






Characteristics and outcomes of thymomas in Latin America: Results from over 10 years of experience (CLICaP-LATimus)

Claudio Martín¹  | Diego Enrico² | Luis Mas³  | Ana Karina Patane⁴ | Oscar Arrieta⁵ | Tannia Soria⁶ | Andrés F. Cardona^{7,8,9}  | Alejandro Ruiz-Patiño^{8,9}  | Rossana Ruiz³ | Patricia Rioja³  | Sophia Lozano³ | Zyanya Lucia Zatarain-Barrón⁵ | Feliciano Barrón⁵ | Carmen Puparelli¹ | Florencia Tsou¹ | Marcelo P. Corassa¹⁰ | Helano C. Freitas¹⁰ | Vladmir Cláudio Cordeiro de Lima¹⁰ | Leonardo Rojas^{7,9,11} | Camila Ordóñez-Reyes⁸ | Luis Corrales¹² | Carolina Sotelo⁸ | July Rodríguez⁸ | Luisa Ricaurte⁸ | Jenny Ávila⁸ | Pilar Archila⁸ | Rafael Rosell¹³ | Mauricio Cuello¹⁴ | Jordi Remon¹⁵ | CLICaP[†]

¹Thoracic Oncology Unit, Alexander Fleming Cancer Institute, Buenos Aires, Argentina

²Clinical Oncology Department, Alexander Fleming Cancer Institute, Buenos Aires, Argentina

³Thoracic Oncology Unit, Oncology Department, Instituto Nacional de Enfermedades Neoplásicas – INEN, Lima, Peru

⁴Hospital de Rehabilitación María Ferrer, Buenos Aires, Argentina

⁵Thoracic Oncology Unit, Instituto Nacional de Cancerología- INCan, México City, Mexico

⁶Thoracic Oncology Unit, Hospital SOLCA, Quito, Ecuador

⁷Clinical and Translational Oncology Group, Clínica del Country, Bogotá, Colombia

⁸Foundation for Clinical and Applied Cancer Research – FICMAC, Bogotá, Colombia

⁹Molecular Oncology and Biology Systems Research Group (Fox-G), Universidad el Bosque, Bogotá, Colombia

¹⁰Department of Medical Oncology, A C Camargo Cancer Center, São Paulo, Brazil

¹¹Oncology Department, Clínica Colsanitas, Bogotá, Colombia

¹²Thoracic Oncology Unit, Hospital San Juan de Dios/Centro de Investigación y Manejo del Cáncer (CIMCA), San José, Costa Rica

¹³Cancer Biology and Precision Medicine Program at the Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Barcelona, Spain

¹⁴Medical Oncology Department, Hospital de Clínicas, Universidad de la República – UdeLAR, Montevideo, Uruguay

¹⁵Department of Medical Oncology, Centro Integral Oncológico Clara Campal (HM-CIOCC), Hospital HM Delfos, HM Hospitales, Barcelona, Spain

Correspondence

Claudio Martín, Thoracic Oncology Unit, Instituto Alexander Fleming, Crámer 1180, Buenos Aires, Argentina.
Email: cmmartin66@gmail.com

Abstract

Background: Thymomas are a group of rare neoplasms of the anterior mediastinum. The objective of this study was to describe the demographics, clinical characteristics and treatment approaches in Latin America.

Methods: This was a retrospective multicenter cohort study including patients with histologically proven thymomas diagnosed between 1997 and 2018. Demographics,

Claudio Martín, Diego Enrico, Oscar Arrieta, Andrés F. Cardona, and Alejandro Ruiz-Patiño contributed equally to the study.

[†]Latin American Consortium for the Investigation of Lung Cancer.

Disclaimer: Preliminary results from this study were previously presented during the 18th World Conference on Lung Cancer – IASLC (October 4 - 10 2017, Yokohama, Japan).

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd.

clinicopathological characteristics and therapeutic outcomes were collected locally and analyzed in a centralized manner.

Results: A total of 135 patients were included. Median age at diagnosis was 53 years old (19–84), 53.3% ($n = 72$) of patients were female and 87.4% had an ECOG performance score ranging from 0–1. A total of 47 patients (34.8%) had metastatic disease at diagnosis. Concurrent myasthenia gravis occurred in 21.5% of patients. Surgery was performed in 74 patients (54.8%), comprising 27 (20%) tumorectomies and 47 (34.8%) thymectomies. According to the Masaoka-Koga system, overall survival (OS) at five-years was 73.4%, 63.8% and 51%, at stages I–II, III–IVA and IVB, respectively ($p = 0.005$). Furthermore, patients with low lactate dehydrogenase (LDH) (≤ 373 IU/L) at baseline and myasthenia gravis concurrence showed significantly better OS ($p = 0.001$ and $p = 0.008$, respectively). In multivariate analysis, high LDH levels (HR 2.8 [95% confidence interval [CI]: 1.1–7.8]; $p = 0.036$) at baseline and not performing a surgical resection (HR 4.1 [95% CI: 1.3–12.7]; $p = 0.016$) were significantly associated with increased risk of death.

Conclusions: Our data provides the largest insight into the clinical characteristics and outcomes of patients with thymomas in Latin America. Survival in patients with thymomas continues to be very favorable, especially when subjected to adequate local control.

KEYWORDS

cohort studies, Latin America, medical oncology, thymoma

INTRODUCTION

Thymic epithelial tumors constitute the most common tumors in the anterior mediastinum, representing 35% of cases.¹ This heterogeneous and rare entity (0.13 per 100 000 person-year) is histopathologically classified by the World Health Organization (WHO), as thymoma and thymic carcinoma. Thymomas are more frequent and subclassified into five main subtypes (A, AB, B1, B2, B3) according to morphology of the epithelial cells, nontumor lymphocytic component, and similarity with normal thymic tissue.^{2,3} Thymomas are usually staged using the Masaoka-Koga system; however, recently with the aim being to unify criteria, both the eighth TNM classification and the Masaoka-Koga have been used.^{4,5} A locally invasive growth pattern rather than a proclivity to distant metastases characterizes thymomas, contrary to thymic carcinomas which present a higher risk of metastatic spread.^{6,7} As a consequence, median sternotomy and complete resection (thymectomies) remain the standard treatment, usually followed by postoperative radiotherapy according to the risk of relapse.^{8,9} Systemic chemotherapy, based on platinum-based combination regimens, may be administered as a preoperative intention for tumor burden reduction, or in a palliative scenario for unresectable or metastatic tumors. Available guidelines have proposed different treatment strategies for this heterogeneous disease with a low level of recommendation, mainly explained by the lack of prospective multicenter randomized studies.⁹

For this reason, survival analysis from large cooperative studies is crucial to evaluate clinical outcomes. In this context, a retrospective multicenter cohort of patients with thymic epithelial tumors was developed (LATImus) as a joint effort of The Latin-American Consortium for the

Investigation of Lung Cancer (CLICaP). This study aimed to analyze the clinical and pathological outcomes of thymomas for patients in this region.

METHODS

Study population

The Latin-American Consortium for the Investigation of Lung Cancer (CLICaP) conducted this retrospective multicenter cohort study, including patients from Mexico, Peru, Colombia, Ecuador, Brazil, and Argentina with histologically-confirmed thymomas diagnosed between 1997 and 2018. Variables, such as demographics, clinicopathological characteristics, treatment strategies, therapy initiation and discontinuation, and progression dates, were extracted from medical records and registered in a centralized database. Tumor clinical stage was classified according to the Masaoka-Koga staging system, and the histological subtype of thymoma was based on the 2004 WHO classification.^{4,10} Among patients with surgical complete resection, staging, and histological characteristics were determined from the post-surgical pathological report. For patients harboring unresectable or metastatic tumors, pathological findings were reported from biopsy specimens and staging was performed using computed tomography (CT) scans.

Statistical analysis

For descriptive purposes, continuous variables were summarized as arithmetic means, median or interquartile ranges.

Categorical variables were reported as proportions with 95% confidence intervals (95% CIs). Overall survival (OS) was defined from the date of diagnosis until death by any cause or loss to follow-up. Relapse-free survival (RFS) was calculated from date of definitive treatment to date of recurrence or death. The survival curves were performed using the Kaplan–Meier method and differences between groups were calculated using the log-rank test.

Relevant prognostic factors for OS and RFS were analyzed by univariate and multivariate Cox regression models. Although serum lactate dehydrogenase (LDH) concentration at the time of diagnosis has been recognized as a prognostic factor in multiple cancer types, including thymic carcinomas, its role on thymomas is unknown.^{11–13} Thus, LDH level was investigated as a prognostic factor, and according to the median baseline serum LDH, patients were stratified into two groups (≤ 373 or >373 IU/L). The association between categorical and continuous variables with LDH groups was evaluated using the chi-square and *t*-test, respectively. Two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software version 23.0 (SPSS, Inc.).

RESULTS

Patient characteristics

Among the 135 patients, median age at diagnosis was 53 years (range 19–84); females represented 53.3% ($n = 72$), and the majority were Eastern Cooperative Oncology Group (ECOG) 0–1 (87.4%) status (Table 1). A total of 47 patients (34.8%) had metastatic disease at baseline, with a median of two metastatic sites (IQR 1–2). The pathological stage distribution according to the Masaoka-Koga system was stage I: 38 (28.1%); stage II: 14 (10.4%); stage III: 20 (14.8%), stage IVA: 25 (18.5%); and stage IVB: 36 (26.7%). In particular, for 52 patients (38.5%), a histological subtype definition according to the WHO classification was not feasible. Among 104 patients with serum LDH levels at baseline, the median value was 373 IU/L (IQR 216.5–552.5). Of note, patients with advanced disease (stages IVA–IVB) showed a statistically higher serum LDH level ($p = 0.014$) (Table 2 and Figure 1). A total of 29 patients (21.5%) concurred with myasthenia gravis, and two also presented autoimmune disorders at tumor diagnosis, including thyroiditis and peripheral neuropathy. Notably, those patients suffering from myasthenia gravis were more commonly B1–B2–B3 tumor types and had lower baseline LDH (≤ 373) ($p = 0.012$ and <0.001 , respectively) (Table 2 and Figure 1). However, this autoimmune condition was not associated with Masaoka stages ($p = 0.475$).

Treatment characteristics

Surgery was performed in 74 patients (54.8%) comprising 27 (20%) tumorectomies and 47 (34.8%) thymectomies.

TABLE 1 Patient demographics and clinical characteristics

Characteristic ($N = 135$)	n (%)
Age, year – Median (range)	53 (19–84)
Sex	
Male	63 (46.7)
Female	72 (53.3)
Smoking history	
Never	43 (31.9)
Current and former	67 (49.6)
NS	25 (18.5)
ECOG at baseline	
0–1	118 (87.4)
2–4	17 (12.6)
Myasthenia gravis	
Yes	29 (21.5)
No	106 (78.5)
Other autoimmune disorder	2 (1.5)
Histological type (WHO classification)	
A	15 (11.1)
AB	28 (20.7)
B1	11 (8.1)
B2	19 (14.1)
B3	10 (7.4)
NS	52 (38.5)
Stage at diagnosis per Masaoka-Koga system	
I	38 (28.1)
IIa–b	14 (10.4)
III	20 (14.8)
IVa	25 (18.5)
IVb	36 (26.7)
NS	2 (1.5)
Tumor size, mean \pm SD (cm)	9 (4.43)
Surgical approach	
Tumorectomy	27 (20)
Thymectomy	47 (34.8)
Biopsy	16 (11.9)
Preoperative treatment	
Chemotherapy	22 (16.3)
Radiotherapy	15 (11.1)
Radiotherapy and chemotherapy	6 (4.4)
Follow-up (months), median (95% IC)	81.6 (67.8–95.4)

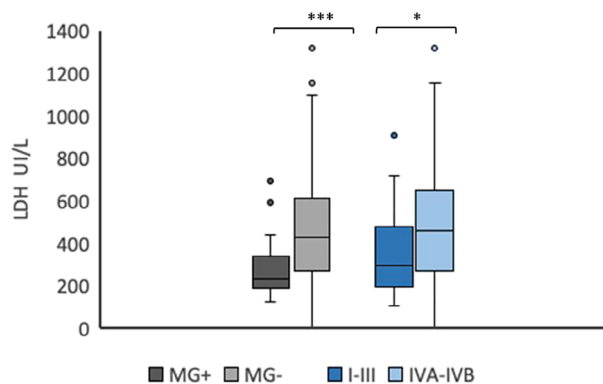
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LDH, lactate dehydrogenase; NS, not specified; SD, standard deviation.

Patients with myasthenia gravis were more likely to receive a thymectomy ($p = 0.014$). R0 resection was achieved in 68.9% of surgical cases. Conversely, preoperative treatment was delivered in 43 cases (31.9%), including chemotherapy ($n = 22$), radiotherapy ($n = 15$), or chemoradiation ($n = 6$). The preferred preoperative chemotherapy regimen was CAP (cyclophosphamide, doxorubicin, and cisplatin) (10, 35.7%),

TABLE 2 Comparison of characteristics of thymoma patients by LDH stratification

Variables, no. (%)	LDH(≤ 373 IU/L) <i>n</i> = 52	LDH(>373 IU/L) <i>n</i> = 52	<i>p</i> -value
Age, year			0.43
≤ 50	26 (50%)	22 (42.3)	
>50	26 (50%)	30 (57.7)	
Sex			1
Male	25 (48.1)	25 (48.1)	
Female	27 (51.9)	27 (51.9)	
Myasthenia gravis			<0.001
Yes	21 (40.4)	5 (9.6)	
No	31 (59.6)	47 (90.4)	
Tumor size, mean \pm SD (cm)	9.29 (4.59)	9.05 (3.98)	0.77
Masaoka stage			0.014
I–III	34 (65.4)	21 (40.4)	
IVA–IVB	18 (34.6)	30 (57.7)	
Histological type (WHO classification)			0.58
A–AB	22 (42.3)	12 (23.1)	
B1–B2–B3	21 (40.1)	15 (28.8)	

Note: Comparisons between groups were performed using the Chi-square test. Missing data were excluded for the statistical analysis. Abbreviations: LDH, lactate dehydrogenase; SD, standard deviation.

**FIGURE 1** Serum LDH level at baseline according to the presence of myasthenia gravis and to Masaoka-Koga stage. Comparison between groups were performed with the *t*-test. **p* ≤ 0.05 ; ****p* ≤ 0.001 . MG, myasthenia gravis

followed by carboplatin and paclitaxel (4, 14.3%). Among patients that underwent surgical resection, adjuvant radiotherapy was offered to 17 patients (23%), chemotherapy to two patients (2.7%), and both to seven patients (9.5%). Overall, 48 patients (35.6%) were exposed to chemotherapy as primary treatment intention, and the regimens employed were CAP (*n* = 22), carboplatin and paclitaxel (*n* = 13), platin and etoposide (*n* = 8), carboplatin and gemcitabine (*n* = 2), others (*n* = 3). The median number of chemotherapy cycles was four (IQR 3–6). Second- and third-line treatments were received by 17 (35.4%) and five (10.4%) patients, respectively. Overall response rate (ORR) and disease control rate (DCR) in the second-line treatment was 29.4% (7/17) and 52.9% (9/17) respectively. Additionally, in

third-line treatment, ORR was 40% (2/5) and DCR 60% (3/5). The median OS from the second and third recurrence was 66.5 and 47.6 months, respectively.

Survival and prognostic analysis

Median follow up was 81.6 months (95% CI: 67.8–95.4). According to the Masaoka-Koga system, the OS at two years was 85.3% among patients with stages I and II disease, 74.3% stages III–IVA, and in stage IVB was 51%. Five-year OS rates were 73.4%, 63.8% and 51%, for stages I–II, III–IVA, and IVB, respectively (*p* = 0.005) (Figure 2(a)). Among patients with local disease, RFS rates at two- and five-years were 76.4%, 58.5% for stage I–II, and 44.2%, 35.4% for stage III, respectively (*p* = 0.024) (Figure 2(b)). Furthermore, patients with low LDH (≤ 373 IU/L) at baseline and myasthenia gravis concurrence showed significantly better OS (*p* = 0.001 and *p* = 0.008, respectively) (Figure 3). In univariate analysis, Masaoka stages (HR 1.812, 95% CI: 1.222–2.687; *p* = 0.003), serum LDH level (HR 4.006, 95% CI: 1.622–9.895; *p* = 0.003), presence of myasthenia gravis (HR 3.315, 95% CI: 1.291–8.511; *p* = 0.013) and surgical resection (HR 4.743, 95% CI: 2.444–9.206; *p* < 0.001) were significantly associated with OS (Table 3). However, in multivariate analysis, high LDH levels (HR 2.814; 95% CI: 1.072–7.784; 0.036) at baseline and not performing surgical resection (HR 4.067; 95% CI: 1.305–12.674; *p* = 0.016) were the only factors significantly associated with an increased risk of death. In the analysis for RFS, Masaoka stages (HR 2.291, 95% CI: 1.088–4.822; *p* = 0.029) and surgical resection (HR 3.221, 95% CI: 1.446–7.175; *p* = 0.004) were

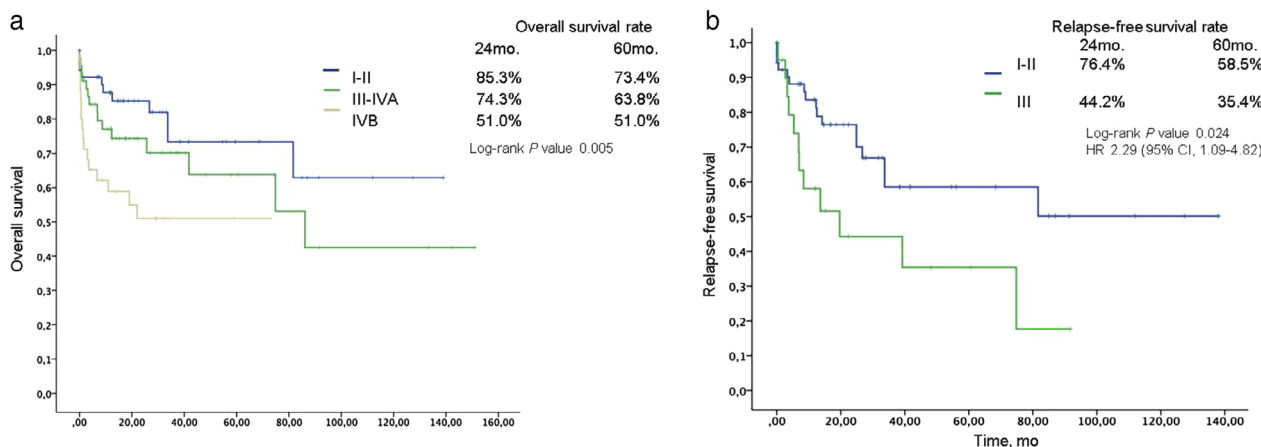


FIGURE 2 (a) Overall survival and (b) relapse-free survival curves according to Masaoka-Koga staging. Curves were performed with Kaplan–Meier methods and compared with the log-rank test

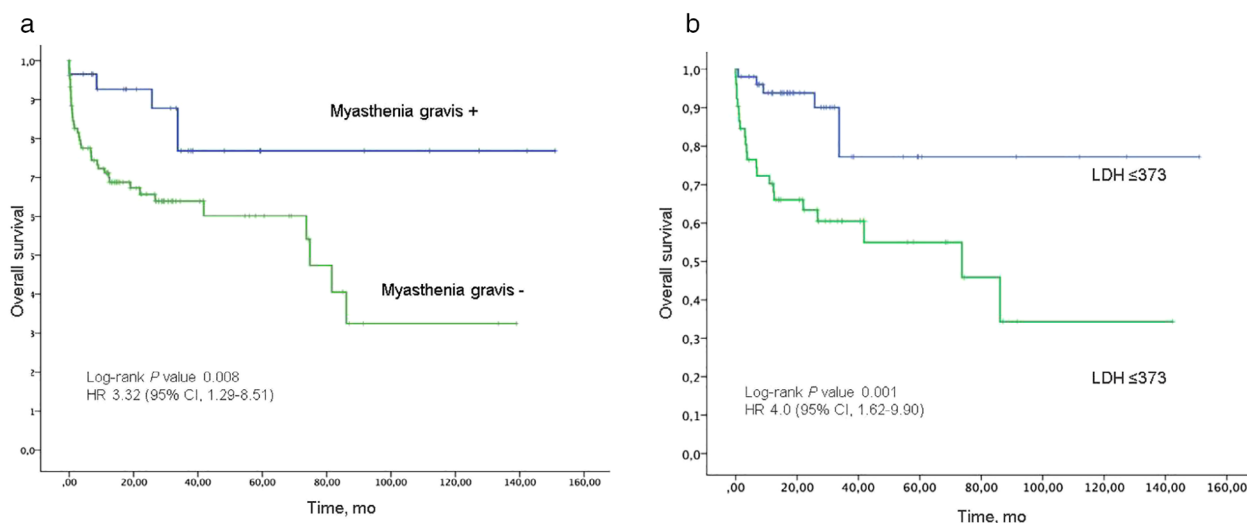


FIGURE 3 (a) Overall survival curves according to the presence or absence of myasthenia gravis at diagnosis, and (b) according to the level of serum LDH at baseline. Curves were performed with Kaplan–Meier methods and compared with the log-rank test

statistically significantly associated with risk of relapse (Table 3).

DISCUSSION

This study represents the largest analysis of clinical characteristics and outcomes of thymomas in Latin American patients. Normally, thymoma is an indolent disease associated with long-term survival. Masaoka-Koga is the routinely used staging system for thymic epithelial tumors and together with the WHO histological classification, represents the most important determinants regarding clinical outcomes.^{4,14} In the present study, we found that Masaoka stage was associated with OS and RFS in the univariate analysis. Although our results are in line with the literature in terms of risk of relapse and survival, this analysis may be difficult

in thymic epithelial tumors since they represent a heterogeneous disease with mixed populations.^{15–20} For this rare tumor, as for most cancer types, the surgical approach remains the most effective treatment to achieve a cure, prolong disease control and improve OS. In terms of reducing local recurrence, complete thymectomy is the preferred strategy.⁹ Evidence shows that in small lesions (usually stage I) without concurrent myasthenia gravis, sole resection of the tumor (thymomectomy) is one of the best treatment options. In this scenario, Tseng et al. reported that recurrence rates following thymomectomy alone versus thymomectomy with thymectomy were not significantly different when analyzing 95 early-stage thymoma patients.²¹ Interestingly, in our cohort, surgical procedure was not only determined by disease burden, but also by the occurrence of myasthenia gravis. It could be explained by the fact that thymomas can be detected in earlier stages in patients

TABLE 3 Univariate and multivariate analysis for relapse-free survival and overall survival

Variable	Overall survival			Relapse-free survival		
	Univariate		Multivariate	Univariate		Multivariate
	HR (95% CI)	p-value	HR (95% CI)	HR (95% CI)	p-value	HR (95% CI)
Masaoka-Koga staging system ^a	1.812 (1.222–2.687)	0.003	1.054 (0.548–2.027)	2.291 (1.088–4.822)	0.029	2.072 (0.719–5.965)
Lactate dehydrogenase (IU/L) ^b	4.006 (1.622–9.895)	0.003	2.814 (1.072–7.784)	1.107 (0.464–2.641)	0.818	1.146 (0.453–2.897)
Myasthenia gravis ^c	3.315 (1.291–8.511)	0.013	1.284 (0.397–4.154)	1.169 (0.497–2.750)	0.721	0.776 (0.265–2.271)
Surgical resection ^d	4.743 (2.444–9.206)	<0.001	4.067 (1.305–12.674)	3.221 (1.446–7.175)	0.004	2.058 (0.555–7.633)

Note: Univariate and multivariate analysis was performed by Cox regression model.

Abbreviations: CI, confidence interval; HR, hazard ratio; LDH, serum lactate dehydrogenase, MG, myasthenia gravis.

^aTVB vs. III–IVA vs. I–II.

^bLDH >373 IU/L vs. ≤ 373 IU/L.

^cNo vs. Yes.

^dNo vs. Yes.

suffering from this autoimmune disorder. However, in our cohort, this procedure was suboptimal with 68.9% of R0 resections in almost a third of thymoma patients who received surgery. Our results clearly showed the relevance of surgery for these cases, since this approach had a significant impact on the OS.

According to the current evidence, a cisplatin-based combination regimen is the preferred option for primary or induction therapy in patients with nonresectable or advanced thymic tumors.²² However, the standard chemotherapy regimen remains unclear given no randomized studies have been conducted in this scenario. Most guidelines recommend CAP regimen (cyclophosphamide, doxorubicin, and cisplatin) as the first option of treatment.^{9,23} In concordance, this combination was the most frequently used in preoperative or advanced settings in our cohort. Additionally, other regimens, supported by phase 2 trials, were used in our patients, such as carboplatin and paclitaxel or platin and etoposide.^{24,25} Of note, a limited number of patients with advanced disease received second or subsequent chemotherapy lines.

As a distinctive feature, thymomas are frequently associated with autoimmune disorders. In this context, myasthenia gravis represent the most common immune-associated entity accounting for between 15%–50% of thymoma patients, particularly type AB, B1, and B2.^{26–29} In our study 21.5% patients concurred with this condition and it was significantly more common in B1–B2–B3 subtypes. Even more interesting, a relevant unsolved issue is whether myasthenia gravis is a prognostic factor in thymoma patients since conflicting results have been published. To address this topic, Margaritora et al. analyzed 317 patients with thymoma from a single institution cohort. They showed that Masaoka staging, WHO classification, and absence of myasthenia gravis were independent prognostic factors for recurrence in multivariate analysis. However, patients suffering from myasthenia gravis presented a significantly better OS.³⁰ Conversely, Zhang et al. analyzed the clinical outcomes of 104 patients with thymoma after thymectomy comparing the clinical outcomes according to occurrence of myasthenia gravis. The multivariate analysis revealed that myasthenia gravis was independently associated with worse survival.³¹ Padda et al. retrospectively reviewed the relationship between autoimmune disorders and thymic epithelial tumors using the International Thymic Malignancy Interest Group (ITMIG) database. They reported that autoimmune syndromes were associated with type B1 thymoma and longer OS (median OS of 21.6 years, $p < 0.0001$). However, it was not significant in the multivariate model for recurrence-free survival and OS.³² Otherwise, different results reported by Yu et al. showed any difference in terms of survival according to myasthenia gravis status.³³ Interestingly, in our study, myasthenia gravis was associated with better survival in the univariate analysis, but not in the multivariate analysis. Further, the group of patients with this condition was associated with a lower LDH. In this respect, it is expected that thymoma is more likely to be found in the earlier stages in patients with

myasthenia gravis. However, in our cohort, no association was observed between Masaoka staging and myasthenia gravis. In summary, the conflicting results of our findings together with previous data hindered a suitable interpretation since the population included in all studies was heterogeneous, presenting at different Masaoka stages and with diverse treatment approaches.

Serum LDH is an enzyme involved in anaerobic glycolysis, which represents a metabolic reprogramming process activated in cancer cells.³⁴ Increased serum LDH level at the time of diagnosis has been recognized as a negative prognostic factor in multiple cancer types, such as melanoma, lymphomas, renal cell carcinoma, hepatocellular carcinoma, germ-cell tumors, and others.^{11,12,35–37} With regard to thymic malignancies, Yuan et al. demonstrated that high serum LDH (>225 IU/L) was an independent predictor of decreased PFS in 95 patients with thymic carcinoma. It was also found that high LDH was significantly associated with advanced Masaoka stage.¹³ Similarly, Liu et al. found that baseline serum LDH level was independently associated with OS and disease-free survival after thymic carcinoma resection. In this case, the cutoff value of LDH was 210.50 IU/L.³⁸ Additionally, Wu and colleagues also reported that serum LDH level was an independent prognostic factor for both OS and PFS in 90 Masaoka III and IV thymic carcinomas.³⁹ Notably, in our cohort, high serum LDH levels were significantly associated with myasthenia gravis and with Masaoka-Koga stages IVA–IVB. Consistently with previous studies, we found that high LDH levels were also significantly associated with reduced OS in both the univariate and multivariate analyses. Given that the preceding reports only included thymic carcinoma patients, as far as we are aware, our study represents the first publication proposing baseline serum LDH level as an independent prognostic factor in thymoma patients.

Finally, our study has limitations, including its retrospective and uncontrolled design. Moreover, patients receiving different treatment according to discretion of the physician may hinder comparisons between groups. The prognostic value of LDH should also be considered with caution since serum level analyses were not centralized. Additionally, in a substantial proportion of our patients, the confirmed histological type per WHO classification was not feasible. It could be explained by the limited number of specialized thoracic oncology units and centralized high-volume pathology departments in Latin America, which may hinder the possibility of an accurate histopathological diagnosis.

In conclusion, our data provide the largest insight into the clinical characteristics and outcomes of patients with thymoma in Latin America. This rare disease has an indolent course with long-term survival rates, compared to other cancer types. It is known that some factors can influence the prognosis, predominantly the Masaoka stage, and the chance of a surgical approach. The presence of myasthenia gravis and low serum LDH at diagnosis were associated with better outcomes in the present study. However, large

prospective studies are needed to validate both parameters as independent prognostic factors.

CONFLICT OF INTEREST

Andrés F. Cardona discloses financial research support from Merck Sharp & Dohme, Boehringer Ingelheim, Roche, Bristol-Myers Squibb and The Foundation for Clinical and Applied Cancer Research – FICMAC. Additionally, he was linked and received honoraria as advisor, participate in speakers' bureau and gave expert testimony to Merck Sharp & Dohme, Boehringer Ingelheim, Roche, Bristol-Myers Squibb, Pfizer, Novartis, Celldex Therapeutics, Foundation Medicine, Eli Lilly and Foundation for Clinical and Applied Cancer Research – FICMAC.

Oscar Arrieta reports personal fees from Pfizer, grants and personal fees from Astra Zeneca, grants and personal fees from Boehringer Ingelheim, personal fees from Lilly, personal fees from Merck, personal fees from Bristol Myers Squibb, grants and personal fees from Roche, outside the submitted work.

ORCID

Claudio Martín  <https://orcid.org/0000-0003-4135-7332>

Luis Mas  <https://orcid.org/0000-0002-2323-9271>

Andrés F. Cardona  <https://orcid.org/0000-0003-3525-4126>

Alejandro Ruiz-Patiño  <https://orcid.org/0000-0003-1274-9273>

Patricia Rioja  <https://orcid.org/0000-0003-3141-7418>

REFERENCES

1. Carter BW, Marom EM, Detterbeck FC. Approaching the patient with an anterior mediastinal mass: a guide for clinicians. *J Thorac Oncol*. 2014;9:S102–9. <https://doi.org/10.1097/JTO.0000000000000294>.
2. Engels EA. Epidemiology of thymoma and associated malignancies. *J Thorac Oncol*. 2010;5:S260–5. <https://doi.org/10.1097/JTO.0b013e3181f1f62d>.
3. Wu J, Fang W, Chen G. The enlightenments from ITMIG consensus on WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting. *J Thorac Dis*. 2016;8:738–43. <https://doi.org/10.21037/jtd.2016.01.84>.
4. Detterbeck FC, Nicholson AG, Kondo K, Schil PV, Moran C. The Masaoka-Koga stage classification for thymic malignancies: clarification and definition of terms. *J Thorac Oncol*. 2011;6:S1710–6. <https://doi.org/10.1097/JTO.0b013e31821e8cfc>.
5. Koppitz H, Rockstroh JK, Schüller H, Standop J, Skowasch D, Müller-Hermelink HK, et al. State-of-the-art classification and multimodality treatment of malignant thymoma. *Cancer Treat Rev*. 2012;38:540–8. <https://doi.org/10.1016/j.ctrv.2011.11.010>.
6. Suster S, Moran CA. Thymoma classification: current status and future trends. *Am J Clin Pathol*. 2006;125:542–54. <https://doi.org/10.1309/CAV8-RNU5-TKNA-CKNC>.
7. Ruffini E, Detterbeck F, Van Raemdonck D, Rocco G, Thomas P, Weder W, et al. European Association of Thoracic Surgeons (ESTS) Thymic working group, tumours of the thymus: a cohort study of prognostic factors from the European Society of Thoracic Surgeons database. *Eur J Cardiothorac Surg*. 2014;46:361–8. <https://doi.org/10.1093/ejcts/ezt649>.
8. Thomas CR, Wright CD, Loehrer PJ. Thymoma: state of the art. *J Clin Oncol*. 1999;17:2280–9. <https://doi.org/10.1200/JCO.1999.17.7.2280>.

9. Girard N, Ruffini E, Marx A, Faivre-Finn C, Peters S. ESMO Guidelines Committee. Thymic epithelial tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(Suppl 5):v40–55. <https://doi.org/10.1093/annonc/mdv277>.
10. Ströbel P, Marx A, Zettl A, Müller-Hermelink HK. Thymoma and thymic carcinoma: an update of the WHO classification 2004. *Surg Today*. 2005;35:805–11. <https://doi.org/10.1007/s00595-005-3047-y>.
11. Petrelli F, Ardito R, Merelli B, Lonati V, Cabiddu M, Seghezzi S, et al. Prognostic and predictive role of elevated lactate dehydrogenase in patients with melanoma treated with immunotherapy and BRAF inhibitors: a systematic review and meta-analysis. *Melanoma Res*. 2019;29:1–12. <https://doi.org/10.1097/CMR.0000000000000520>.
12. Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, et al. An enhanced international prognostic index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood*. 2014;123:837–42. <https://doi.org/10.1182/blood-2013-09-524108>.
13. Yuan Z-Y, Gao S-G, Mu J-W, Xue Q, Mao Y-S, Wang D-L, et al. Prognostic value of preoperative serum lactate dehydrogenase in thymic carcinoma. *J Thorac Dis*. 2016;8:2464–72. <https://doi.org/10.21037/jtd.2016.08.56>.
14. Chen G, Marx A, Chen W-H, Yong J, Puppe B, Stroebel P, et al. New WHO histologic classification predicts prognosis of thymic epithelial tumors: a clinicopathologic study of 200 thymoma cases from China. *Cancer*. 2002;95:420–9. <https://doi.org/10.1002/cncr.10665>.
15. Rea F, Marulli G, Girardi R, Bortolotti L, Favaretto A, Galligioni A, et al. Long-term survival and prognostic factors in thymic epithelial tumours. *Eur J Cardiothorac Surg*. 2004;26:412–8. <https://doi.org/10.1016/j.ejcts.2004.04.041>.
16. Huang J, Detterbeck FC, Wang Z, Loehrer PJ. Standard outcome measures for thymic malignancies. *J Thorac Oncol*. 2010;5:2017–23. <https://doi.org/10.1097/JTO.0b013e3181f13682>.
17. Yuan Z-Y, Gao S-G, Mu J-W, Xue Q, Mao Y-S, Wang D-L, et al. Long-term outcomes of 307 patients after complete thymoma resection. *Chin J Cancer*. 2017;36:36. <https://doi.org/10.1186/s40880-017-0213-8>.
18. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. *Ann Thorac Surg*. 2003;76:878–84. [https://doi.org/10.1016/S0003-4975\(03\)00555-1](https://doi.org/10.1016/S0003-4975(03)00555-1).
19. Detterbeck F, Youssef S, Ruffini E, Okumura M. A review of prognostic factors in thymic malignancies. *J Thorac Oncol*. 2011;6:S1698–704. <https://doi.org/10.1097/JTO.0b013e31821e7b12>.
20. Weis C-A, Yao X, Deng Y, Detterbeck FC, Marino M, Nicholson AG, et al. The impact of thymoma histotype on prognosis in a worldwide database. *J Thorac Oncol*. 2015;10:367–72. <https://doi.org/10.1097/JTO.0000000000000393>.
21. Tseng Y-C, Hsieh C-C, Huang H-Y, Huang C-S, Hsu W-H, Huang B-S, et al. Is thymectomy necessary in nonmyasthenic patients with early thymoma? *J Thorac Oncol*. 2013;8:952–8. <https://doi.org/10.1097/JTO.0b013e31828cb3c2>.
22. Kelly RJ. Systemic treatment of advanced thymic malignancies. *Am Soc Clin Oncol Educ Book*. 2014;34:e367–73. https://doi.org/10.14694/EdBook_AM.2014.34.e367.
23. Ettinger DS, Wood DE, Aisner DL. NCCN clinical practice guidelines in oncology (NCCN guidelines®) thymomas and thymic Carcinomas, National Comprehensive Cancer Network. (2017). https://www.nccn.org/Professionals/Physician_gls/Pdf/Thymic.Pdf. Accessed 7 2017.
24. Lemma GL, Lee J-W, Aisner SC, Langer CJ, Tester WJ, Johnson DH, et al. Phase II study of carboplatin and paclitaxel in advanced thymoma and thymic carcinoma. *J Clin Oncol*. 2011;29:2060–5. <https://doi.org/10.1200/JCO.2010.32.9607>.
25. Giaccone G, Ardizzoni A, Kirkpatrick A, Clerico M, Sahnoud T, van Zandwijk N. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and treatment of cancer lung cancer cooperative group. *J Clin Oncol*. 1996;14:814–20. <https://doi.org/10.1200/JCO.1996.14.3.814>.
26. Evoli A, Lancaster E. Paraneoplastic disorders in thymoma patients. *J Thorac Oncol*. 2014;9:S143–7. <https://doi.org/10.1097/JTO.0000000000000300>.
27. Fujii Y. Thymus, thymoma and myasthenia gravis. *Surg Today*. 2013;43:461–6. <https://doi.org/10.1007/s00595-012-0318-2>.
28. Osserman KE, Genkins G. Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. *Mt Sinai J Med*. 1971;38:497–537.
29. Lewis JE, Wick MR, Scheithauer BW, Bernatz PE, Taylor WF. Thymoma. A clinicopathologic review. *Cancer*. 1987;60:2727–43. [https://doi.org/10.1002/1097-0142\(19871201\)60:11<2727::aid-cncr2820601125>3.0.co;2-d](https://doi.org/10.1002/1097-0142(19871201)60:11<2727::aid-cncr2820601125>3.0.co;2-d).
30. Margaritora S, Cesario A, Cusumano G, Meacci E, D'Angelillo R, Bonassi S, et al. Thirty-five-year follow-up analysis of clinical and pathologic outcomes of thymoma surgery. *Ann Thorac Surg*. 2010;89:245–52. <https://doi.org/10.1016/j.athoracsurg.2009.08.074>.
31. Zhang Z, Cui Y, Jia R, Xue L, Liang H. Myasthenia gravis in patients with thymoma affects survival rate following extended thymectomy. *Oncol Lett*. 2016;11:4177–82. <https://doi.org/10.3892/ol.2016.4528>.
32. Padda SK, Yao X, Antonicelli A, Riess JW, Shang Y, Shrager JB, et al. Paraneoplastic syndromes and thymic malignancies: an examination of the International Thymic Malignancy Interest Group retrospective database. *J Thorac Oncol*. 2018;13:436–46. <https://doi.org/10.1016/j.jtho.2017.11.118>.
33. Yu L, Zhang X-J, Ma S, Jing Y, Li F, Krasna MJ. Different characteristics of thymomas with and without myasthenia gravis. *Ann Surg Oncol*. 2012;19:94–8. <https://doi.org/10.1245/s10434-011-1896-8>.
34. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646–74. <https://doi.org/10.1016/j.cell.2011.02.013>.
35. Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2004;22:454–63. <https://doi.org/10.1200/JCO.2004.06.132>.
36. Faloppi L, Scartozzi M, Bianconi M, Svegliati Baroni G, Toniutto P, Giampieri R, et al. The role of LDH serum levels in predicting global outcome in HCC patients treated with sorafenib: implications for clinical management. *BMC Cancer*. 2014;14:110. <https://doi.org/10.1186/1471-2407-14-110>.
37. Shamash J, Oliver RT, Gallagher CJ, Newland AC, Lister TA, Kelsey S, et al. Pre-induction LDH as a prognostic factor for outcome of high dose chemotherapy (HDCT) for germ cell tumours relapsing or refractory to conventional chemotherapy. *Br J Cancer*. 2000;82:2022–3. <https://doi.org/10.1054/bjoc.1999.1140>.
38. Liu Q, Fu X, Su X, Wang X, Zhang Y, Yang H, et al. Elevated pre-treatment serum lactate dehydrogenase level predicts inferior overall survival and disease-free survival after resection of thymic carcinoma. *J Thorac Dis*. 2017;9:4550–60. <https://doi.org/10.21037/jtd.2017.10.86>.
39. Wu J, Chen H, Shao L, Qiu S, Ni Q, Zheng B, et al. Long-term follow-up and prognostic factors for advanced thymic carcinoma. *Medicine*. 2014;93:e324. <https://doi.org/10.1097/MD.0000000000000324>.

How to cite this article: Martín C, Enrico D, Mas L, et al. Characteristics and outcomes of thymomas in Latin America: Results from over 10 years of experience (CLICaP-LATImus). *Thorac Cancer*. 2021; 12:1328–1335. <https://doi.org/10.1111/1759-7714.13901>