.8%, T2 in 24.3%, T3 in 20.7%, and T4 in 44.1%. The N category of HPC was N0 in 16.2%, N1 in 17.1%, N2 in 60.4%, and N3 in 6.3%. The stage, T category, and N category were based on the 7th edition of the UICC TNM staging system.

Cut-off values for prognostic markers. ROC curves for PFS were plotted to verify the optimal cut-off values for NLR, fibrinogen, LMR, PLR, albumin and PNI as shown in Figure 1A-F. A cut-off point of 3.59 was selected for NLR with an area under the curve (AUC) of 0.584. A cut-off point of 341 mg/dl was selected for fibrinogen with AUC of 0.567. A cut-off point of 3.09 was selected for LMR with AUC of 0.525. A cut-off point of 149.7 was selected for PLR with AUC of 0.547. A cut-off point of 4.0 g/dl was selected for albumin with AUC of 0.558. A cut-off point of 48.5 was selected for PNI with AUC of 0.567.

To examine the correlations between NLR or fibrinogen and the clinicopathological characteristics, the patient characteristics between the high and low NLR and fibrinogen groups were compared in Table I. There were 74 (66.7%) patients with NLR <3.59, 37 (33.3%) patients with NLR ≥3.59, 50 (45.0%) patients with fibrinogen <341, and 61 (55.0%) patients with fibrinogen ≥341. We found that both higher N category and higher stage were significantly

Table I. *Patient characteristics*.

Characteristics		NLR			Fibrinogen		
		<3.59 (n=74)	≥3.59 (n=37)	*p*-Value	<341 (n=50)	≥341 (n=61)	*p*-Value
Median age (range, in years)	67 (47-83)			0.55			0.56
<67 (percentage)	52 (46.8)	33	19		18	34	
≥67 (percentage)	59 (53.2)	41	18		32	27	
Median follow-up term (range, m)	38 (2-101)						
Sex (percentage)				1.00			0.73
Male	102 (91.9)	68	34		45	57	
Female	9 (8.1)	6	3		5	4	
Smoking status (percentage)				0.57			0.95
Absent	15 (13.5)	9	6		10	5	
Present	96 (86.5)	65	31		40	56	
Drinking status (percentage)				1.00			0.18
Absent	16 (14.4)	11	5		10	6	
Present	95 (85.6)	63	32		40	55	
Tumor location (percentage)				0.23			0.77
PS	85 (76.6)	60	25		37	48	
PC	5 (4.5)	3	2		3	2	
PW	21 (18.9)	11	10		10	11	
T category (percentage)				0.57			0.05
T1	12 (10.8)	10	2		9	3	
T2	27 (24.3)	18	9		15	12	
T3	23 (20.7)	16	7		8	15	
T4	49 (44.1)	30	19		18	31	
N category (percentage)				0.18			0.0001
N0	18 (16.2)	13	5		11	7	
N1	19 (17.1)	14	5		15	4	
N2	67 (60.4)	45	22		24	43	
N3	7 (6.3)	2	5		0	7	
Stage (percentage)				0.47			0.0004
III	23 (20.7)	17	6		18	5	
IV	88 (79.3)	57	31		32	56	

NLR: Neutrophil-to-lymphocyte ratio score; *p*-Values <0.05 were considered significant. Smoking status: present is a person who has smoked more than one hundred cigarettes and cigars during the course of his life, and absent is a person who has smoked fewer. Drinking status: Present is a person who has drunk more than 1 unit/day, and absent is a person who has drunk fewer.

associated with higher plasma fibrinogen ($p<0.001$). There were no significant associations between fibrinogen and any other parameters examined. F-NLR score was classified into three groups based on each cut-off value of plasma fibrinogen and NLR as follows; F-NLR score of 2: both hyperfibrinogenemia (≥341 mg/dl) and high NLR (≥3.59), F-NLR score of 1: either hyperfibrinogenemia or high NLR, and F-NLR score of 0: neither hyperfibrinogenemia nor high NLR.

Prognostic impact of F-NLR score. Univariate and multivariate analyses of pretreatment prognostic markers for OS and PFS were performed as shown in Tables II, III and IV. Univariate analysis revealed that patients with an F-NLR score of 2 had a significantly lower OS and PFS ($p=0.014$, and $p=0.0012$, respectively) as did those with NLR≥3.59 ($p=0.018$, and $p=0.005$, respectively). Patients with stage IV and fibrinogen≥341 mg/dl also showed a significantly lower PFS ($p=0.043$ and $p=0.037$, respectively). In the present cohort, other parameters such as age, sex, smoking or drinking status, stage, PLR, LMR, serum albumin and PNI were not significantly correlated with PFS or OS.

As F-NLR score had significant correlation with NLR and fibrinogen value, we performed two sets of Cox multivariate analyses; one including age, sex, stage, albumin, and F-NLR score, and the other including age, sex, stage, albumin, fibrinogen and NLR.

As shown in Table III, the results indicated that F-NLR score of 2 was an independent prognostic factor for OS (HR=3.39, 95%CI=1.47-8.14, $p=0.043$) and PFS (HR=3.06, 95%CI=1.31-7.48, $p=0.0099$) in the multivariate analysis with age, sex, stage, albumin, and F-NLR score. In addition,

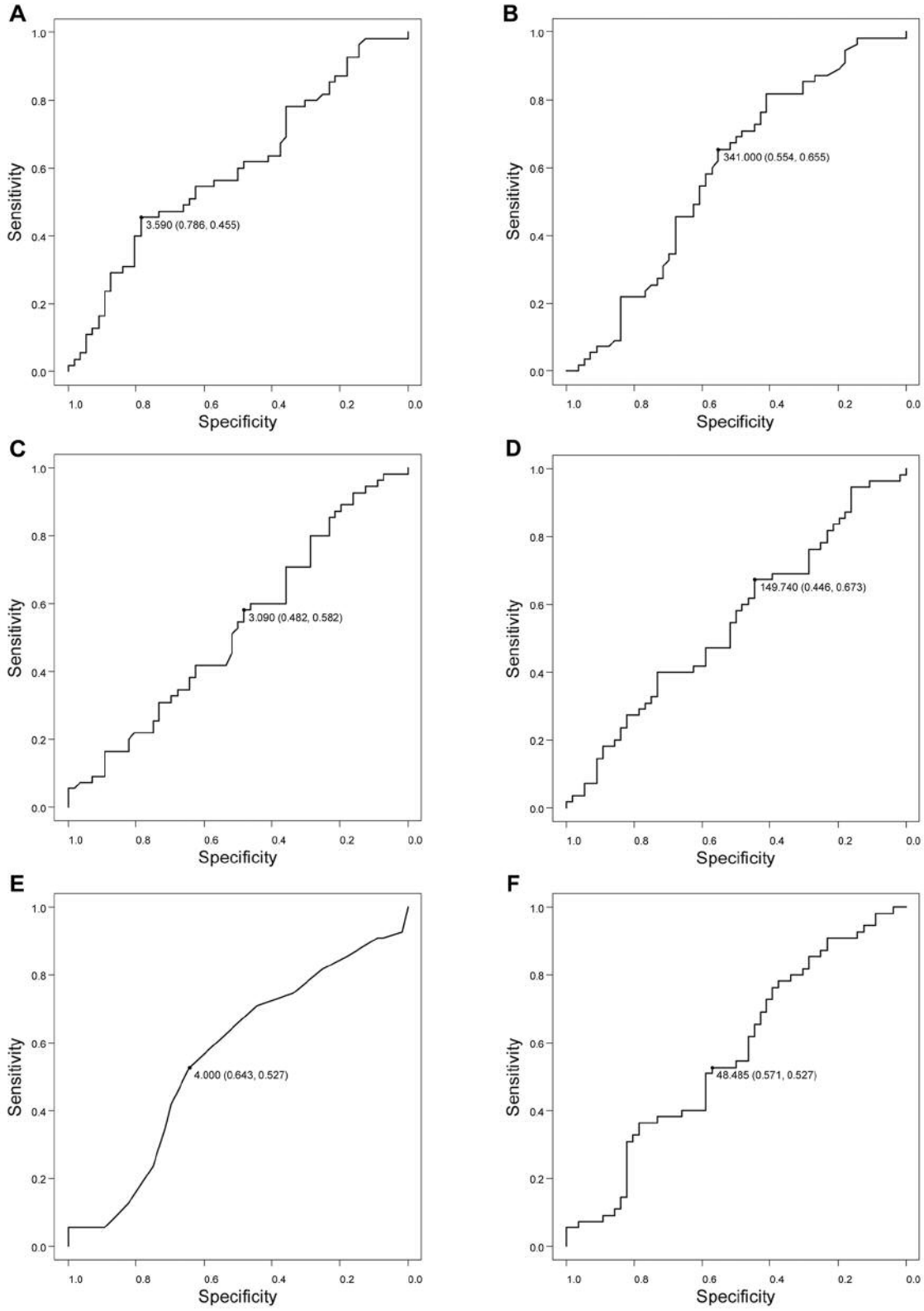

Figure 1. *Receiver operating characteristics curves for progression-free survival (PFS). ROC curves for PFS were plotted to verify the optimal cut-off values for NLR, fibrinogen, LMR, PLR, albumin and PNI. The area under the curve for NLR, fibrinogen, LMR, PLR, albumin and PNI was 0.584 (A), 0.567 (B), 0.525(C), 0.547 (D), 0.558 (E) and 0.567 (F), respectively.*

Table II. *Univariate analysis for overall and progression-free survival in patients with advanced hypopharyngeal carcinoma.*

		OS			PFS		
Variables	Cases(n)	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age							
<67	52	1.00	Reference		1.00	Reference	
≥67	59	0.81	0.39-1.64	0.55	0.80	0.45-1.45	0.46
Gender							
Female	9	1.00	Reference		1.00	Reference	
Male	102	0.89	0.31-3.72	0.85	0.77	0.33-2.23	0.59
Smoking status							
Absent	15	1.00	Reference		1.00	Reference	
Present	96	1.68	0.59-7.03	0.36	1.12	0.51-2.94	0.80
Drinking status							
Absent	16	1.00	Reference		1.00	Reference	
Present	95	1.75	0.62-7.31	0.32	1.49	0.64-4.31	0.38
Tumor location							
PS	85	1.00	Reference		1.00	Reference	
PC	5	0.44	0.13-2.78	0.32	0.42	0.15-1.76	0.20
PW	21	1.15	0.31-7.41	0.85	1.08	0.25-3.25	0.90
Stage							
III	23	1.00	Reference		1.00	Reference	
IV	88	1.79	0.75-5.30	0.21	2.25	1.02-5.92	0.043
Fibrinogen							
<341	50	1.00	Reference		1.00	Reference	
≥341	61	1.69	0.83-3.59	0.15	1.89	1.04-3.57	0.037
NLR							
<3.59	74	1.00	Reference		1.00	Reference	
≥3.59	37	2.39	1.17-4.86	0.018	2.37	1.30-4.26	0.005
F-NLR sore							
0	38	1.00	Reference		1.00	Reference	
1	48	1.95	0.81-5.16	0.14	1.87	0.90-4.17	0.097
2	25	3.37	1.29-9.29	0.014	3.72	1.69-8.59	0.0012
PLR							
<149.7	43	1.00	Reference		1.00	Reference	
≥149.7	68	1.40	0.68-3.02	0.37	1.53	0.84-2.92	0.17
LMR							
<3.09	60	1.00	Reference		1.00	Reference	
≥3.09	51	0.79	0.38-1.60	0.51	0.69	0.38-1.24	0.22
Albumin							
<4.0	40	1.00	Reference		1.00	Reference	
≥4.0	71	0.51	0.25-1.06	0.070	0.55	0.31-1.01	0.054
PNI							
<48.5	52	1.00	Reference		1.00	Reference	
≥48.5	59	0.77	0.38-1.57	0.46	0.75	0.42-1.35	0.34

PFS: Progression-free survival; OS: overall survival; HR: hazard ratio; 95%CI: 95% confidence interval; F-NLR: fibrinogen and neutrophil-to-lymphocyte ratio score; LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index. *p*-Values <0.05 were considered significant.

as shown in Table IV, NLR value was also an independent prognostic factor for OS (HR=2.30, 95%CI=1.12-4.71, p=0.024) and PFS (HR=2.12, 95%CI=1.15-3.86, p=0.017) in the multivariate analysis with age, sex, stage, albumin, fibrinogen and NLR.

Our Kaplan–Meier analysis revealed that patients with F-NLR score of 2 had a significantly lower OS and PFS compared with F-NLR score of 0 (HR=3.35, 95%CI=1.18-9.44, p=0.0087, and HR=3.60, 95%CI=1.52-8.51, p=0.0006, respectively, Figure 2A and B). 3-year OS rates of patients with F-NLR scores of 0, 1, and 2 were 84.1%, 73.0% and 52.0%, respectively. Similarly, 3-year PFS rates of patients with F-NLR scores of 0, 1, and 2 were 68.7%, 56.5% and 35.2%, respectively. These results indicated that a high F-NLR score was a significant pretreatment predictor of a poor prognosis in patients with HPC.

Table III. *Multivariate analysis including age, sex, stage, albumin, and F-NLR score for overall and progression-free survival in patients with advanced hypopharyngeal carcinoma.*

	OS			PFS		
Variables	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age						
<67	1.00	Reference		1.00	Reference	
≥67	0.97	0.53-1.78	0.93	1.00	0.55-1.84	0.99
Gender						
Female	1.00	Reference		1.00	Reference	
Male	0.59	0.24-1.78	0.32	0.63	0.25-1.91	0.38
Stage						
III				1.00	Reference	
IV				1.55	0.67-4.22	0.32
Albumin						
<4.0	1.00	Reference		1.00	Reference	
≥4.0	0.65	0.35-1.23	0.190	0.68	0.36-1.29	0.23
F-NLR sore						
0	1.00	Reference		1.00	Reference	
1	1.79	0.85-4.01	0.12	1.72	0.81-3.86	0.16
2	3.39	1.47-8.14	0.043	3.06	1.31-7.48	0.0099

PFS: Progression-free survival; OS: overall survival; HR: hazard ratio; 95%CI: 95% confidence interval; F-NLR: fibrinogen and neutrophil-to-lymphocyte ratio score. *p*-Values <0.05 were considered significant.

Discussion

In this study, it was determined that a high F-NLR score using cut-off values of 341 mg/dl for fibrinogen and 3.59 for NLR was an independent prognostic factor for OS and PFS in patients with advanced HPC treated with RT, BRT or CRT. We also confirmed the significance of NLR using the same cut-off value as prognostic predictors for both of OS and PFS in advanced HNSCC patients. This novel scoring system of F-NLR score with adding the concentration of plasma fibrinogen on the concept of NLR could stratify HPC patients to extract poor prognostic characteristics. These findings suggest that F-NLR score could be a convenient pretreatment marker calculated by conventional blood tests to predict prognosis of patients with advanced HPC.

Several hematological inflammatory parameters, which could be measured easily, have emerged as prognostic factors for a wide spectrum of malignancies. Neutrophils are associated with tumor invasion and angiogenesis by the production of proangiogenic factors such as vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) (33), proteases such as matrix metalloproteinases (34) and elastases (35). Neutrophils might also contribute to genetic instability in tumors (36). On the other hand, lymphocytes play important roles in the immune defense against cancer, thereby low lymphocyte count would be considered as immune deficiency (37, 38). Particularly, many studies have reported the significance of tumor-infiltrating lymphocytes (TILs), such as infiltrating CD8+ T lymphocytes, playing an important role in cancer immunity by targeting tumor cells through binding to MHC class I molecules in the tumor microenvironment (39). In fact, high levels of infiltrating TILs have been reported to be associated with improvement in prognosis of cancer patients (40), including HNSCC (41). Fibrinogen is transformed to fibrin by activated thrombin in the coagulation cascade, and hyperfibrinogenemia could be thus involved in the malignant behaviors of various cancers (42). Thus, NLR could reflect the balance between tumor promoting environment and antitumor immune status (43). In addition, fibrinogen plays a key role in the formation of tumor thrombus by promoting platelet adhesion to cancer cells (44), and tumor thrombus is known to act defensively against the immune system of the host (45, 46). Although the detailed mechanism has not been yet understood, these findings indicate that fibrinogen acts as a stimulating factor during tumor progression.

As monocytes could differentiate into tissue macrophages, facilitating angiogenesis, matrix breakdown and tumor cell motility, a high monocyte count has also been reported to be related to tumor progression, angiogenesis and distant metastasis (47). An increase in platelet number (thrombocytosis) and activity has also been observed in patients with a variety of cancer types, as activated platelets could interact with cancer cells within the tumor microenvironment promoting tumor cell growth (48). Thus, both PLR and LMR could be prognostic pretreatment

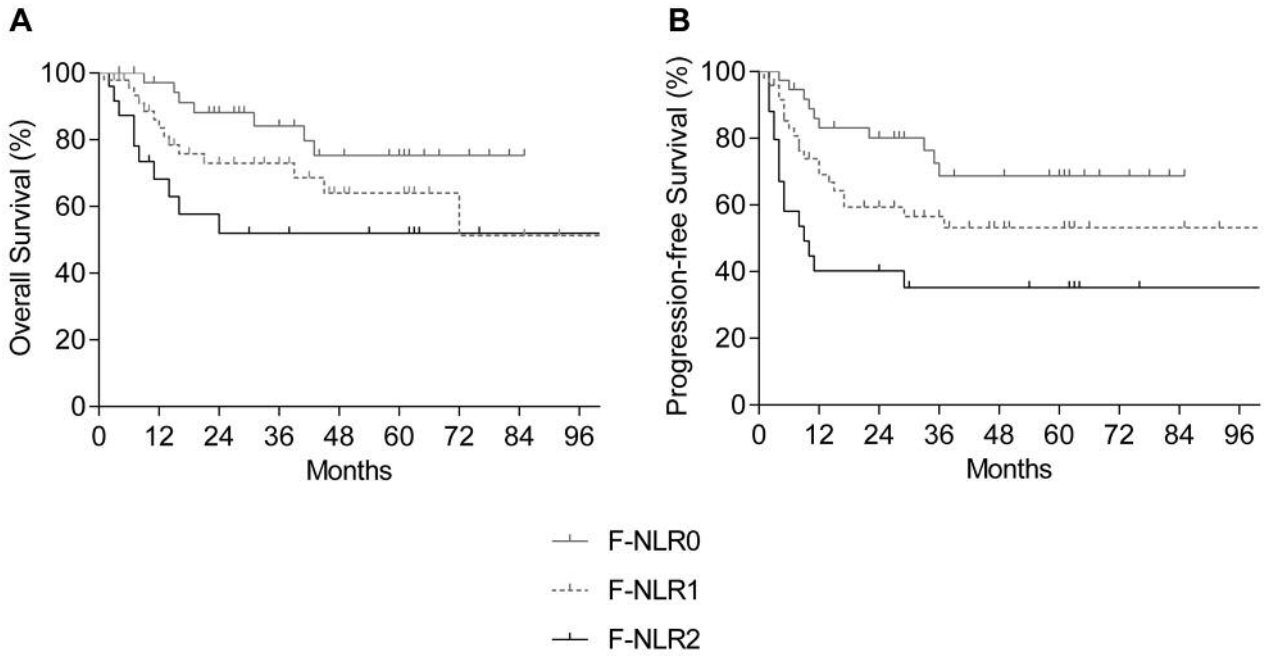

Figure 2. *Kaplan–Meier curves for overall (OS) and progression-free survival (PFS). OS (A) and PFS (B) were significantly shorter in patients with high F-NLR score. 3-year overall survival rates of patients with F-NLR scores of 0, 1 and 2 were 84.1%, 73.0% and 52.0%, respectively, and 3-year progression-free survival rates of patients with F-NLR scores of 0, 1 and 2 were 68.7%, 56.5% and 35.2%, respectively. In OS, patients with F-NLR score of 2 were inferior compared to the group with F-NLR score of 0 (HR=3.35, 95%CI=1.18-9.44, p=0.0087). Similarly, in PFS, patients with F-NLR score of 2 were inferior as compared to the group with F-NLR score of 0 (HR=3.60, 95%CI=1.52-8.51, p=0.0006).*

Table IV. *Multivariate analysis including age, sex, stage, albumin, and NLR for overall and progression-free survival in patients with advanced hypopharyngeal carcinoma.*

	OS			PFS		
Variables	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Age						
<67	1.00	Reference		1.00	Reference	
≥67	0.90	0.43-1.86	0.77	0.98	0.53-1.80	0.94
Gender						
Female	1.00	Reference		1.00	Reference	
Male	0.72	0.24-3.11	0.61	0.65	0.26-1.95	0.41
Stage						
III				1.00	Reference	
IV				1.66	0.70-4.57	0.26
Fibrinogen						
<341				1.00	Reference	
≥341				1.38	0.71-2.78	0.34
NLR						
<3.59	1.00	Reference		1.00	Reference	
≥3.59	2.30	1.12-4.71	0.024	2.12	1.15-3.86	0.017
Albumin						
<4.0	1.00	Reference		1.00	Reference	
≥4.0	0.51	0.25-1.08	0.078	0.67	0.35-1.26	0.21

PFS: Progression-free survival; OS: overall survival; HR: hazard ratio; 95%CI: 95% confidence interval; NLR: neutrophil-to-lymphocyte ratio. p-Values<0.05 were considered to be significant.

hematological markers as prognostic factors in patients with different types of cancer. While we determined the significance of high F-NLR score and high NLR value as independent prognostic factors for survival of patients with advanced HPC, PLR and LMR had no significant relationship with prognosis of advanced HPC patients in this study. These results suggested that a high neutrophil count might have an impact on shorter survival in our data set including only advanced HPC patients. This might be because some of the HPC patients with poor nutritional condition could have chronic inflammation such as aspiration pneumonia, thereby resulting in a high neutrophil count and reduced fibrinogen production in the present study. F-NLR, the grading system with adding the concentration of plasma fibrinogen on the concept of NLR, might be able to reflect the potential of tumor progression and tumor immunity through combining two pretreatment markers more comprehensively. F-NLR score was, thus, useful to stratify HPC patients to extract patients with poor prognosis in the present study, consistent with a previous report indicating that patients with advanced ESCC and a high F-NLR score had significantly shorter OS (32).

Other pretreatment prognostic markers in HNSCC have been also reported. Particularly, in patients with HNC, 25-50% of patients present with nutritional deterioration at diagnosis, as the tumor invasion could cause stenosis of the upper aerodigestive tract where HPC is predominant (49). Malnutrition may lead to weakened treatment intensity, and treatment itself (RT, CRT or BRT) could worsen the conditions of dysphagia, odynophagia, or anorexia because of mucositis, fibrosis, and change in taste. As malnutrition has been, thus, proven to be correlated with deteriorated quality of life and survival in HNC patients (50), assessment of the pretreatment nutritional status is important. Thus, the usefulness of serum albumin (51) and prognostic nutritional index (31, 52) as indicators of nutritional status and prognosis has been reported, however, neither PNI nor albumin value showed any significance as a prognostic marker in the present study. This might be because lymphocyte number did not have predictive significance on survival of HPC patients in the present study.

One of the limitations in the present study is that our retrospective study comprised 111 HPC patients including several clinical stages in a single institution. We, therefore, performed an additional subgroup analysis for HPC patients with stage IV. The result revealed that patients with F-NLR score of 2 also showed a significantly lower PFS in the univariate and multivariate analyses (data not shown). Relatively low AUC for the cut-off value of NLR and fibrinogen might be due to the design of the present study comprising insufficient sample size. Miscellaneous chemotherapy or biotherapy regimens combined with RT in this study might be another limitation, affecting survival outcomes. To confirm the reliability and applicability of this novel scoring system using F-NLR as a prognostic predictor for advanced HNSCC patients, further multi-institutional studies will be required in the future. Some additional concepts might be considered to examine the impact of this F-NLR score on prognosis of HPC patients, such as comparative analysis between pretreatment and post-treatment time points with several treatment modalities.

In conclusion, our study revealed the significance of both NLR and F-NLR scores as prognostic biomarkers in patients with advanced HPC treated with RT, BRT or CRT. In addition, F-NLR score with adding the concentration of plasma fibrinogen on the concept of NLR was useful to stratify HPC patients to extract poor prognostic characteristics. Further analysis should be conducted to validate the reliability and applicability of this novel scoring system as an economical prognostic predictor for determining the therapeutic plan in patients with advanced HPC in other clinical settings in the future.

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