ORIGINAL ARTICLE

Association of lung immune prognostic index with survival outcome in advanced thymic carcinoma patients treated with palliative intent chemotherapy

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Abstract

Background: The prognostic implications of palliative chemotherapy for advanced or recurrent thymic carcinomas require full elucidation. The lung immune prognostic index (LIPI) is a novel prognostic index whose effectiveness has recently been reported in lung cancer patients. This study aimed to evaluate the clinical value of the LIPI in advanced or recurrent thymic carcinoma patients.

Methods: We retrospectively analyzed 41 advanced or recurrent thymic carcinoma patients undergoing palliative chemotherapy between January 2001 and December 2020. Survival-time analysis was conducted using the Kaplan–Meier method and log-rank test. Multivariate analysis using the Cox proportional hazards model was performed to investigate the predictive and/or prognostic value of the LIPI.

Results: Median progression-free survival (PFS) for first-line chemotherapy and overall survival (OS) were significantly longer in the good-LIPI group (LIPI: 0) than in the intermediate/poor-LIPI group (LIPI: 1 or 2) (PFS: 13.4 vs. 6.8 months, $p = 0.025$; OS: 48.2 vs. 28.9 months, $p = 0.00506$). Multivariate analysis revealed that intermediate/poor LIPI was the adverse prognostic factor for PFS. With regard to OS, serum albumin <3.5 g/dl and an intermediate/poor LIPI were identified as independent adverse prognostic factors.

Conclusions: Our study indicates that the LIPI is a potential prognostic marker in patients with advanced or recurrent thymic carcinoma undergoing palliative chemotherapy.

KEYWORDS
derived NLR, lactate dehydrogenase, lung immune prognostic index, prognostic marker, thymic carcinoma

INTRODUCTION

Thymic carcinomas are rare neoplasms that arise in the anterior mediastinum, with a reported annual incidence of 0.29 per 100 000 population in Japan.[1] Thymic carcinoma is a highly progressive disease characterized by a poor survival rate, local invasion, and distant metastases often present at the time of diagnosis.[2,3] Patients with advanced (stage IVa and IVb according to the Masaoka–Koga stage classification) or recurrent thymic carcinoma are usually treated with palliative intent chemotherapy or radiotherapy. However, due to the rarity of this patient population, the optimal chemotherapeutic strategy and sequence of treatment are debatable. Thus, there are conflicting findings in previous reports regarding the prognostic implications of palliative intent chemotherapy for patients with advanced and/or recurrent thymic carcinoma.

Inflammatory dynamics in the tumor microenvironment play a key role in carcinogenesis.[4] In recent years, the prognostic utility of hematological and biochemical parameters

that can be routinely evaluated in daily clinical practice and that potentially reflect tumor inflammation have been validated. Typically, the neutrophil-to-lymphocyte ratio (NLR) and derived NLR (dNLR), comprising leukocyte fractions, are commonly used parameters.[5,6] In cancer patients, these parameters have been reported to act as predictive and/or prognostic biomarkers, indicating tumor inflammatory status reflected by alterations in peripheral blood leukocytes.[6] In addition, other types of clinical parameters such as prognostic nutrition index,[7] C-reactive protein (CRP) -to-albumin ratio (CAR)[8] have been reported to have prognostic value in various cancers. Furthermore, serum lactate dehydrogenase (LDH) is a well-known prognostic marker for various types of cancer. Elevated LDH levels have been reported to reflect tumor inflammation[9] and significant tumor growth potential.[10] Based on these perspectives, Mezquita et al. proposed the lung immune prognostic index (LIPI), a composite index comprising the dNLR and LDH, and demonstrated its prognostic and predictive value in non-small cell lung cancer (NSCLC) patients treated with immune checkpoint inhibitors (ICIs).[11] Since then, numerous reports on the clinical utility of the LIPI, especially in lung cancer, have been published.[12,13] However, the clinical value of the LIPI in thymic carcinoma remains uncertain, and its prognostic role is unclear. Therefore, we conducted this study to validate the clinical value of the LIPI in patients with advanced or recurrent thymic carcinoma undergoing palliative intent chemotherapy.

METHODS

Patients and setting

The present study was conducted retrospectively at a single institution. Analysis data were collected from paper-based or electronic medical records. We extracted data on patients diagnosed with thymic carcinoma at our institute between January 2001 and December 2020. Patients meeting the following criteria were included: histopathological diagnosis of thymic carcinoma based on the 2015 World Health Organization classification of thymic tumors,[14] unresectable and advanced-stage (Masaoka–Koga stage IVa or IVb) carcinoma or postoperative recurrence thereof, receiving at least one regimen of systemic chemotherapy with cytotoxic agents, and not receiving curative treatment other than chemotherapy (i.e., curative intent radiotherapy, salvage surgery, etc.).

Data collection

Data on patient characteristics included age, sex, smoking history, histology, and clinical stage according to the Masaoka–Koga stage classification for thymic tumors, metastatic lesions, and PS as evaluated by the Eastern Cooperative Oncology Group. The laboratory data measured at the

initiation of first-line chemotherapy included serum Alb and CRP to evaluate CAR; peripheral complete blood count, including absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) to calculate the NLR and dNLR; and serum LDH to evaluate the LIPI. NLR was calculated as the ratio of ANC to ALC. CAR was calculated as the ratio of

TABLE 1 Patient characteristics (N = 41)

Variables		n	%
Age, years, median (range)		66 (35–79)	
Sex	Male	27	65.9
	Female	14	34.1
Smoking history	Current or former	22	53.7
ECOG-PS	0–1	31	75.6
	2–3	10	24.4
Histology	Squamous cell carcinoma	35	85.4
	LCNEC	1	2.4
	Undifferentiated carcinoma	5	12.2
Tumor stage	IVa	12	29.3
	IVb	21	51.2
	Post-ope.	8	19.5
Metastatic location	Serosal	19	46.3
	Bone	9	22
	Lung	9	22
	Lymph node	6	14.6
	Liver	6	14.6
No. of metastatic sites	1	23	56.1
	≥2	18	43.9
Laboratory test results, mean ± SD	Alb, g/dl	3.8 ± 0.5	
	CRP, mg/dl	2.3 ± 3.4	
	CAR	0.7 ± 1.1	
	NLR	4.5 ± 2.6	
	dNLR	2.8 ± 1.5	
	LDH, U/ml	266 ± 133	
LIPI	0	13	31.7
	1	20	48.8
	2	8	19.5
No. of treatment lines, median (range)		2 (1–10)	
PFS, months, median (95% CI)		7.6 (6.5–11.3)	
OS, months, median (95% CI)		34.9 (23.9–41.6)	

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group Performance Status; LCNEC, large cell neuroendocrine carcinoma; Alb, albumin; CRP, C-reactive protein; CAR, CRP-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; LIPI, lung immune prognostic index; PFS, progression-free survival; OS, overall survival; CI, confidence interval.

TABLE 2 Comparison according to LIPI score

n	N (%)	Good LIPILIPI: 0 13 (%)	Intermediate/poor LIPILIPI: 1-2 28 (%)	p-value
Age, years, median (range)		65.5 (35-79)	65.5 (36-79)	0.483
Sex	Male	10 (76.9)	17 (60.7)	0.482
	Female	3 (23.1)	11 (39.3)	
ECOG-PS	0-1	11 (84.6)	20 (71.4)	0.458
	2-3	2 (15.4)	8 (28.6)	
Histology	Squamous cell carcinoma	12 (92.3)	22 (78.6)	0.399
	Other	1 (7.7)	6 (21.4)	
Tumor stage	IVa	2 (15.4)	10 (35.7)	0.276
	IVb	6 (46.1)	15 (53.6)	0.744
	Post-ope.	5 (38.5)	3 (10.7)	0.084
Metastatic location	Serosal	5 (38.5)	14 (50)	0.524
	Liver	2 (15.4)	4 (14.3)	1.00
	Bone	1 (7.7)	8 (28.6)	0.228
	Lymph node	4 (30.8)	2 (7.1)	0.0685
	Lung	4 (30.8)	5 (17.9)	0.429
No. of metastatic sites	1	8 (61.5)	15 (53.6)	0.742
	≥2	5 (38.5)	13 (46.4)	
First-line regimen	Platinum with anthracycline	11 (84.6)	25 (89.3)	0.645
	Platinum doublet	2 (15.4)	2 (7.1)	0.58
	Monotherapy	0 (0)	1 (3.6)	1.00
Response to first-line treatment	PR	7	14	
	SD	5	9	
	PD	1	2	
	NE	0	3	
ORR, % (95% CI)		53.8 (25.1-80.8)	50 (30.6-69.4)	1.00
DCR, % (95% CI)		92.3 (64-99.8)	82.1 (63.1-93.9)	0.645
Survival time, months, median (95% CI)	PFS	13.4 (6.3-18.9)	6.8 (5.8-8.4)	
	OS	48.2 (25.3-NA)	28.9 (10.4-35.6)	
No. of treatment lines, median (range)		2 (1-6)	2 (1-10)	

Abbreviations: CI, confidence interval; LIPI, lung immune prognostic index; Alb, albumin; PR, partial response; SD, stable disease; PD; progressive disease; NE, not evaluated; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; NA, not applicable.

CRP to Alb. The LIPI was evaluated according to the dNLR (ANC/[WBC−ALC]) and serum LDH levels, with scores ranging from 0 to 2 and calculated as follows: dNLR <3 and LDH <223 U/l = 0, dNLR ≥3 and LDH <223 U/l or dNLR <3 and LDH ≥223 U/l = 1, and dNLR ≥3 and LDH ≥223 U/l = 2. The median values of NLR and CAR were employed as cutoff values for univariate and multivariate analysis (NLR: 3.7, CAR: 0.22). In this study, the patients were divided into the following two groups according their LIPI scores: the "good-LIPI group," including patients with an LIPI score of 0, and "intermediate/poor-LIPI group," including those with LIPI scores of 1 or 2. Regarding clinical course, data on the types of first-line chemotherapy regimen, treatment response, palliative intent radiotherapy, and survival time were collected. The treatment response for first-line chemotherapy was evaluated according to the revised Response Evaluation Criteria in Solid Tumors guidelines (v.1.1).[15] The response evaluation was performed by computed tomography scans and/or 18F-fluorodeoxyglucose-positron emission tomography according to the discretion of the first physician. The radiological images of all patients were reviewed by two expert pulmonologists (TA and KT, with 10 and 16 years of experience, respectively) to evaluate treatment response and disease progression. Accordingly, ORR, the ratio of patients with complete remission (CR) and partial response (PR) to all patients, and DCR, the ratio of patients with CR, PR and stable disease to all patients were recorded. OS was defined as the period from initiation of chemotherapy to either a fatal event or censored observation. PFS for first-line chemotherapy was defined as the period from initiation of first-line chemotherapy to death or disease progression.
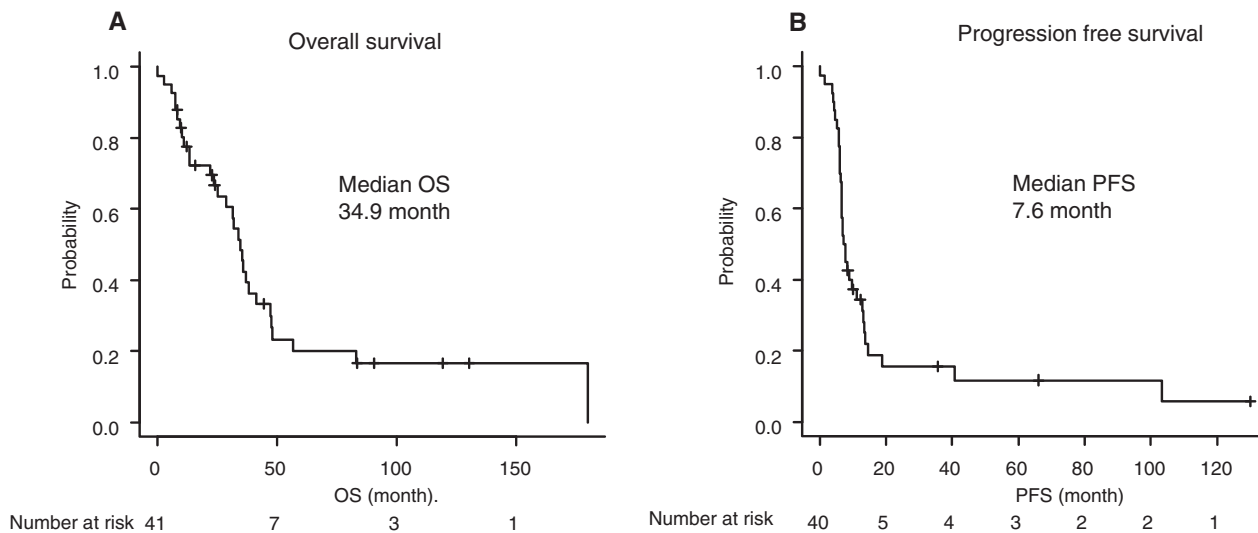
FIGURE 1 Kaplan–Meier curves of (a) overall survival and (b) progression-free survival in all patients
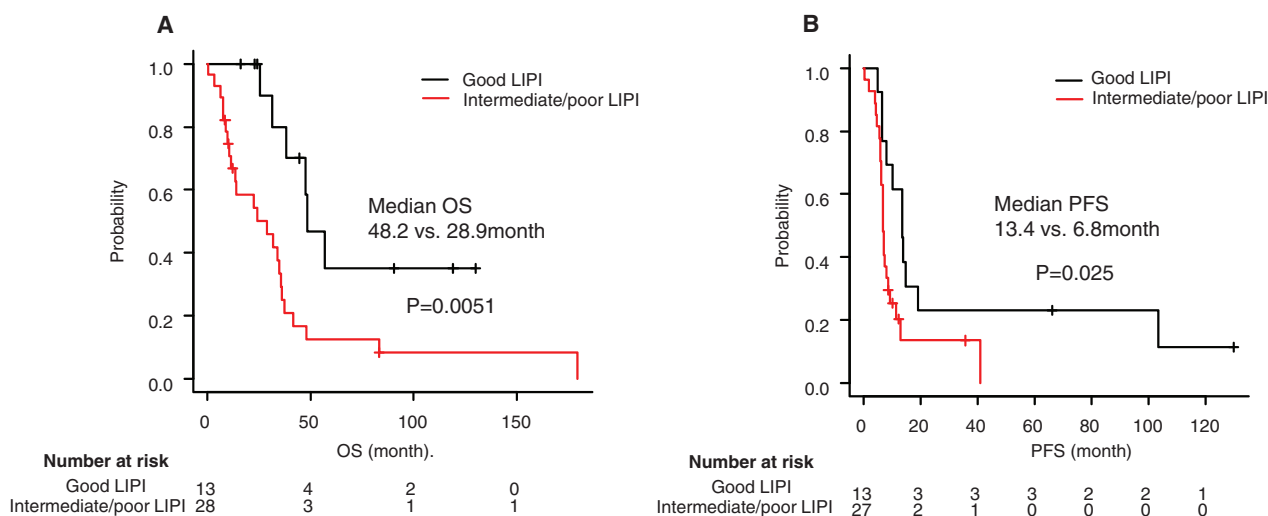

FIGURE 2 Kaplan–Meier curves of (a) overall survival and (b) progression-free survival stratified by LIPI score. The black line represents the good-LIPI group and the red line the intermediate/poor-LIPI group

Statistical analysis

Kaplan–Meier analysis was performed to plot the PFS and OS curves, and the log-rank test was employed for inter-group comparisons of PFS and OS. A Cox proportional hazards model was used to identify the prognostic factors for PFS and OS, with statistically significant variables used for the univariate model and clinically important variables further analyzed using multivariate analysis. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at $p < 0.05$.[16]

RESULTS

Patient characteristics

During the study period, data on 54 patients with thymic carcinomas were collected from their medical records. Ten patients with insufficient clinical data for analysis and three who had been administered curative treatment, including radiotherapy or salvage thoracic surgery, were excluded; therefore, a total of 41 eligible patients were enrolled. The patient characteristics are presented in Table 1. The median age was 66 years (range: 35–79 years), with 27 (65.9%) men and 14 (34.1%) women. Squamous cell carcinoma was the most common histological type (85.4%). According to the

TABLE 3 Cox proportional hazards model for PFS

Variables	Univariate analysis HR (95% CI)	p-value	Multivariate analysis HR (95% CI)	p-value
Age: <65 vs. ≥65	0.84 (0.42–1.67)	0.614		
Sex: Female vs. male	1.06 (0.5–2.23)	0.879		
ECOG-PS: 0–1 vs. 2–3	0.86 (0.38–1.91)	0.705		
Histology: Other vs. SCC	0.91 (0.35–2.39)	0.845		
Stage (Masaoka–Koga): IVa, post-op. Vs. IVb	1.18 (0.51–2.74)	0.695		
No. of metastatic sites: 1 vs. ≥2	1.39 (0.69–2.81)	0.355	1.26 (0.62–2.57)	0.522
NLR: ≤3.7 vs. >3.7	1.48 (0.75–2.93)	0.255		
Alb: ≥3.5 vs. <3.5	0.93 (0.43–1.99)	0.846	0.67 (0.3–1.49)	0.522
CAR: ≤0.22 vs. >0.22	1.23 (0.61–2.47)	0.559		
LIPI: Good (0) vs. intermediate/poor (1–2)	2.39 (1.1–5.21)	0.0285	2.6 (1.15–5.89)	0.0216

Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; SCC, squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; Alb, albumin; CAR, C-reactive protein-to-albumin ratio; LIPI, lung immune prognostic index.

TABLE 4 Cox proportional hazards model for OS

Variables	Univariate analysis HR (95% CI)	p-value	Multivariate analysis HR (95% CI)	p-value
Age: <65 vs. ≥65	0.96 (0.45–2.01)	0.904		
Sex: Female vs. male	0.54 (0.25–1.14)	0.106		
ECOG-PS: 0–1 vs. 2–3	1.60 (0.72–3.53)	0.247		
Histology: Other vs. SCC	0.89 (0.36–2.21)	0.803		
Stage (Masaoka–Koga): IVa, post-op. vs. IVb	1.17 (0.56–2.43)	0.682		
No. of metastatic sites: 1 vs. ≥2	2.16 (1.03–4.53)	0.043	1.74 (0.78–3.85)	0.174
NLR: ≤3.7 vs. >3.7	1.59 (0.8–3.16)	0.188		
Alb: ≥3.5 vs. <3.5	2.85 (1.29–6.29)	0.00977	2.85 (1.24–6.58)	0.0139
CAR: ≤0.22 vs. >0.22	0.92 (0.44–1.91)	0.819		
LIPI: Good (0) vs. intermediate/poor (1–2)	3.41 (1.38–8.46)	0.008	2.85 (1.08–7.54)	0.0347

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; SCC, squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; Alb, albumin; CAR, C-reactive protein-to-albumin ratio; LIPI, lung immune prognostic index.

Masaoka–Koga stage classification, 12 (29.3%) and 21 (51.2%) patients were classified as stage IVa and IVb, respectively. Regarding the locations of metastatic sites, serosal metastasis was the most prevalent (46.3%), followed by bone and lung metastases (22% each). A total of 18 (43.9%) patients presented multiple metastatic lesions at the time of diagnosis. Regarding laboratory test values, the mean albumin (Alb), CRP, CAR, NLR, dNLR, and LDH values were 3.8 ± 0.5 g/dl, 2.3 ± 3.4 mg/dl, 0.7 ± 1.1, 4.5 ± 2.6, 2.8 ± 1.5, and 266 ± 133 U/ml, respectively. LIPI scores of 0, 1, and 2 were present in 13 (31.7%), 20 (48.8%), and eight (19.5%) patients, respectively. Comparisons of patient characteristics according to LIPI score are presented in Table 2. The intermediate/poor-LIPI group exhibited a higher prevalence of poor performance status (PS) scores of 2 or 3 (good LIPI vs. intermediate/poor LIPI: 15.4% vs. 28.6%), bone metastasis (7.7% vs. 28.6%), and presented more metastatic sites (38.5% vs. 46.4%) than the good-LIPI group; however, none of these differences was statistically significant. Anthracycline with platinum-based chemotherapy was the most frequently administered first-line chemotherapy both in good and intermediate/poor LIPI group (84.6% vs. 89.1%), followed by platinum doublet chemotherapy (15.4% vs. 7.1%). Objective response rate (ORR) and disease control rate (DCR) were slightly higher in the good-LIPI group but not with significant difference. In addition, 30.7% of good-LIPI patients and 28.6% of intermediate/poor-LIPI patients received palliative radiotherapy during their clinical course.

Survival-time analysis

Median progression free survival (PFS) and overall survival (OS) were 7.6 months (95% confidence interval [CI]: 6.5–11.3) and 34.9 months (95% CI: 23.9–41.6), respectively (Figure 1). PFS and OS were both superior in the good-LIPI group (good LIPI vs. intermediate/poor LIPI: PFS, 13.4

vs. 6.8 months, $p = 0.025$; OS, 48.2 vs. 28.9 months, $p = 0.00506$; Figure 2).

Prognostic factors for PFS and OS

The results of univariate and multivariate analyses of PFS and OS using the Cox proportional hazards model are presented in Tables 3 and 4, respectively. Univariate analysis revealed an association between an intermediate/poor LIPI and inferior PFS (hazard ratio [HR] = 2.39, $p = 0.0285$); moreover, an intermediate/poor LIPI was also an independent prognostic factor in multivariate analysis (HR = 2.6, 95% CI: 1.15–5.89, $p = 0.0216$). In univariate analysis of OS, two or more metastatic sites (HR = 2.16, $p = 0.043$), Alb <3.5 g/dl (HR = 2.85, $p = 0.00977$), and an intermediate/ poor LIPI (HR = 3.41, $p = 0.008$) were associated with inferior OS. Multivariate analysis also revealed that Alb <3.5 g/dL [HR = 2.85, 95% CI: 1.24–6.58, $p = 0.0139$) and an intermediate/poor LIPI (HR = 2.85, 95% CI: 1.08–7.54, $p = 0.0347$) were independent prognostic factors for OS.

DISCUSSION

The present study demonstrated that pretreatment LIPI has prognostic potential for patients with thymic carcinoma treated exclusively with palliative intent chemotherapy. Pretreatment LIPI was also associated with PFS for first-line chemotherapy. The patients were divided into the following two groups according to LIPI score: the "good-LIPI group" and "intermediate/poor-LIPI group," based on the study by Mezquita et al.[11] In the intermediate/poor-LIPI group, there were higher rates of poor PS, histological types other than squamous cell carcinoma, and multiple metastatic lesions, and these differences were not statistically significant. In the survival-time analysis, PFS and OS were both significantly shorter in the intermediate/poor-LIPI group. In the multivariate analysis for PFS for the first-line chemotherapy, an intermediate/poor LIPI was an independent adverse prognostic factor. Multivariate analysis for OS revealed that Alb <3.5 g/dl and an intermediate/poor LIPI were independent adverse prognostic factors. Of investigated clinical parameters (NLR, CAR and LIPI), LIPI may have had the superior prognostic potential in this study. To the best of our knowledge, this is the first study to demonstrate the prognostic potential of the LIPI in patients with advanced and metastatic thymic carcinoma.

Recently, a multicenter, retrospective study on advanced thymic carcinoma, involving a comparatively large sample size, was conducted in Japan.[17-19] The results of the study revealed no significant difference in OS between the first-line chemotherapy regimens, whereas tumor staging (Masaoka–Koga stage IVa) was an independent prognostic factor for OS.[17,18] In addition, hypoalbuminemia was identified as an independent prognostic factor.[17] These findings indicate that in patients with advanced or metastatic thymic

carcinoma, clinical characteristics and laboratory findings may have prognostic potential superior to that of chemotherapy regimen. Thus, in the present study, we applied the LIPI and evaluated its clinical utility as a novel prognostic marker in patients with thymic carcinoma.

LDH plays an unfavorable role in various cancers; it is reportedly associated with tumor invasion and proliferation,[20] metastatic potential,[21] and drug resistance.[22] Elevated dNLR indicates a preference for granulocytes and monocytes over lymphocytes, reflecting the promotion of inflammatory dynamics in the tumor microenvironment.[6] The LIPI is a novel clinical indicator initially proposed by Mezquita et al., who validated its prognostic value in NSCLC patients treated with ICIs.[11] In their seminal report, it was suggested that LIPI potentially strengthens the prognostic power of LDH and the dNLR and facilitates better stratification of the patient population. Thereafter, its prognostic value was reported not only in ICIs but also in NSCLC patients treated with epidermal growth factor receptor tyrosine kinase inhibitors[13] and cyto-toxic chemotherapy[12] as well as in patients with small cell lung cancer.[23] In recent years, the LIPI has been applied not only in lung cancer but also in the analysis of other cancer types. In their retrospective analysis of 361 resected esophageal squamous cell carcinomas, Feng et al. reported that a good LIPI was significantly associated with a superior 5-year survival rate, and this was observable at any stage of the disease.[24] Daniel et al. retrospectively analyzed 578 solid-tumor patients, including 145 renal cell carcinoma patients treated with ICIs, and demonstrated that in the renal cell carcinoma cohort, an intermediate/poor LIPI was significantly associated with shorter PFS and OS.[25] Chen et al. also analyzed 108 patients with advanced hepatocellular carcinoma treated with ICIs and found that an intermediate/poor LIPI was significantly associated with a poor disease control rate as well as shorter PFS and OS.[26] To date, the clinical value of the LIPI for advanced thymic carcinoma has not been investigated. Only one observational study suggested that elevated serum LDH is an independent prognostic factor for advanced thymic carcinoma, although, unlike our patient population, it included patients who underwent curative surgical or radio-logical treatment.[27]

Our data revealed that hypoalbuminemia and an intermediate/poor LIPI were significantly associated with unfavorable survival outcomes. Serum albumin is a well-known prognostic marker for several cancer types.[28] In addition to being a nutritional indicator, albumin also acts as a parameter representing inflammatory dynamics, and it is affected by several factors, such as extracellular fluid volume, dehydration status, and inflammatory dynamics. Our results corroborate those of a previous study by Okuma et al., in which hypoalbuminemia was found to be an adverse prognostic factor for OS in advanced thymic carcinoma.[17] Notably, the present study demonstrated that an intermediate/poor LIPI was an independent negative prognostic factor for both PFS and OS. Although there was no significant difference in response rate according to LIPI score, pretreatment LIPI was associated with longer PFS to first-line treatment, which

might have better stratified subsequent long-term survival. We believe that, in advanced thymic carcinoma, for which the optimal chemotherapeutic strategy is debatable, the LIPI, an easy stratification tool, may be beneficial in clinical practice.

This study had certain limitations. First, the small sample size and retrospective nature of this study might have influenced patient background and selection. Due to the small sample size, it was difficult to make a comparison between three LIPI groups; that is, good (0), intermediate (1), and poor (2), as in the previous studies. Thus, the results of this study, which was conducted on a small sample size, should be cautiously interpreted. Even though thymic carcinoma is a relatively rare disease, it is challenging to perform prognostic evaluation on a small sample population; the results of the present study lack external validity. Second, in our study, patients who underwent curative radiotherapy or surgical resection during their clinical course were excluded, whereas those who received palliative radiotherapy were included. As the definition of "palliative radiotherapy" is unclear, there might have been selection bias in the process of patient recruitment. Furthermore, we did not examine treatment beyond second-line chemotherapy; although there is no established strategy for chemotherapy beyond second-line therapy in advanced thymic carcinoma, the course of post-treatment may affect OS.

In conclusion, this is the first study to suggest the clinical benefits of the LIPI in the prognosis of advanced or recurrent thymic carcinoma. The results of the present study suggested that LIPI might be superior to Alb, a universal cancer prognostic marker; the intensity of tumor growth reflected by LDH and the inflammatory dynamics in the tumor microenvironment reflected by dNLR could have better stratified the patients.

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