Original Article

Prognostic value of preoperative serum lactate dehydrogenase in thymic carcinoma

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Background: The prognostic value of serum lactate dehydrogenase (LDH) has been demonstrated in various solid tumors. We attempted to determine whether serum LDH was predictive of survival in thymic carcinoma after surgical resection.

Methods: Ninety-five patients with thymic carcinoma treated in our hospital between January 2005 and December 2015 were retrospectively enrolled. Serum LDH was measured before surgery and categorized as low or high relative to the upper limit of normal (ULN) (225 U/L). The relationships of serum LDH level and other clinical variables with survival were estimated by Cox regression and Kaplan-Meier survival analysis.

Results: Serum LDH levels were found to be significantly associated with overall survival (OS) and progression-free survival (PFS) of these patients. The 1-, 3-, and 5-year PFS were 76%, 51%, and 38%, and the 1-, 3- and 5-year OS were 97%, 75%, and 46%, respectively. Univariate analysis found that high serum LDH (>225 U/L) was associated with both lower OS [hazard ratio (HR) =2.710; 95% confidence interval (CI): 1.363–1.5.391; P=0.004] and PFS (HR =3.365; 95% CI: 1.776–6.374; P<0.001). Multivariate analysis found that high serum LDH was associated with lower PFS (HR =2.122; 95% CI: 1.056–4.267; P=0.035). Moreover, high LDH was significantly associated with advanced Masaoka stage (P=0.001).

Conclusions: High serum LDH (>225 U/L) was an independent predictor of decreased PFS in thymic carcinoma patients. It was also significantly associated with reduced OS, but was not an independent predictor of death in those patients.

Keywords: Thymic carcinoma; lactate dehydrogenase (LDH); 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). Thymic carcinoma, which accounts for 10% of TETs approximately, can be distinguished from thymoma by its clinicopathological and biological characteristics. Unlike thymoma, thymic carcinoma is aggressive and has a generally poor prognosis, with a 5-year survival rate of approximately 40% (2-4). Complete resection is the first line treatment of operable thymic carcinomas; radiotherapy and chemotherapy appear to benefit patients with inoperable or incompletely resected tumors (5-7).

Recently, metabolic reprogramming has been recognized as a hallmark of cancer (8). In the presence of oxygen, most normal cells metabolize glucose to carbon dioxide and water by oxidation of glycolytic pyruvate via the tricarboxylic acid (TCA) cycle, which occurs in the mitochondrial matrix. The reaction produces the reduced form of nicotinamide-adenine dinucleotide (NADH), which participates in mitochondrial oxidative phosphorylation (OXPHOS) to maximize adenosine triphosphate (ATP) production. Cancer cells, on the other hand, preferentially metabolize pyruvate via the glycolysis pathway regardless of available oxygen, which results in production of relatively large amounts of lactate (9) and creates an acidic microenvironment that promotes tumor growth and metastasis (10).

This abnormal metabolic preference for aerobic glycolysis is known as the 'Warburg effect' (11), and the last step in the pathway, conversion of pyruvate to lactate, is reversibly catalyzed by lactate dehydrogenase (LDH). Increased serum LDH levels detected before treatment have been shown to indicate poor prognosis in a number of solid tumors, including breast (12), colorectal (13), gastric (14), and renal cell cancer (15), hepatocellular carcinoma (HCC) (16) and nasopharyngeal carcinoma (NPC) (17). Serum LDH has also been proposed as a biomarker of distant metastasis in the TNM staging of melanoma by the European and American Joint Committee on Cancer (AJCC) (18). In this study, we investigated the possible correlation of serum LDH level with prognosis of thymic carcinoma.

Methods

Patients

A total of 106 consecutive patients with pathologically confirmed thymic carcinoma were treated surgically in the department of Thoracic Surgery of the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, between January 2005 and December 2015. All were considered for inclusion. Eleven patients who received radiotherapy and/or chemotherapy before surgery or had coexistent malignancies or other comorbidities, such as inflammation, anemia, severe lung or liver disease, all of which might influence serum LDH concentration, were excluded. The remaining 95 patients were included in the analysis. Complete resection was possible in 76 patients and subtotal resection or debulking surgery was carried out in 19. Complete resection included thymectomy, dissection of enlarged regional lymph nodes and mediastinal fat tissue, and resection of adjacent invaded tissues. Incomplete resection included subtotal removal and debulking in patients with aggressive lesions that could not be completely removed. Patients with complete resection, who were considered to have a high risk of recurrence based on operative findings, and all those with incomplete resection, were offered postoperative radiotherapy and/or chemotherapy in our department. The study followed the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Informed consent was not required for this retrospective study.

Serum LDH

Serum LDH levels were determined within 1 week of surgery and assayed spectrophotometrically by a standard enzyme-based method (Roche Holding AG, Basel, Switzerland) in the clinical laboratory of our hospital following the standards of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). The normal reference range of serum LDH was 135–225 U/L, and the coefficient of variance of the LDH assay was <6.0%. Patients were stratified into two groups by LDH concentration; >225 U/L, the ULN, or ≤225 U/L.

Data collection

Patient demographic and clinicopathological characteristics were obtained by review of their medical records. Age, sex, tumor size, serum LDH levels, histologic classification, staging information, surgical approach, and adjuvant therapy were collected. 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). In patients with complete resection, staging and histologic classification were determined by postoperative histopathological analysis. In patients with incomplete resection, intraoperative and pathological findings, description of tumor characteristics, lymph nodes, and distant metastasis mainly depended on systemic physical examination, chest computed tomography (CT) scans, cervical and abdominal ultrasound, and radionuclide whole bone scans, and/or position emission tomography-computed tomography (PET-CT) before surgery. Overall survival (OS) was defined as the interval between the date of surgery and the date of death from any

Table 1 Patient characteristics

Variables	Total
No. of patients	95
Age (years)	
Mean ± SD	52.7±11.1
≤60 [%]	70 [74]
>60 [%]	25 [26]
Sex [%]	
Female	30 [32]
Male	65 [68]
Tumor size, mean ± SD (cm)	6.6±2.9
LDH (U/L)	
Mean ± SD	187.9±59.0
≤225 [%]	71 [75]
>225 [%]	24 [25]
Histologic classification [%]	
Squamous cell	80 [84]
Basaloid	1 [1]
Lymphoepithelioma-like	4 [4]
Neuroendocrine	10 [11]
Masaoka stage [%]	
IIa & IIb	33 [35]
IIIa & IIIb	40 [42]
IVa & IVb	22 [23]
Surgical approach [%]	
Complete resection	76 [80]
Incomplete resection	19 [20]
Adjuvant therapy [%]	
No	23 [24]
Radiotherapy	33 [35]
Chemotherapy	9 [9]
Radiotherapy & chemotherapy	30 [32]
Follow-up (months)	
Median	53
Range	1–130

SD, standard deviation; LDH, lactate dehydrogenase.

cause or the last follow-up. Progression-free survival (PFS) was defined as the interval between the date of surgery and regional disease progression (mainly for cases with incomplete resection), the first recurrence or metastasis, or the last follow-up.

Statistical analysis

Values of continuous variables were expressed as means ± standard deviation (SD) or medians and range. Categorical variables were reported as numbers and percentages. Patients who were alive at the end of follow-up were censored from the analysis of OS. The Kaplan-Meier method was used to calculate the 1-, 3-, and 5-year OS and 1-, 3-, and 5-year PFS. Cox proportional regression analysis was used to determine the significance of associations between each variable, OS, and PFS. Variables found to be associated with survival in the univariate analysis were further tested in a multivariate model stepwise when α=0.05. The association between each continuous variable and LDH level, i.e., ≤225 or >225 U/L, was evaluated using the *t*-test. The association between each categorical variable and LDH level was evaluated using the chi-square test. Kaplan-Meier plots were calculated to estimate survival stratified by significant clinical variables with differences tested for significance by the log-rank test. All tests were two-sided, and P values <0.05 were considered significant. All data were analyzed by SPSS 19.0 (IBM Corp. Armonk, NY, USA).

Results

Patient characteristics

The demographic and clinical characteristics of the 95 enrolled patients are shown in *Table 1*. The Masaoka stage of patients with high LDH levels >225 U/L was more advanced than that of patients with low LDH levels ≤225 U/L (P=0.001). However, serum LDH levels were not significantly associated with age (P=0.214), sex (P=0.769), tumor size (P=0.124) and histologic classification (P=0.928) (*Table 2*).

PFS

During the follow-up period, the 1-, 3-, and 5-year PFS rates were 76%, 51% and 38% respectively. Disease progression (regional progression, recurrence, or metastasis) was observed in 40 patients (42%). In the Cox univariate regression analysis, LDH level (HR =3.365; 95% CI: 1.776–6.374;

Table 2 Characteristics of thymic carcinoma patients by LDH stratification

Variables	LDH (≤225 U/L)	LDH (>225 U/L)	P value
Total numbers	71	24	
Age [%]			0.214
≤60	50 [70]	20 [83]	
>60	21 [30]	4 [17]	
Sex [%]			0.769
Female	23 [32]	7 [29]	
Male	48 [68]	17 [71]	
Tumor size, mean ± SD (cm)	6.1±2.4	8.3±3.4	0.124
Histologic classification (%)			0.928
Squamous cell	60 [85]	20 [83]	
Basaloid	1 [1]	0 [0]	
Lymphoepithelioma-like	3 [4]	1 [4]	
Neuroendocrine	7 [10]	3 [13]	
Masaoka stage			0.001
IIa & IIb	31 [44]	2 [8]	
IIIa & IIIb	29 [41]	11 [46]	
IVa & IVb	11 [15]	11 [46]	

LDH, lactate dehydrogenase; SD, standard deviation.

P<0.001), Masaoka stages IIIa and IIIb (HR =3.772; 95% CI: 1.521–9.353; P=0.004, IVa and IVb (HR =5.490; 95% CI: 2.015–14.958; P=0.001), and surgical approach (HR =2.193; 95% CI: 1.137–4.231; P=0.019) were significantly associated with PFS. Age (P=0.241), sex (P=0.353), tumor size (P=0.477), histological classification (P>0.05) and adjuvant therapy (P>0.05) were not significantly associated with PFS. Cox multivariate regression analysis found that LDH level (HR =2.122; 95% CI: 1.056–4.267; P=0.035), Masaoka stages IIIa and IIIb (HR =3.348; 95% CI: 1.340–8.367; P=0.010), IVa and IVb (HR =4.613; 95% CI: 1.555–13.684; P=0.006), and surgical approach (HR =2.333; 95% CI: 1.168–4.660; P=0.016) remained as independent prognostic factors (*Table 3*). Kaplan-Meier analysis found high serum LDH level was associated with a significantly increased risk of disease progression, recurrence or metastasis (P<0.001, log-rank test) (*Figure 1*).

OS

There were 34 deaths (36%) during follow-up, and Kaplan-Meier analysis indicated 1-, 3-, and 5-year OS rates of 97%, 75% and 46% respectively. Of the 34 deaths, 32 (94%) patients died from tumor progression, 1 (3%) patient died from acute cerebral infarction and 1 (3%) case died from unknown cause. In the Cox univariate regression model, serum LDH level (HR =2.710; 95% CI: 1.363–5.391; P=0.004), Masaoka stages IVa and IVb (HR =3.655; 95% CI: 1.490–8.963; P=0.005), and surgical approach (HR =3.089; 95% CI: 1.5597–6.128; P=0.001) were significantly associated with OS. However, age (P=0.950), sex (P=0.514), tumor size (P=0.772), histologic classification (P>0.05) and adjuvant therapy (P>0.05) were not significantly associated with OS. In the Cox multivariate model, advanced Masaoka stages IVa and IVb (HR =3.056; 95% CI: 1.060–8.815; P=0.039) and incomplete resection (HR =3.054; 95% CI: 1.508–6.182; P=0.002) indicated of increased risk of death, i.e., indicated poor prognosis, while LDH level (P=0.496) was not independently associated with OS (*Table 4*). Kaplan-Meier analysis and log-rank tests found that patients with serum LDH >225 U/L had a significantly shorter OS than other thymic carcinoma patients (P=0.003, *Figure 2*).

Discussion

In this study of serum LDH level and prognosis of thymic carcinoma, we found that increased preoperative serum LDH levels were significantly associated with the Masaoka stage, disease progression, and poor survival. Moreover, when patients were stratified by serum LDH level found that the subgroup with an LDH concentration above the 225 U/L ULN had shorter OS and PFS than the subgroup with a an LDH level at or below the 225 U/L threshold. Furthermore, we found that high serum LDH was significantly associated with an advanced Masaoka stage. Preoperative serum LDH level was an independent prognostic factor of PFS in patients with thymic carcinoma. Although it was not an independent predictor of death, a high preoperative LDH level was associated with decreased OS. Consequently, the results support use of preoperative serum LDH level as a prognostic marker for patients with thymic carcinoma. In addition, both Masaoka stage and complete resection were independent prognostic indicators of OS and PFS in these thymic carcinoma patients, which is consistent with previous reports (20,21). Patients with

Table 3 Univariate and multivariate Cox regression analysis for PFS of thymic carcinoma

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (≤60)						
>60	0.629	0.289–1.367	0.241			
Sex (female)						
Male	0.703	0.334–1.478	0.353			
Tumor size	1.036	0.940–1.142	0.477			
LDH (≤225 U/L)						
>225 U/L	3.365	1.776–6.374	<0.001	2.122	1.056–4.267	0.035
Histologic classification (squamous cell)						
Basaloid	1.779	0.241–13.144	0.572			
Lymphoepithelioma-like	1.958	0.595–6.444	0.269			
Neuroendocrine	1.074	0.415–2.778	0.883			
Masaoka stage (IIa & IIb)						
IIIa & IIIb	3.772	1.521–9.353	0.004	3.348	1.340–8.367	0.010
IVa & IVb	5.490	2.015–14.958	0.001	4.613	1.555–13.684	0.006
Surgical approach (complete resection)						
Incomplete resection	2.193	1.137–4.231	0.019	2.333	1.168–4.660	0.016
Adjuvant therapy (no)						
Radiotherapy	1.309	0.553–3.099	0.540			
Chemotherapy	2.204	0.715–6.797	0.169			
Radiotherapy & chemotherapy	0.865	0.352–2.131	0.753			

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase.

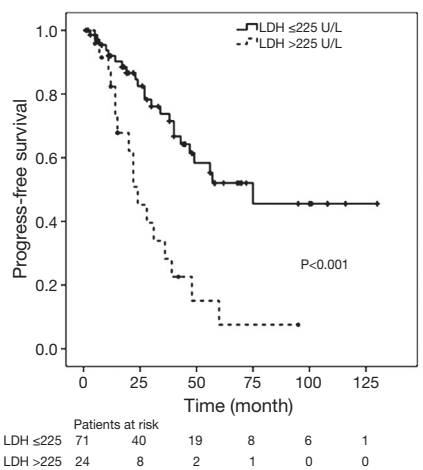

Figure 1 Kaplan-Meier progression-free survival curves stratified by lactate dehydrogenase (LDH) level.

thymic carcinoma and complete resection are known to have better survival than those with incomplete resection (20). The 5-year OS and the 5-year PFS of thymic carcinoma patients in our hospital were comparable to those reported in other retrospective studies (2-4,22,23) (46% *vs.* an average of 40% and 38% *vs.* an average 42%, respectively).

In the 1920s, Otto Warburg observed that lactate was produced almost exclusively during hypoxia and, was not reduced in cancer tissues by the presence of sufficient oxygen, and production even exceeded that of normal tissue. This remarkable phenomenon was termed the "Warburg effect" or "aerobic glycolysis" by Racker and Spector (24). Nevertheless, in succeeding decades, cancer has come to be considered as exclusively driven by the activation of proto-oncogenes and functional deficiency of tumor-suppressor genes (25). Warburg's findings and his

Table 4 Univariate and multivariate Cox regression analysis for OS of thymic carcinoma

Variables	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Age (≤60)						
>60	0.975	0.441–2.155	0.950			
Sex (female)						
Male	1.280	0.611–2.681	0.514			
Tumor size	1.016	0.913–1.131	0.772			
LDH (≤225 U/L)						
>225 U/L	2.710	1.363–5.391	0.004	1.347	0.571–3.179	0.496
Histologic classification (squamous cell)						
Basaloid	2.750	0.364–20.752	0.327			
Lymphoepithelioma-like	1.468	0.443–4.861	0.530			
Neuroendocrine	0.591	0.179–1.953	0.388			
Masaoka stage (IIa & IIb)						
IIIa & IIIb	1.450	0.599–3.511	0.410	1.220	0.500–2.978	0.662
IVa & IVb	3.655	1.490–8.963	0.005	3.056	1.060–8.815	0.039
Surgical approach (complete resection)						
Incomplete resection	3.089	1.557–6.128	0.001	3.054	1.508–6.182	0.002
Adjuvant therapy (no)						
Radiotherapy	0.909	0.374–2.209	0.833			
Chemotherapy	0.461	0.097–2.203	0.332			
Radiotherapy & chemotherapy	0.552	0.215–1.418	0.217			

OS, overall survival; HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase.

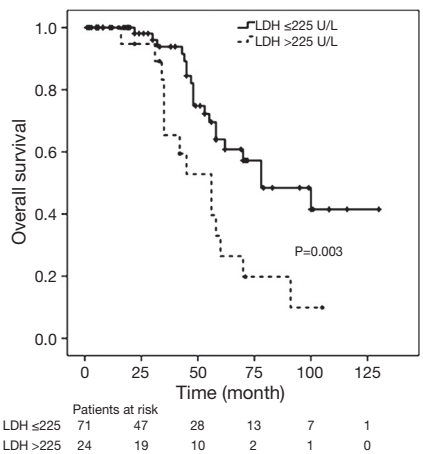

Figure 2 Kaplan-Meier overall survival curves stratified by lactate dehydrogenase (LDH) level.

hypothesis of carcinogenesis were ignored by most cancer researchers until Hanahan and Weinberg demonstrated in 2011 that reprogramming of energy metabolism was an important event in cancer (8,26). The metabolic program of tumor cells continuously adapts to deal with the challenges of harsh environments (27). Hypoxia gradients, which are characteristic of solid tumors (28), induce the constitutive expression of hypoxia-inducible factor (HIF)-1, an important transcriptional factor. HIF-1 is responsible for a nutrient-driven genomic response that allows cancer cells to adapt to hypoxia by increasing glycolysis (29). It just allows cancer cells to metabolize glucose through the glycolysis pathway instead of aerobic respiration. The continued consumption of glucose gives rise to a glycolytic flux that is adequate to produce the ATP needed for tumor

growth. However, pyruvate dehydrogenase (PDH), which transfers pyruvate to the TCA cycle, cannot meet the requirements of high glycolytic flux. Consequently, in tumor cells the pyruvate generated by glycolysis is converted into lactate and protons by LDH (30). Excess lactate and protons produced by glycolysis are secreted from the cytoplasm and produce an acidic microenvironment that promotes cancer cell proliferation, neovascularization, and can even trigger apoptosis of adjacent normal cells, all of which facilitate tumor invasion and metastasis (31-33). The molecular events underlying the Warburg effect are not clearly understood. However, it has been proposed that mitochondrial uncoupling, rather than irreversible OXPHOS defects, drives the metabolic reprogramming of tumor cells (34).

LDH is an enzyme involved in anaerobic glycolysis, and is regulated by the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin (mTOR)-containing complex 1 (PI3K/Akt/mTORC1) signal transduction pathway, tumor hypoxia, or nutrient deprivation (35). It is a cytoplasmic enzyme that reversibly catalyzes the transformation of pyruvate to lactate and protons. It is highly expressed and activated in solid tumors that have increased rates of glycolysis and lactate production. The acidity generated by lactate and protons stimulates epithelial-mesenchymal transition (EMT), invasiveness, and metastatic dissemination of cancer cells, which are correlated with resistance to therapy and poor clinical prognosis (36). This might explain the decreased survival of patients with high serum LDH levels. LDH has two subunits, LDH-A (also known as the M subunit) and LDH-B (also known as the H subunit) that are encoded by separate genes (*A* and *B*). LDH-B is the major form of LDH in serum, while LDH-A, which is present in smaller amounts, is closely correlated with cancer metabolism (37,38). The LDH-A and LDH-B polypeptides form tetramers to generate five LDH isoenzymes, LDH-1 to LDH-5, which have tissue specificity. LDH-1 includes four LDH-B subunits, and LDH-5 includes four LDH-A subunits. LDH-A primarily catalyzes conversion of pyruvate to lactate in hypoxic microenvironments; LDH-B kinetically favors the reverse conversion, i.e., lactate to pyruvate. Increase in the number of LDH-A subunits (LDH-5) in a tetramer favors the conversion of pyruvate to lactate; increase of LDH-B subunits (LDH-1) favors the conversion of pyruvate to acetyl-CoA that enters the TCA cycle (39,40). A recent meta-analysis of 12 studies concluded that LDH-5 overexpression is associated with poor survival in patients with solid tumors, including head and neck squamous cell cancer, colorectal adenocarcinoma, renal clear cell carcinoma, oral squamous cell carcinoma, non-small cell lung cancer (NSCLC), melanoma, gastric cancer, and endometrial cancer (41).

The LDH-1 isoenzyme has been proposed as an important marker of germ cell tumors, particularly ovarian and testicular tumors (42). However, LDH-A and LDH-B have often been studied individually, which may impede a deeper understanding of their roles in cancer metabolism. Recent evidence indicates that the ratio of LDH-B to LDH-A might be a biomarker of tumor aggressiveness, particularly for triple-negative breast cancers (TNBCs) (43), which highlights the importance of interaction between LDH-A and LDH-B in cancer progression.

The prognostic value of serum LDH has been confirmed in both hematological malignancies and solid tumors. High serum LDH level predicts poor survival in diffuse large B-cell lymphoma (DBCL) and is one of the five risk factors included in the International Prognostic Index (IPI) for patients with DBCL (44,45). A recent meta-analysis found that high serum LDH levels were associated with significant HRs of 1.7 (95% CI: 1.62–1.79; P<0.00001) for OS and 1.75 (95% CI: 1.31–2.33; P<0.0001) PFS of patients with solid tumors (46). Other investigators have studied the prognostic value of serum LDH in thymic carcinoma. Wu and colleagues (22) reported that serum LDH level was an independent prognostic factor for both OS and PFS. We did not find an independent relationship of LDH with OS in our patients, but that might be explained by differences in the patient series. Wu *et al.* evaluated 90 patients with advanced thymic carcinoma (Masaoka stages III and IV), but only 62 Masaoka stage III and IV patients were included in our study. Thus, high serum LDH may be an independent predictor of OS in patients with advanced thymic carcinoma. In addition, patients in our series underwent total or subtotal surgical resection, but only 40 of 90 patients (44%) studied by Wu *et al.* underwent surgical resection and the other patients were treated by chemotherapy and/or radiotherapy only. Therefore, the differences in stage of disease and treatment methods may account for the difference in results.

The rarity of thymic carcinoma limited the size of our patient sample. Nevertheless, it was the largest patient series to demonstrate a correlation between serum LDH levels and prognosis of thymic carcinoma. It was also limited by being a retrospective study that evaluated clinical data from only one institution, which may lead to selection bias. Finally, the clinical effects of different LDH subunits

or isoenzymes in predicting survival were not studied due to the lack of laboratory data. Further studies are needed to evaluate the predictive value of various LDH isoforms or isoenzymes in thymic carcinoma.

Conclusions

High serum LDH level (>225 U/L) was an independent marker of poor prognosis in thymic carcinoma patients, indicating decreased PFS. It was also significantly associated with advanced Masaoka stage and decreased OS, but was not an independent predictor of death after surgical resection. Masaoka stage and complete resection were also independent prognostic factors for thymic carcinoma. We recommend use of preoperative serum LDH level in discussing treatment options and possible outcomes with patients. Serum LDH 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 institutional ethics committee board of Cancer Hospital, Chinese Academy of Medical sciences (NO. 16-012/1164).

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