Original Article

Prognostic value of preoperative neutrophil-lymphocyte ratio is superior to platelet-lymphocyte ratio for survival in patients who underwent complete resection of thymic carcinoma

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Background: Preoperative neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have prognostic value in patients with various operable tumors. The aim of our study was to determine whether NLR and PLR are predictive of survival in thymic carcinoma patients after complete resection.

Methods: A total of seventy-nine patients who underwent complete resection of thymic carcinoma at our hospital between January 2005 and December 2015 were retrospectively enrolled. Differential leukocyte counts were collected before surgery, and the relationships of NLR, PLR, and other patient clinical variables with survival were estimated by Cox regression analysis and Kaplan-Meier survival analysis.

Results: Univariate analysis found that a high level of NLR was associated with lower disease-free survival (DFS) (HR: 3.385, 95% CI: 1.073–10.678, P=0.037) and lower overall survival (OS) (HR: 12.836, 95% CI: 1.615–101.990, P=0.016). The optimal NLR threshold of 4.1 could stratify the patients with high risk of recurrence or metastasis (P=0.026) and death (P=0.006). Meanwhile, the NLR value of >4.1 in those patients was associated with bigger tumor size (P=0.035) and more advanced Masaoka stages (P=0.040) compared with NLR ≤4.1. However, the PLR and other variables were not significantly associated with survival in thymic carcinoma patients.

Conclusions: The preoperative NLR of >4.1 was significantly associated with larger tumor size, more advanced Masaoka stages and reduced DFS and OS, but was not an independent predictor of survival in thymic carcinoma patients after complete resection.

Keywords: Thymic carcinoma; neutrophil-lymphocyte ratio (NLR); platelet-lymphocyte ratio (PLR); prognosis

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Introduction

Thymic epithelial tumors (TETs), which include thymoma and thymic carcinoma, are most common tumors in the anterior mediastinum (1). Unlike thymoma, thymic carcinoma which accounts for only 0.06% of all thymic neoplasms (2) is aggressive and has a generally poor prognosis, with a 5-year survival rate of approximately 40% (3-5). The complete resection (R0) is the gold standard treatment for operable thymic carcinoma. Radiotherapy and chemotherapy appear to benefit inoperable or incompletely resected patients (6-8).

Over the past decade, the evidence that cancer-related

inflammation has a strong influence on outcome in cancer patients has increased and is consistent. A number of inflammation markers have been evaluated to stratify patients for treatment and to predict survival (9). The prognostic value of preoperative systemic inflammation-related neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) has been demonstrated in patients with a variety of cancers (10-18). However, no previous studies have evaluated the association between NLR and PLR with the prognosis of thymic tumors. The purpose of our study was to investigate the prognostic value of preoperative NLR and PLR for patients with thymic carcinoma.

Methods

A total of 90 thymic carcinoma patients underwent complete resection and were treated in the Department of Thoracic Surgery of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China between January 2005 and December 2015. To ensure that the white cell count was representative of a normal baseline, we excluded eleven patients who received preoperative radiotherapy or chemotherapy and those with coexistent hematologic disorders or active infection at the time of surgery. Finally, there were 79 eligible patients with thymic carcinoma included in the study. Complete resection included thymectomy, dissection of mediastinal fat tissue, regional lymph node dissection and resection of adjacent invaded tissues. Regardless of the operative approaches including open surgery and video-assisted thoracoscopic surgery (VATS), all procedures followed the criteria of complete resection. Pathological evaluation of intraoperative frozen sections distinguished thymic carcinoma from other mediastinal masses. Patients who were considered to have a high risk of recurrence based on operative findings were offered postoperative radiotherapy and/or chemotherapy.

This retrospective, observational study evaluated the relationship of a number of cellular markers of systemic inflammation with patient survival. Blood samples of all eligible patients were obtained before surgery. All cases were staged according to the Masaoka system, and histologic classification of thymic carcinoma was based on the World Health Organization (WHO) histologic criteria (19), which were determined by postoperative histopathological analysis and the clinicopathological characteristics of all patients by review of their medical records. The NLR, PLR, absolute neutrophil, lymphocyte, and platelet counts were evaluated to determine whether they were predictive of survival. Overall survival (OS) was defined as the interval between the date of surgery and the date of death from any cause or the last follow-up. Disease-free survival (DFS) was defined as the interval between the date of surgery and the first recurrence or metastasis, or the last follow-up. The study was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Because the study was a retrospective analysis of patient data and followed the guidelines of the Declaration of Helsinki, the requirement for patient consent was not required.

Statistical analysis

Values of continuous variables were presented as means ± standard deviation (SD) or medians and range. Patients were divided into equal quartiles according to the 25th, 50th and 75th NLR and PLR percentile. Categorical variables were reported as number and percentages. The Kaplan-Meier method was used to calculate the 1-, 3-, and 5-year OS and 1-, 3-, and 5-year DFS. The variables we entered into the univariate analysis may be associated with prognosis of thymic carcinoma according to previous studies. Variables that were found to be associated with survival in the univariate analysis were further tested in a multivariate model. The association between each continuous variable and stratification by threshold was evaluated using the *t*-test. The association between each categorical variable and stratification was evaluated using the chi-square test. Kaplan-Meier plots were calculated to estimate survival stratified by a significant indicator; differences were tested by the log-rank test. All tests were two-sided, and P values <0.05 were considered significant. All collected data were analyzed by SPSS 19.0 (IBM Corp. Armonk, NY, USA).

Results

Patient characteristics

Baseline characteristics of the 79 thymic carcinoma patients are shown in *Table 1*. There were no perioperative deaths or severe morbidities that were related to the surgical procedures. Median follow-up was 40 months (range, 1–130 months); 18 deaths (23%) and 26 recurrences or metastasis (33%) occurred during that time. The

Table 1 Baseline characteristics of patients with thymic carcinoma

Variables	Total
No.	79
Age (years)	
Mean	54
SD	12
≤60 (%)	52 [66]
>60 (%)	27 [34]
Sex (%)	
Female	31 [39]
Male	48 [61]
Tumor size (cm)	
Mean	6.6
SD	2.8
Histologic classification (%)	
Squamous cell	66 [84]
Basaloid	1 [1]
Lymphoepitheliema-like	3 [4]
Neuroendocrine	9 [11]
Differentiation (%)	
High	9 [11]
Moderately	17 [22]
Low	53 [67]
Masaoka stage (%)	
IIA and IIB	29 [37]
IIIA and IIIB	30 [38]
IVA and IVB	20 [25]
Neutrophil count ($\times 10^9$/L)	
Mean	4.5
SD	2.2
Lymphocyte count ($\times 10^9$/L)	
Mean	1.7
SD	0.7
Platelet count ($\times 10^9$/L)	
Mean	239.2
SD	68.9
NLR	
Mean	3.1
SD	2.1
25th percentile	1.7
50th percentile	2.5
75th percentile	4.1
PLR	
Mean	164.7
SD	80.4
25th percentile	120.2
50th percentile	150.4
75th percentile	184.8
Surgical approach (%)	
Open surgery	69 [87]
VATS	10 [13]
Adjuvant therapy (%)	
Radiotherapy	56 [71]
Chemotherapy	33 [42]
Follow-up (month)	
Median	40
Range	1–130
Recurrence or metastasis (%)	26 [33]
Death (%)	18 [23]

SD, standard deviation; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; VATS, video-assisted thoracoscopic surgery.

mean age was 54±12 years, 52 (66%) were ≤60 years of age and 27 (34%) were >60 years of age, 31 (39%) were women and 48 (61%) were men. The mean tumor size was 6.6±2.8 cm. Of the four histologic classifications, squamous cell carcinoma was the most common (n=66, 84%), followed by neuroendocrine (n=9, 11%), lymphoepithelioma-like (n=3, 4%), and basaloid (n=1, 1%). Nine patients (11%) had highly differentiated tumors, 17 (22%) had moderately differentiated tumors, and 53 (67%) had low differentiated tumors. Twenty-nine

patients (37%) were as Masaoka stages IIA and IIB, 30 (38%) were stages IIIA and IIIB, and 20 (25%) were stages IVA and IVB. The mean neutrophil count was (4.5±2.2) $\times 10^9$, lymphocyte count was (1.7±0.7) $\times 10^9$ and platelet count was (239.2±68.9) $\times 10^9$. The mean NLR was 3.1±2.1. The 25th, 50th and 75th NLR percentile were 1.7, 2.5 and 4.1 respectively. The mean PLR was 164.7±80.4 and the 25th, 50th and 75th PLR percentile were 120.2, 150.4 and 184.8 individually. Sixty-nine patients (87%) underwent open surgery and 10 patients (13%) with VATS. Of the patients given adjuvant therapy after surgery, 56 (71%) received radiotherapy and 33 (42%) received chemotherapy (10 cases received both radiotherapy and chemotherapy).

Disease-free survival

During the follow-up period, the 1-, 3-, and 5-year DFS rates were 78%, 57% and 44% respectively. In the Cox univariate regression analysis, both NLR, as a continuous variable (HR: 1.215, 95% CI: 1.018–1.451, P=0.031) and presence in the 4th NLR quartile (NLR >4.1, i.e., the 75th percentile), as a categorical variable (HR: 3.385, 95% CI: 1.073–10.678, P=0.037), and Masaoka stage IIIa and IIIb (HR =5.571; 95% CI: 1.584–19.597; P=0.007), IVa and IVb (HR =7.159; 95% CI: 1.897–27.014; P=0.004) were significantly associated with DFS. However, neither PLR (as a continuous variable, P=0.061) nor the PLR quartiles (as a categorical variable, P>0.05), neutrophil count (P=0.184), lymphocyte count (P=0.598) and platelet count (P=0.844) as well as age (P=0.998), sex (P=0.913), tumor size (P=0.729), histological classification (P>0.05), tumor differentiation (P>0.05), surgical approach (P>0.05) and adjuvant therapy (P>0.05) were not significantly associated with DFS. When analyzed by Cox multivariate regression analysis, only the Masaoka stage remained as an independent prognostic factor (IIIA and IIIB: HR =5.855; 95% CI: 1.647–20.805; P=0.006, IVA and IVB: HR =5.154; 95% CI: 1.123–23.655; P=0.035) (*Table 2*). Kaplan-Meier analysis found the highest NLR quartile (i.e., NLR >75th percentile) was associated with a significantly increased risk of recurrence or metastasis (P=0.026, log-rank test) (*Figure 1A*).

Overall survival

The Kaplan-Meier analysis indicated 1-, 3-, and 5-year OS rates of 96%, 79% and 60% respectively during follow-up. In the Cox univariate regression model, both NLR, as a continuous variable (HR: 1.342, 95% CI: 1.091–1.650, P=0.005) and the 4th NLR quartile (NLR >4.1, i.e., the 75th percentile), as a categorical variable (HR: 12.836, 95% CI: 1.615–101.990, P=0.016), and Masaoka stage IVa and IVb (HR =11.111; 95% CI: 2.416–51.107; P=0.002) was significantly associated with OS. However, age (P=0.524), sex (P=0.096), tumor size (P=0.687), histological classification (P>0.05), tumor differentiation (P>0.05), surgical approach (P>0.05), adjuvant therapy (P>0.05) and neither PLR (as a continuous variable, P=0.052) nor the PLR quartiles (as a categorical variable, P>0.05), neutrophil count (P=0.351), lymphocyte count (P=0.143) and platelet count (P=0.125) were not significantly associated with OS. Subsequently, the Cox multivariate analysis indicated that Masaoka stage (HR =7.773; 95% CI: 1.559–38.768; P=0.012) was the only variable found to be an independent predictor of OS (*Table 3*). The Kaplan-Meier analysis and log-rank tests found that patients in the 4th NLR quartile had a significantly shorter OS than other thymic carcinoma patients (P=0.006) (*Figure 1B*).

Further, compared with those in the lower NLR quartiles (NLR ≤4.1, i.e., the 75th percentile), the patients in the highest NLR quartile (NLR >4.1) who had high risk of recurrence or metastasis and death had larger tumor size (P=0.035) and more advanced Masaoka stages (P=0.040) (*Table 4*).

Discussion

In the present study of NLR, PLR and prognosis of thymic carcinoma, we found that increased preoperative NLR was significantly associated with tumor size, the Masaoka stage, disease recurrence or metastasis, and poor survival. Moreover, when patients were stratified by the 4th NLR percentile (NLR =4.1) found that the subgroup with NLR >4.1 had shorter DFS and OS than the subgroup with NLR at or below the 4.1 threshold. Furthermore, we found that Patients with an NLR >4.1 had bigger tumor volumes and more advanced Masaoka stages than those with an NLR ≤4.1. Although it was not an independent predictor of death and recurrence or metastasis, a high preoperative NLR of >4.1 was associated with decreased DFS and OS. The Masaoka staging system was an independent prognostic indicator of OS and DFS in these thymic carcinoma patients, which is consistent with previous reports. However, preoperative PLR and other variables, such as age, sex, tumor size, histologic classification, tumor differentiation,

Table 2 Univariate and multivariate Cox regression analysis for DFS of thymic carcinoma patients

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (years)						
≤60						
>60	1.001	0.445–2.250	0.998			
Sex						
Male						
Female	1.046	0.466–2.352	0.913			
Tumor size	1.022	0.904–1.155	0.729			
Histologic classification (squamous cell)						
Basaloid	2.164	0.287–16.333	0.454			
Lymphoepitheliema-like	6.120	0.667–56.184	0.109			
Neuroendocrine	1.286	0.437–3.790	0.648			
Differentiation						
High						
Moderately	0.403	0.094–1.718	0.219			
Low	0.572	0.165–1.979	0.378			
Masaoka stage						
IIA and IIB						
IIIA and IIIB	5.571	1.584–19.597	0.007	5.855	1.647–20.805	0.006
IVA and IVB	7.159	1.897–27.014	0.004	5.154	1.123–23.655	0.035
Neutrophil count	1.088	0.961–1.233	0.184			
Lymphocyte count	1.183	0.634–2.207	0.598			
Platelet count	0.999	0.994–1.005	0.844			
NLR	1.215	1.018–1.451	0.031	0.954	0.625–1.457	0.829
1st quartile						
2nd quartile	1.971	0.576–6.750	0.280	1.801	0.503–6.452	0.366
3rd quartile	0.932	0.233–3.729	0.921	0.788	0.161–3.858	0.769
4th quartile	3.385	1.073–10.678	0.037	3.007	0.386–23.442	0.293
PLR	1.004	1.000–1.009	0.061			
1st quartile						
2nd quartile	0.823	0.287–2.355	0.716			
3rd quartile	0.667	0.195–2.285	0.520			
4th quartile	1.193	0.431–3.299	0.734			
Surgical approach						
Open surgery						
VATS	0.445	0.060–3.305	0.429			
Adjuvant therapy						
Radiotherapy	1.069	0.402–2.841	0.894			
Chemotherapy	0.675	0.309–1.477	0.325			

HR, hazard ratio; CI, confidence interval; DFS, disease-free survival; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; VATS, video-assisted thoracoscopic surgery.

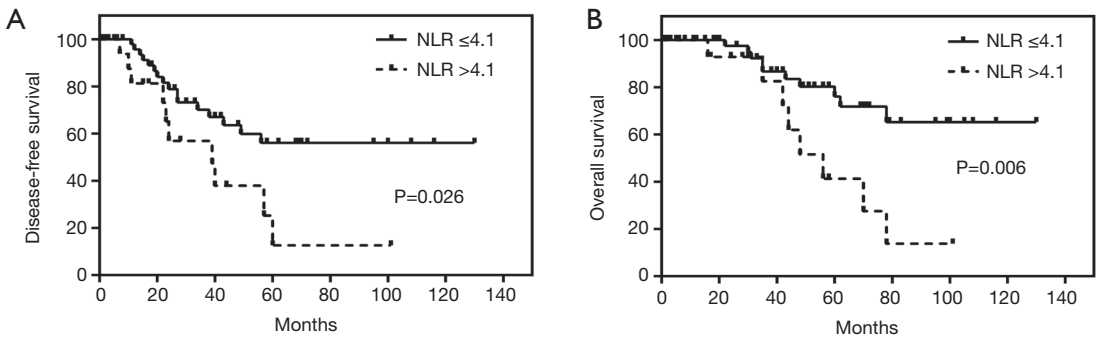

Figure 1 Survival curves stratified by NLR. (A) Disease-free survival curves stratified by NLR; (B) overall survival curves stratified by NLR. NLR, neutrophil-lymphocyte ratio.

absolute white cells and platelet count, surgical approach and adjuvant therapy were not significantly associated with DFS and OS. Taking all these into consideration, the preoperative NLR can be an alternative prognostic marker for patients with thymic carcinoma and a supplementary for the Masaoka staging system. The 5-year DFS and the 5-year OS of thymic carcinoma patients after complete resection in our hospital seem to be better than those reported in other retrospective studies (3-5,20,21) (44% *vs.* an average of 40% and 60% *vs.* an average 42%, respectively).

Cancer-related inflammation has been shown to have adverse effects on cancer prognosis. The development and progression of cancer depends on a complex interaction of the tumor characteristics and the host inflammatory response, but many of the molecular and cellular mechanisms mediating this relationship remain unresolved (22-24). The host inflammatory response triggered by a tumor is complex and involves alterations in neuroendocrine metabolism, hormones and hematopoietic changes including the relative numbers of circulating white cells and platelets. Changes in protein and energy metabolism include loss of muscle protein and acute-phase responses including C-reactive protein (CRP) and albumin (25). In addition, the tumor microenvironment influences the invading white cells and platelets to promote angiogenesis, invasion, motility and viability (26,27). The NLR and PLR reflect the populations of circulating white cells and platelets and have clinical advantages of being inexpensive and routinely measured in perioperative practice. They are, inferior to some other markers of a cancer-related systemic inflammatory response, such as serum CRP and albumin, the Glasgow prognostic score (GPS) or modified GPS (mGPS) (28,29), but serum CRP levels and other markers are not routinely performed as part of the preoperative assessment of patients. Hence, the NLR and PLR plus the absolute neutrophil, lymphocyte and platelet counts were assessed in patients with thymic carcinoma who were retrospectively evaluated in our study.

Recently, several studies have shown that an elevated pretreatment NLR or PLR was associated with poor prognosis in patients with various cancers. Moreover, the majority of those studies showed that the prognostic value of NLR seemed to be superior to that of PLR (25). The increasing evidence demonstrates that pro-inflammatory cytokines play a significant role in the tumor host interaction, such as IL-1ra, IL-6, IL-7, IL-8, IL-12, IL-17 and MCP-1. These inflammatory cytokines may establish and keep a tumor microenvironment favoring aggressive tumor behavior. An elevated NLR is considered to be associated with elevated circulating concentrations of these cytokines, which offers an insight into mechanisms underlying an elevated NLR (30,31). Nevertheless, the cutoff points of NLR proposed in previous studies differ, including NLR thresholds of 2.3, 4.02 or 5 in gastric cancer (14,32,33), 0.38, 2.4 or 3 in colorectal cancer (15,34,35), 2.3 or 2.5 in NSCLC (10,36), and consensus has not been established. The heterogeneity of those studies may contribute to the different results. Eagerly, a future prospective study with large sample is needed to give a definitive cut-off value of NLR with good sensitivity and specificity. To the best of our knowledge, this is the first evaluation of the prognostic value of the NLR and PLR in patients with thymic carcinoma. We found that an NLR threshold of 4.1 could stratify patients by risk of recurrence or metastasis and death. Patients with an NLR >4.1 had shorter DFS and OS as well as bigger tumor volumes and

Table 3 Univariate and multivariate Cox regression analysis of OS of thymic carcinoma patients

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age						
≤60						
>60	1.362	0.526–3.527	0.524			
Sex						
Male						
Female	2.203	0.869–5.585	0.096			
Tumor size	1.029	0.895–1.184	0.687			
Histologic classification (squamous cell)						
Basaloid	3.563	0.452–28.071	0.228			
Lymphoepitheliema-like	2.775	0.356–21.643	0.330			
Neuroendocrine	0.754	0.171–3.324	0.709			
Differentiation						
High						
Moderately	0.179	0.011–2.928	0.227			
Low	1.100	0.142–8.506	0.927			
Masaoka stage						
IIA and IIB						
IIIA and IIIB	3.183	0.639–15.861	0.158	3.807	0.733–19.782	0.112
IVA and IVB	11.111	2.416–51.107	0.002	7.773	1.559–38.768	0.012
Neutrophil count	1.074	0.924–1.248	0.351			
Lymphocyte count	0.551	0.248–1.223	0.143			
Platelet count	0.993	0.984–1.002	0.125			
NLR	1.342	1.091–1.650	0.005	0.833	0.505–1.373	0.473
1st quartile						
2nd quartile	6.656	0.799–55.472	0.080	5.148	0.581–45.591	0.141
3rd quartile	2.134	0.193–23.605	0.536	1.966	0.150–25.834	0.607
4th quartile	12.836	1.615–101.990	0.016	14.641	0.679–315.919	0.087
PLR	1.005	1.000–1.010	0.052			
1st quartile						
2nd quartile	0.943	0.210–4.236	0.939			
3rd quartile	3.342	0.828–13.491	0.090			
4th quartile	1.894	0.452–7.940	0.382			
Surgical approach						
Open surgery						
VATS	0.934	0.124–7.050	0.948			
Adjuvant therapy						
Radiotherapy	4.204	0.558–31.696	0.164			
Chemotherapy	0.999	0.396–2.518	0.997			

HR, hazard ratio; CI, confidence interval; OS, overall survival; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; VATS, video-assisted thoracoscopic surgery.

Table 4 Characteristics of thymic carcinoma patients stratified by NLR

Variables	NLR ≤4.1	NLR >4.1	P value
No. (%)	60 [76]	19 [24]	
Age (%)			0.052
≤60 years	43 [72]	9 [47]	
>60 years	17 [28]	10 [53]	
Sex (%)			0.769
Female	23 [38]	8 [42]	
Male	37 [62]	11 [58]	
Tumor size			0.035
Mean (SD)	6.2 [2.5]	7.8 [3.3]	
Histologic classification (%)			0.092
Squamous cell	52 [87]	14 [74]	
Basaloid	0 [0]	1 [5]	
Lymphoepitheliema-like	3 [5]	0 [0]	
Neuroendocrine	5 [8]	4 [21]	
Differentiation (%)			0.177
High	5 [8]	4 [21]	
Moderately	15 [25]	2 [11]	
Low	40 [67]	13 [68]	
Masaoka stage (%)			0.040
IIA and IIB	24 [40]	5 [26]	
IIIA and IIIB	25 [42]	5 [26]	
IVA and IVB	11 [18]	9 [48]	

NLR, neutrophil-lymphocyte ratio; SD, standard deviation.

more advanced Masaoka stages than those with an NLR ≤4.1. The results are consistent with the hypothesis that a greater preoperative NLR reflects an enhanced host inflammatory response to more aggressive tumors (9).

Inflammation is known to play an important role in the origin of many cancers, and cancer-related inflammation is a key determinant of patient outcome (22). For example, some colorectal cancers derive from ulcerative colitis, which is characterized by recurrent ulceration with chronic irritation and inflammation. Many markers of the systemic inflammatory response have been shown to be associated with prognosis of patients with colorectal cancer (37). However, the cause of thymic tumors is unknown, and thymic carcinoma does not arise as a result of obvious acute or chronic inflammation. For this reason, it seems to be very difficult to detect the traces of a cancer-related inflammation response in thymic carcinoma. In addition, given the rarity of thymic carcinoma, the small patient sample was enrolled in our study, which contributed to the bias of the study inevitably. All these factors may explain the difference in our study results compared with previous investigations conducted in a number of other cancers.

The limitations of this study include the small sample of clinical cases due to the rarity of thymic carcinoma, which may partially account for the negative outcome for the prognostic value of the NLR and PLR in thymic carcinoma. Secondly, it was a retrospective study that analyzed clinical data from only one institute, which may lead to inaccurate

results. Thirdly, the mechanism of the association between increasing NLR and progression of thymic carcinoma is not fully clarified. In the future, we are looking forward to prospective studies with large patient samples that will be able to clarify the relationship between the NLR, PLR and other systemic inflammation-based markers and prognosis in thymic carcinoma patients as well as the mechanism of the association between cancer-related inflammatory markers and progression of thymic carcinoma.

Conclusions

The present study demonstrated that a preoperative NLR >4.1 was significantly associated with reduced DFS and OS as well as larger tumor size and more advanced Masaoka stages, but was not an independent predictor of DFS and OS in thymic carcinoma after complete resection. The Masaoka stage was an independent prognostic indicator for thymic carcinoma. However, the PLR was not significantly associated with survival in thymic carcinoma patients in our study. While the NLR is not independent prognostic factor for thymic carcinoma, it may be useful for counseling patients with respect to treatment options and possible outcomes, and may also supplement the Masaoka staging system.

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None.

Footnote

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

Ethical Statement: The study was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

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