Original Article

Elevated pretreatment serum lactate dehydrogenase level predicts inferior overall survival and disease-free survival after resection of thymic carcinoma

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Background: The prognostic significance of serum lactate dehydrogenase (LDH) level in thymic carcinoma (TC) remains unclear. Therefore, we evaluated the role of pretreatment serum LDH level in the prognosis for TC in this study.

Methods: Sixty consecutive surgical patients were analyzed in this study with pathologic confirmed TC in Sun Yat-sen University Cancer Center from June 1996 to June 2014.

Results: The cut-off value of LDH was 210.50 IU/L. In both univariate analysis and multivariable analysis, only pretreatment serum LDH level (P=0.027) and pathological Masaoka stage (P=0.041) were associated with overall survival (OS). In univariate analysis, pretreatment serum LDH level, tumor size, postoperative radiotherapy (PORT) and pathological Masaoka stage were associated with disease-free survival (DFS) (all P<0.050). Multivariable analysis showed that LDH level (P=0.001), PORT (P=0.001) and pathological Masaoka stage (P=0.038) were independently prognostic factors of DFS. This study also revealed that male patients and larger tumor size had a significantly higher rate of elevated pretreatment serum LDH level than in the other groups.

Conclusions: In conclusion, pretreatment serum LDH level was an independent prognosis factor of OS and DFS for patients with TC.

Keywords: Lactate dehydrogenase (LDH); thymic carcinoma (TC); overall survival (OS); disease-free survival (DFS)

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Introduction

Thymic carcinoma (TC) is relatively rare thymic neoplasms (1), accounts for 10% to 20% of thymic epithelial tumors (2-4). Surgical resection is the mainstay treatment for TC (5). To date, some studies on treatment modality and prognostic factors after surgery of TC have been published (2,4,6-18). However, these issues have not been well clarified.

TC is an aggressive neoplasm of the anterior mediastinum, and is hard to be found until the presence of symptoms such as chest pain, shortness of breath, cough, and hoarseness, caused by the pressure effect of the large tumor burden to

surrounding mediastinal tissues. The large tumor burden might result in elevated serum lactate dehydrogenase (LDH) levels (19). Elevated serum LDH levels were considered as a negative prognostic indicator for many solid tumors, including small-cell lung cancer (20), nasopharyngeal carcinoma (21), germ cell tumors (22), and others. As for TC, no study on serum LDH has been reported.

Therefore, in the present study, medical records of TC patients underwent surgical treatment were retrospectively analyzed. Pretreatment serum LDH levels were evaluated, particularly with respect to their role in prognostic significance of TC.

Methods

Study population

Sixty consecutive surgical patients were analyzed in this study with pathologic confirmed TC in Sun Yat-sen University Cancer Center from June 1996 to June 2014. The inclusion criteria were: (I) histologically confirmed TC and (II) surgical resection. Patients who only underwent surgical biopsy were excluded. Patients' clinical and demographic information (gender, age, symptom, smoking history, alcohol abusing history, family history of any cancer, tumor size, surgical approach, locoregional invasion, completeness of resection, PORT, pre/postoperative chemotherapy, histology, pathological Masaoka stage, recurrence, and prognosis) was retrospectively reviewed. Histologic subtypes were determined by the 2004 World Health Organization (WHO) histologic classification. The stage of TC was classified based on the Masaoka staging system. A waiver of informed consent was requested, and the approval was obtained from independent ethics committees at Sun Yat-Sen University Cancer Center (number of the ethic approval: B2017-041).

Laboratory measurement of LDH

All patients analyzed in this study had serum LDH levels measured at admission for primary treatment. Briefly, 5 mL of peripheral blood was collected, centrifuged at 3,000 g for 5 min at room temperature, and then the plasma sample was carefully separated and transferred to polypropylene tubes. The samples were stored at –20 ℃ until further processing. Levels of LDH were tested by Hitachi Automatic Analyzer 7600-020 (Hitachi High-Technologies, Tokyo, Japan), and the coefficient of variance of a LDH measurement was <5.0%. Normal serum LDH enzyme activities ranged from 109 to 245 IU/L.

Treatment

All patients underwent surgery. Thoracotomy and sternotomy were performed in 43 patients and 17 patients, respectively. Involvement of adjacent organs was confirmed during operation. Pericardium invasion occurred in 24 patients, followed by invasion of the lung in 23 and invasion of the great vessels in 9. Forty-one patients were treated with postoperative radiotherapy (PORT), 4 patients received neoadjuvant chemotherapy, and 22 patients received postoperative chemotherapy.

Follow-up

A follow-up examination was generally carried out every 3 months for the first 2 years and twice a year thereafter. The regular follow-up assessment included physical examination, blood chemistry analysis, tumor markers, computed tomography scan, and ultrasonography. However, examinations were performed sooner if the patient had specific symptoms. The last censoring date for survival was June 2015. Two (3.3%) patients were lost to follow-up. The mean follow-up of patients was 73.3 months ranging from 8.8 to 204.8 months.

Statistical analysis

Overall survival (OS) was measured from the date of surgery to the date of death or last follow-up. Disease-free survival (DFS) was determined as the time interval between date of surgery and the date when recurrence was noted or the date of last follow-up without recurrence for patients with complete resection. The survival curves were generated using the Kaplan-Meier method. Survival differences between the two groups were tested using the log-rank test. Prognostic factors for survival were calculated with Cox regression univariate and multivariate analysis. Any variables reaching P=0.05 were introduced in multivariate analysis. The optimal cut-off value of LDH was determined using X-tile software (http://www.giuspen.com/x-tile/) (23). The chi-square test or Fisher's exact test was applied as appropriate for the comparison of backgrounds of patients with a low level of LDH and patients with a high level of LDH. Two-sided P<0.050 was considered statistically significant. Statistical analysis was performed by SPSS version 16.0 (SPSS,

Chicago, IL, USA) statistical software.

Results

Patient characteristics

The median age was 50 years (range, 13–83 years). Among 60 patients, 47 achieved R0 resection. The most frequent histological subtypes were squamous cell carcinoma (n=37, 61.67%), followed by lymphoepithelioma-like carcinoma (n=11, 18.33%), and other tumors (n=12, 20.00%). The pathological stage distribution according to the Masaoka system was as follows: stage I, 17 (28.33%); stage IIa, 3 (5.00%); stage IIb, 6 (10.00%); stage III, 24 (40.00%); stage IVa, 4 (6.67%); and stage IVb, 6 (10.00%). The clinical and histologic characteristics of these patients are shown in *Table 1*.

Pretreatment serum LDH levels

The median serum LDH levels for the entire cohort was 179.00 IU/L, with values ranging from 109.00 to 685.10 IU/L. The optimal cut-off value of LDH determined by X-tile software was 210.50 IU/L. Of the 60 patients with TC, 39 (65.00%) had pretreatment serum LDH levels less than or equal to 210.50 IU/L, and 21 (35.00%) had serum LDH levels higher than 210.50 IU/L.

Survival and prognostic analysis

The overall 1-, 3-, 5-, and 10-year survival rate were 88.2%, 75.4%, 66.1%, and 62.8%, respectively. The 1-, 3-, 5-, and 10-year DFS rate were 78.7%, 66.8%, 58.5%, and 42.3%, respectively. The 1-, and 3-year survival after recurrence were 53.8%, and 37.8%, respectively. In both univariate analysis and multivariable analysis, only pretreatment serum LDH level (hazard ratio =2.749, P=0.027) (*Figure 1A*) and pathological Masaoka stage (hazard ratio =2.931, P=0.041) were associated with OS (*Table 2*). In univariate analysis, pretreatment serum LDH level (P=0.008) (*Figure 1B*), tumor size (P=0.034), PORT (P=0.029) and pathological Masaoka stage (P=0.005) were associated with DFS. Multivariate analysis was also performed to adjust for various prognostic factors. Consistent with the univariate analysis results, pretreatment serum LDH level (hazard ratio =4.587, P=0.001) was found to be an independent prognostic factor for DFS. PORT (hazard ratio =5.752, P=0.001) and pathological Masaoka stage (hazard ratio =2.841, P=0.038) were also identified as independent prognostic factors for DFS (*Table 3*).

Association between pretreatment serum LDH level and other clinical and histologic characteristics

The elevated pretreatment serum LDH level was associated with male patients (P=0.034) and larger tumor size (P=0.042). However, it was not associated with age, symptom, smoking history, alcohol abusing history, family history of any cancer, surgical approach, completeness of resection, PORT, pre/postoperative thermotherapy, histology, or pathological Masaoka stage (*Table 1*).

Treatment

The treatment modalities are listed in *Table 4*. All patients underwent surgical resection. Forty-seven patients received complete resection and 13 received incomplete resection. Forty-one patients were treated with PORT (prescribed dose ranged from 46 to 70 Gy). Twenty-three patients received chemotherapy (4 patients received neoadjuvant chemotherapy, 8 patients received postoperative chemotherapy, 14 patients received chemoradiotherapy). Among 47 patients with complete resection, 25 patients developed recurrence. After recurrence, 13 patients did not receive any treatment. Two patients received chemoradiotherapy. Nine patients received chemotherapy. One patient underwent surgical resection (*Table 5*).

Discussion

Our study demonstrated several important findings: (I) pretreatment serum LDH was a strong predictor of OS and DFS for TC patients treated with surgical resection; (II) PORT could prolong DFS but not OS; (III) male patients and larger tumor size were associated with elevated pretreatment serum LDH level.

TC is a rare neoplasm that is biologically and morphologically distinct from thymoma (24). According to WHO classification (25), TC was classified as a subtype of thymic epithelial neoplasms, including large cell carcinoma, small cell carcinoma, thymic neuroendocrine carcinoma and some other infrequent entities (3). Due to the limited cases, clinicopathologic features and treatment modalities have not yet been established. Masaoka staging (26) is considered as the most widely used prognostic tool for thymic epithelial neoplasms, however, the reliability is still controversial.

Table 1 Clinicopathological characteristics

Variables	LDH ≤210.50 U/L	LDH >210.50 U/L	P value
Gender			0.034
Male	23	18	
Female	16	3	
Age (year)			0.639
≤60	30	15	
>60	9	6	
Symptom			0.349
Yes	27	12	
No	12	9	
Smoking history			0.978
Yes	15	8	
No	24	13	
Alcohol abusing history			0.718*
Yes	3	3	
No	36	18	
Family history of any cancer			0.423*
Yes	6	1	
No	33	20	
Tumor size (cm)			0.042
≤5	13	2	
>5	26	19	
Surgical approach			0.528
Sternotomy	10	7	
Thoracotomy	29	14	
Completeness of resection			0.974*
Complete	30	17	
Incomplete	9	4	
Postoperative radiotherapy			0.705
Yes	26	15	
No	13	6	
Pre/postoperative chemotherapy			0.101
Yes	12	11	
No	27	10	
Histology			0.805
Squamous cell carcinoma	23	14	
Lymphoepithelioma-like carcinoma	8	3	
Other	8	4	
Pathological Masaoka stage			0.251
I+II	19	7	
III+IV	20	14	

*, Fisher's exact test. LDH, lactate dehydrogenase.

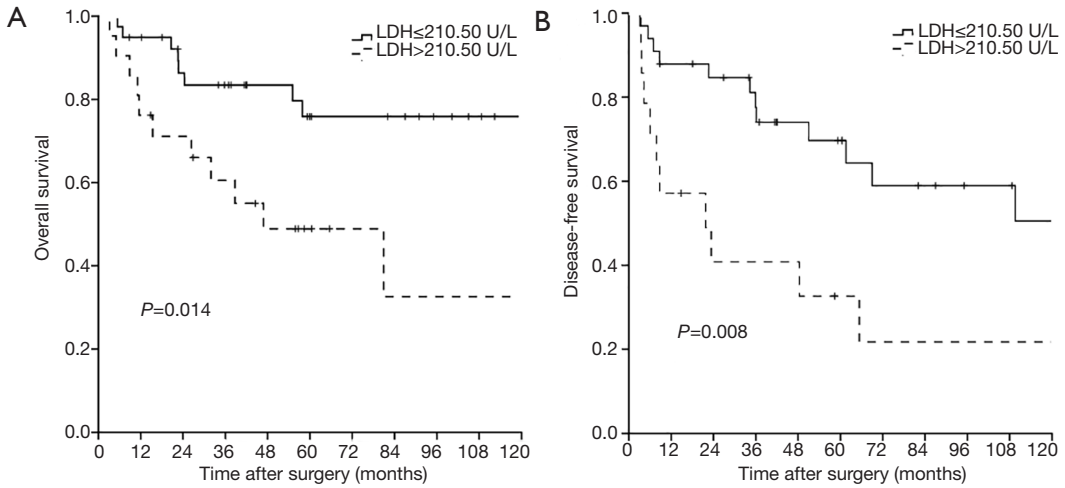

Figure 1 Kaplan-Meier estimation of overall survival and disease-free survival according to LDH levels. Compared to the lower subset (LDH ≤210.50 U/L), elevated serum LDH level (>210.50 U/L) had an inferior overall survival (A) and disease-free survival (B). LDH, lactate dehydrogenase.

Table 2 Univariate and multivariate prognostic factors analysis for overall survival

Variables	Univariate			Multivariate		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Gender			0.188			–
Male	1	Reference		–	–	
Female	0.486	0.162–1.458		–	–	
Age (year)			0.065			–
≤60	1	Reference		–	–	
>60	0.276	0.064–1.192		–	–	
Symptom			0.104			–
Yes	1	Reference		–	–	
No	0.414	0.138–1.241		–	–	
Smoking history			0.809			–
Yes	1	Reference		–	–	
No	0.893	0.356–2.241		–	–	
Alcohol abusing history			0.338			–
Yes	1	Reference		–	–	
No	0.388	0.052–2.899		–	–	
Family history of any cancer			0.462			–
Yes	1	Reference		–	–	
No	0.575	0.129–2.555		–	–	

Table 2 *(continued)*

Table 2 *(continued)*

Variables	Univariate			Multivariate		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Tumor size (cm)			0.136			–
≤5	1	Reference		–	–	
>5	2.482	0.723–8.523		–	–	
Lactate dehydrogenase (U/L)			0.014			0.027
≤210.50	1	Reference		1	Reference	
>210.50	2.907	1.197–7.064		2.749	1.121–6.739	
Surgical approach			0.816			–
Thoracotomy	1	Reference		–	–	
Sternotomy	1.128	0.408–3.118		–	–	
Invasion of lung			0.244			–
Yes	1	Reference		–	–	
No	0.597	0.248–1.436		–	–	
Invasion of pericardium			0.27			–
Yes	1	Reference		–	–	
No	0.596	0.270–1.314		–	–	
Invasion of great vessels			0.283			–
Yes	1	Reference		–	–	
No	2.208	0.503–9.697		–	–	
Completeness of resection			0.095			–
Complete	1	Reference		–	–	
Incomplete	2.181	0.853–5.578		–	–	
Postoperative radiotherapy			0.097			–
Yes	1	Reference		–	–	
No	2.141	0.853–5.377		–	–	
Pre/postoperative chemotherapy			0.415			–
Yes	1	Reference		–	–	
No	0.701	0.297–1.653		–	–	
Histology						
Squamous cell carcinoma	1	Reference	0.429	–	–	–
Lymphoepithelioma-like carcinoma	1.764	0.653–4.763	0.263	–	–	–
Other	0.784	0.219–2.804	0.708	–	–	–
Pathological Masaoka stage			0.023			0.041
I+II	1	Reference		1	Reference	
III+IV	3.07	1.110–8.489		2.931	1.043–8.242	

Table 3 Univariate and multivariate prognostic factors analysis for disease-free survival

Variables	Univariate			Multivariate		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Gender			0.542			–
Male	1	Reference		–	–	
Female	0.767	0.328–1.797		–	–	
Age (year)			0.121			–
≤60	1	Reference		–	–	
>60	0.427	0.146–1.250		–	–	
Symptom			0.192			–
Yes	1	Reference		–	–	
No	0.554	0.228–1.345		–	–	
Smoking history			0.477			–
Yes	1	Reference		–	–	
No	1.351	0.590–3.092		–	–	
Alcohol abusing history			0.844			–
Yes	1	Reference		–	–	
No	0.864	0.201–3.709		–	–	
Family history of any cancer			0.522			–
Yes	1	Reference		–	–	
No	0.669	0.196–2.286		–	–	
Tumor size (cm)			0.034			0.231
≤5	1	Reference		1	Reference	
>5	3.762	1.104–12.818		2.363	0.578–9.649	
Lactate dehydrogenase (U/L)			0.008			0.001
≤210.50	1	Reference		1	Reference	
>210.50	3.001	1.336–6.741		4.587	1.816–11.585	
Surgical approach			0.919			–
Thoracotomy	1	Reference		–	–	
Sternotomy	0.949	0.349–2.585		–	–	
Invasion of lung			0.289			–
Yes	1	Reference		–	–	
No	0.643	0.284–1.455		–	–	
Invasion of pericardium			0.511			–
Yes	1	Reference		–	–	
No	0.770	0.353–1.679		–	–	

Table 3 *(continued)*

Table 3 *(continued)*

Variables	Univariate			Multivariate		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Invasion of great vessels			0.982			–
Yes	1	Reference		–	–	
No	0.987	0.328–2.973		–	–	
Postoperative radiotherapy			0.029			0.001
Yes	1	Reference		1	Reference	
No	2.686	1.104–6.534		5.752	2.065–16.023	
Pre/postoperative chemotherapy			0.259			–
Yes	1	Reference		–	–	
No	0.634	0.287–1.399		–	–	
Histology						
Squamous cell carcinoma	1	Reference	0.244	–	–	–
Lymphoepithelioma-like carcinoma	1.886	0.732–4.859	0.189	–	–	–
Other	2.104	0.756–5.853	0.154	–	–	–
Pathological Masaoka stage			0.005			0.038
I+II	1	Reference		1	Reference	
III+IV	3.326	1.438–7.693		2.841	1.060–7.615	

Table 4 Treatment modality

Variables	n (%)
S alone	11 (18.3)
S + RT	26 (43.3)
S + CT	6 (10.0)
S + CRT	13 (21.7)
CT + S + CT	2 (3.3)
CT + S + RT	1 (1.7)
CT + S + CRT	1 (1.7)

S, surgery; RT, radiotherapy; CT, chemotherapy; CRT, chemoradiotherapy.

Table 5 Treatment after recurrence

Treatment	n (%)
CRT	2 (8.0)
CT	9 (36.0)
S + CT	1 (4.0)
No treatment	13 (52.0)

Compared to thymoma, TC possesses more aggressive biological behavior, with a higher tendency for early relapse (27). Mixture of thymoma and TC may largely result in the stage migration, especially for TC (28,29). Therefore, it is necessary to identify novel prognostic factors.

Our study demonstrated that pretreatment serum LDH was strongly associated with OS and DFS. LDH is a crucial enzyme in the interconversion of pyruvate to lactate in anaerobic glycolysis (30). Commonly, the enzyme is stored in many different types of cell and maintains a relatively low serological level. LDH is abundant in some organs, such as heart, liver, kidney and muscle. When these organs are affected by malignancies, inflammation and toxicity, LDH releases from the cracked cell, which finally results in the elevation of serum LDH level (31,32). Rapid progression of malignancies leads to low-oxygen conditions in tumor microenvironment (33), for adapting to these conditions,

internal anaerobic metabolism of cancer cells is highly activated (34), therefore, LDH acts as a biomarker for tumor burden, and reflects tumor progression and tumor burden (35). In resent, several studies on cancer related elevation of LDH have been reported, and prognostic significance of serum LDH has been verified (21,31,35-38). Similarly, in this study on the prognostic role of LDH in TC, we found that the elevated pretreatment serum LDH level was associated with poor OS and short DFS after resection of TC. It implied that management in patients with high LDH levels should be change. Multimodality therapy, such as neoadjuvant chemotherapy should be considered for these patients.

In addition, we found that the elevated pretreatment serum LDH level was associated with male patients and larger tumor size, which indicated that male patients and larger tumor size might predict the elevated pretreatment serum LDH level.

PORT is usually administrated for TC. However, the role of PORT in TC is still controversial. Due to the rarity of TC, no prospective studies that focused on PORT are available. There are only several large-sample retrospective studies on PORT. Studies from the European Society of Thoracic Surgeons (ESTS) and the Chinese Alliance for Research of Thymoma (ChART) showed that PORT improved OS of TC (4,18). However, studies from the International Thymic Malignancy Interest Group (ITMIG) and the Japanese Association for Research on the Thymus (JART) showed PORT improved DFS but not OS for TC (7,17). The present analysis also showed that PORT improved only DFS but not OS rate of the patients.

Bott *et al.* note that treatment of patients with recurrent or progressive thymic tumors is associated with long-term survival (39). In the present study, the 1-, and 3-year survival after recurrence were 53.8%, and 37.8%, respectively. It indicated that treatments after recurrence such as surgical resection were still effective for patients with TC.

Completeness of resection is an important prognostic factor of TC. Almost all reports on surgical treatment of TC indicate that complete resection is an independent prognostic factor in patients with TC (4,7,17,18). In this study, R0 resection was not associated with OS. The possible explanation was effective PORT and treatments after recurrence.

The major limitations of this study are small series and its retrospective nature. The reference range of LDH was different among different institution, and we used the values specified in our center.

To our knowledge, this is the first study to report pretreatment serum LDH level in relation to prognosis of TC patients treated with surgical resection. In this study, we found that elevated pretreatment serum LDH level was associated with inferior OS and DFS, and might have therapeutic implication for these patients. Since the study was small series, larger prospective study is necessary for verifying the prognostic role of pretreatment serum LDH level in TC in the future.

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None.

Footnote

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

Ethical Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A waiver of informed consent was requested, and the approval was obtained from independent ethics committees at Sun Yat-Sen University Cancer Center (number of the ethic approval: B2017-041).

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