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Histotyping of Indian thymomas: A clinicopathologic study from north India

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***Background & objectives*: Thymomas are rare, but most common anterior mediastinal lesions. The histomorphologic spectrum of thymic epithelial tumours (TETs) in Indian population has not been explored in depth. This study was aimed to assess the histomorphology of TETs in the Indian patients and correlate clinical parameters with pathological features.**

***Methods*: It was a retrospective study conducted in a tertiary referral hospital in north India. All morphologically confirmed cases of TETs since 2009 were included. Clinical details and histology slides were reviewed using the Modified Masaoka-Koga staging system and WHO 2015 classification. Clinicopathological correlation and survival analysis were done. A comparative review from other published Indian studies was performed.**

***Results*: A total of 219 cases of TETs (138 resections and 81 biopsies) were identified. The most common histomorphologic type was B2, and the most frequent stage was I. Types A/AB were common in older age (P<0.01). Clinically, higher stage tumours were found mostly in men (P<0.01), and these were Type B thymomas (P<0.01). Myasthenia gravis was more common in women (P<0.02) and in lower stages (P<0.05). Survival analysis revealed significant association between recurrence and tumour stage. Although thymic carcinoma was diagnosed on biopsy, no resectable case was identified.**

***Interpretation & conclusions*: Our findings showed that the thymomas in Indian patients were most commonly Stage I tumours of B2 and AB histotypes. Resected thymic carcinomas were conspicuously absent in our study. More studies need to be done to establish the frequency and biology of TETs from India.**

Key words Histomorphology - thymic carcinoma - thymic epithelial tumours - thymoma - World Health Organization 2015 classification

Thymomas account for 20-30 per cent of tumours in the antero-superior mediastinum, and are the most common tumour of adults in this location[1]. A spectrum of thymic epithelial tumours (TETs) exists, comprising encapsulated thymoma, invasive thymoma and thymic carcinoma. Although thymomas and thymic carcinomas are histologically distinct, rare cases may demonstrate borderline features between them.

The latest 2015 World Health Organization (WHO) classification, subsequent to the International

Thymic Malignancy Interest Group (ITMIG) consensus[2-4], has revised and refined the histological and immunohistochemical (IHC) diagnostic criteria for a more foolproof and reproducible subtyping for the distinction between thymomas and thymic carcinomas and to differentiate different subtypes of thymomas (Type A and AB vs. Type B1/B2/B3)[2-4].

All global data available regarding TETs exist from the West, and very few studies have been carried out to ascertain their histologic characteristics in the Indian population. Most of the Indian studies available in the literature are based on the clinical and imaging characteristics of thymomas. This study was aimed to evaluate the pathologic spectrum of TETs diagnosed at a tertiary care hospital in India during a period of eight years and determine its morphological and survival characteristics.

Material & Methods

All surgically resected specimens and small biopsies diagnosed as thymoma/thymic carcinomas between July 2009 and October 2017 were retrieved from the archives of the department of Pathology, All India Institute of Medical Sciences (AIIMS), New Delhi, India. The clinical details including age, sex, clinical presentation, status of myasthenia gravis (MG) and other paraneoplastic syndromes (PNS) and follow up status were obtained from the case files. The study protocol was approved by the AIIMS Ethics Committee.

Pathology analysis: Pathology reports and histology slides were reviewed. The tumours were reclassified according to the WHO 2015 classification and staged in accordance with the Modified Masaoka-Koga staging system for thymic malignancies[2,3,5,6]. The variations of histomorphological features in various subtypes of TETs were also recorded.

Follow up and survival: Analysis of survival was performed based on the clinical outcome. Death of a patient due to myasthenic crisis or surgical complications was recorded. Recurrence of the disease was considered as poor prognostic feature.

Statistical analysis: Data analysis was done using statistical software Stata 14.0 (StataCorp LLC, Texas, USA). Categorical data were expressed as frequency and percentage, and quantitative data as mean±standard deviation and median (minimum and maximum). Chi-square/Fisher's exact test, independent *t* test and rank-sum test were used to check the statistical significance of the data. Survival analysis (Kaplan-Meier) was used to check the time to event (death or recurrence) relationship.

For all statistical analyses, Types A and AB thymomas were grouped and Types B1, B2 and B3 were combined as two separate categories of thymoma subtypes. All small biopsies were excluded while correlating the type and stage with survival characteristics. A comparison of survival between operable and inoperable cases was also attempted.

Results

A total of 219 cases of thymomas (138 resections and 81 biopsies) were identified. There was a male preponderance (men 135 and women 84), with a male-to-female ratio of 1.6:1. The age of the patients varied from 17 to 82 yr. The mean age among women was 45.3±13.95 yr and among men was 44.3±14 yr. The resection cases (n=138) were analysed to determine if there were differences in the mean age based on thymoma subtype, consisting of group 1 (Types A and AB) and group 2 (Types B1, B2 and B3), as shown in Table I. Group 1 had 51 and group 2 had 87 participants. The results showed that the mean age of Type A and AB thymomas (48.1±12.3 yr) was significantly (P<0.01) higher as compared to Type B (42.3±12.6 yr), Table I. However, age of the patient had no effect on the stage of disease (Table II).

Types A and AB were almost equally distributed between either sex, but thymomas with Type B histology (B1, B2 and B3) were predominant in men. It was also observed that men had higher stage of the tumour as compared to women (P<0.01) (Table II). The clinical

Table I. Comparison of clinical parameters in different thymoma subtypes of the resection specimens (n=138)

Parameters	Type A/AB (n=51)	Type B1/B2/B3 (n=87)
Age (mean±SD) (yr)	48.1±12.3**	42.3±12.6
Sex (frequency) (%)		
Male	31 (54.3)*	56 (69.1)*
Female	26 (45.6)	25 (30.9)
Tumour size (cm)		
Mean±SD	7.4±3.16	6.7±3.15
Median (minimum-maximum)	7 (2.8-15)	6 (2-18)

*P<0.05 compared to females; **P<0.01 compared to Types B1/B2/B3

Table II. Comparison of clinical parameters in different stages of thymoma (n=125)

Parameters	Stage I (n=70)	Stage II/III/IV (n=55)
Age (mean±SD) (yr)	44±13.1	45.3±13
Sex (frequency) (%)		
Male	33 (45.8)	39 (54.2)**
Female	37 (69.8)	16 (30.2)
Tumour size (cm)		
Mean±SD	6.9±3.3	6.8±3.1
Median (minimum-maximum)	6 (2-7)	6.25 (2-18)
Myasthenia gravis (%)	34/41 (82.9)*	1/3 (33.3)

*P<0.05 compared to Stage II/III/IV; **P<0.01 compared to females

case details were available in 67 cases, of whom 37 cases (55.2%) had presented with features of PNS, of whom 35 had MG, one had pure red cell aplasia (PRCA) and one presented with Cushing syndrome. The rest of the patients had symptoms of either chest pain, cough and breathlessness or were incidentally detected. The association of MG was observed in women (P<0.05) and in lower stage tumours (P<0.05) (Table II). Forty nine of these 67 cases (73.1%) had been surgically resected, whereas the rest were surgically inoperable. Eight of the unresectable cases were lost to follow up, leaving with only 10 unresectable cases to evaluate for survival analysis.

Gross examination: The weight of the tumour ranged from 2.5 to 1000 g. The maximum tumour dimension ranged from 2 to 18 cm, with a mean of 4.2 cm. The size of the tumour had no significant association with histology, stage and the presence of MG in patients.

Histomorphologic findings: The most common histomorphologic type was B2 (46 of 138 cases; 33.3%) followed by AB (39 of 138 cases; 28.2%). Types A, B1 and B3 had 12 (8.7%), 15 (10.8%) and 26 (18.8%) cases in each subtype, respectively.

Type A and AB thymoma: The morphological spectrum of Type A and AB thymomas showed solid sheets, cystic changes, glandular differentiation, rosette formation and meningothelial whorling (Fig. 1A-E). Areas with hemangioma-like features and squamoid differentiation were also seen (Fig. 1C and F). The epithelial component of these cases showed purely spindle cells and an admixture of spindle cells with lymphocytes in Types A and AB, respectively (Fig. 1G). Terminal deoxynucleotidyl transferase (TdT) immunostain failed to detect TdT-positive lymphocytes in abundance (>10% of tumour area or crowded) in Type A thymoma, whereas Type AB tumours showed moderate-to-abundant TdT-positive lymphocytes in the background of a spindle cell tumour (Fig. 1H and I). A few cases which were earlier diagnosed as Type A were reclassified as AB using the new criteria of the current WHO classification, namely (*i*) presence of TdT-positive lymphocytes of at least moderate cell density in >10 per cent of the studied tumour area, or (*ii*) presence of areas with 'crowded' TdT-positive lymphocytes[7]. Three cases showed atypical features such as hypercellularity, atypical mitoses and bizarre nuclei, of which one was Type A (Fig. 2A) and two were Type AB, thereby leading to a reclassification of the first case as atypical Type A thymoma which had a Ki-67 index of 10-12 per cent[7]. Because atypical AB thymoma[8] has not yet been described as a separate entity in the WHO classification[4], the other two cases were designated as 'AB with atypical features'.

Type B1, B2 and B3 thymomas: Type B1 thymomas showed lymphocyte predominance along with network-like pattern on IHC staining with pan-cytokeratin. Type B2 had increased epithelial component as compared to Type B1 along with the presence of prominent perivascular lymph spaces in some cases (Fig. 2B and C). Type B3 looked pink on haematoxylin and eosin (H and E) staining with sheets of epithelial cells that showed nuclear atypia in some cases and sparse population of lymphoid cells (Fig. 2D-F). Seventeen of the 138 cases (12.3%) showed a mixed pattern in various combinations with a predominant histology of one subtype co-existing with minor components of other subtypes. The two most common combinations were predominant Type B2 with B3 as the minor component (8 cases) and predominant Type B3 with B2 as the minor component (5 cases). Focal areas of clear cell change forming approximately 10 per cent of the entire tumour were identified in nine cases (Fig. 2D). The background histology comprised either Type B2 or B3 thymoma. Regressive changes in the form of necrosis, cholesterol clefts, dystrophic calcification and collections of foamy histiocytes were seen concomitantly in some cases (Fig. 3A-D). Sclerosis was a prominent accompanying feature in 12 cases (Fig. 3B).

Small biopsies: There were 81 small biopsies which were provisionally diagnosed as thymomas based on

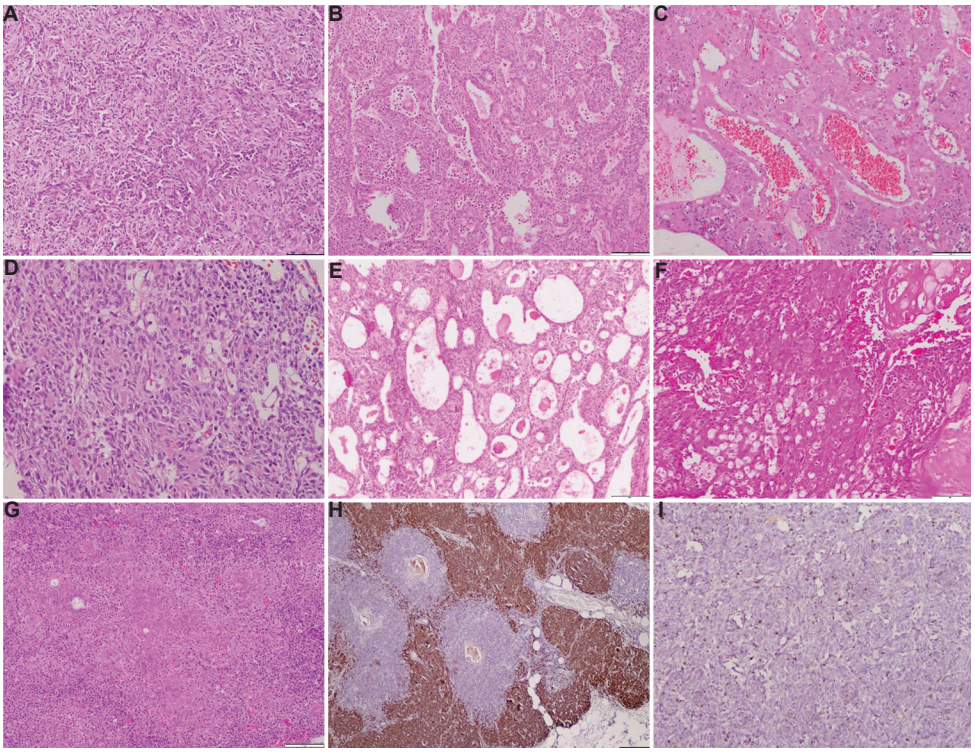

Fig. 1. Photomicrographs of Type A thymoma showing different growth patterns which include (**A**) meningioma-like whorls (H and E, ×100), (**B**) glandular structures (H and E, ×100), (**C**) haemangioma-like areas (H and E, ×100), (**D**) rosettes without a central lumen (H and E, ×200), (**E**) microcystic change (H and E, ×10), (**F**) squamoid areas (H and E, ×100), (**G**) histomorphology of Type AB thymoma (H and E, ×100), and comparison of terminal deoxynucleotidyl transferase immunostain in (**H**) Type AB (×100) and (**I**) Type A thymomas (×200).

the IHC stains for cytokeratin (CK) on epithelial cells and TdT on lymphocytes (77 cases) or carcinomas (4 cases). The resection specimens of these 81 cases were not received either because these were inoperable or were operated at a different hospital. The small biopsies for which subsequent resection specimens were available, were excluded from the total count of small biopsies.

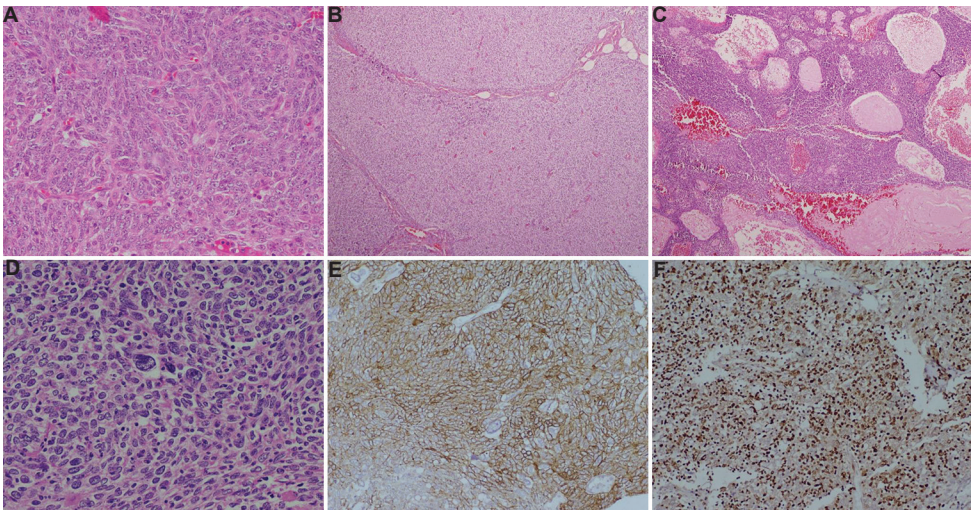

Fig. 2. (**A**) Photomicrograph of atypical A thymoma shows hypercellularity and mitotic figures (H and E, ×200). (**B**) A case of Type B2 thymoma with epithelial-rich areas (H and E, ×40), (**C**) characteristic perivascular spaces (H and E, ×40), (**D**) Type B3 with clear cell change and atypical, pleomorphic, bizarre cells (H and E, ×200), with (**E**) positive immunostain for pan-cytokeratin (×100), and (**F**) high MIB-1 labelling index (×100).

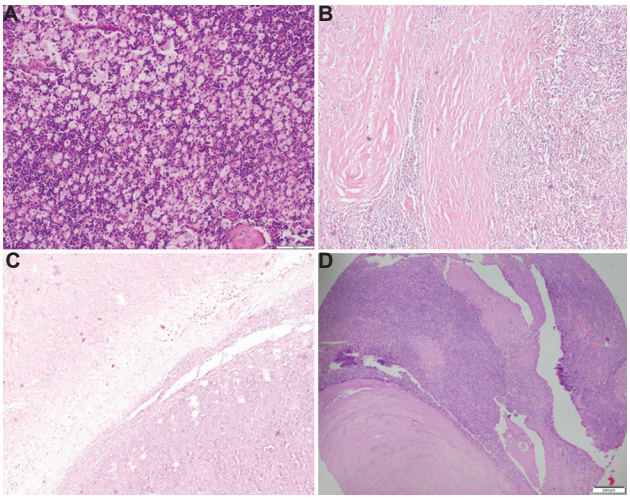

Fig. 3. Regressive changes in the form of (**A**) histiocytic infiltrates (H and E, ×100), (**B**) sclerosis (H and E, ×40), (**C**) necrosis (H and E, ×40) and (**D**) depletion of lymphocytes (H and E, ×40) are seen.

Survival analysis: To perform the survival statistics, it was considered prudent to compare Stages I+II (limited) versus Stages III+IV (advanced disease)[5,9] and different subtypes of thymomas as grouped earlier. The follow up was available in only 67 patients, and the period ranged from two to 87 months, with a median follow up period of 22.6 months. Of these, 14 patients were lost to follow up after a median follow up time of six months; hence, survival analysis could be carried out only for 53 patients. Six patients had died, of whom four deaths were due to myasthenic crisis and two died due to surgery-related complications. The median time to death was 4.5 months, with no significant association with neither the type nor the stage of thymoma. Eleven patients had recurrence with a median time to recurrence of 19 months. The Kaplan-Meier curves revealed that the recurrence of the disease was significantly more in

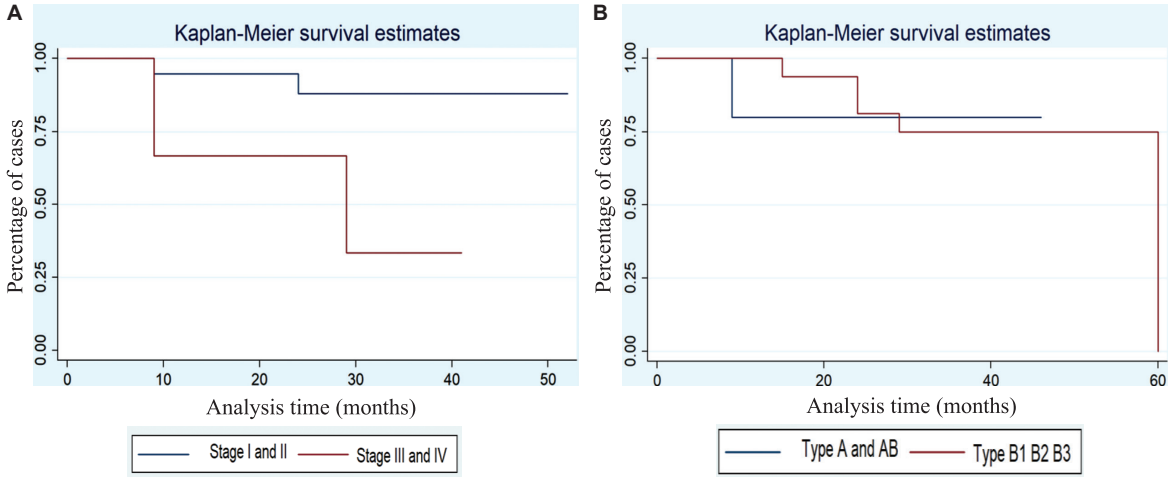

Fig. 4. Kaplan-Meier survival curves with respect to recurrence of tumour. (**A**) Recurrence compared in different stages of tumour (*P* value of log rank test=0.03). (**B**) Recurrence compared in different tumour subtypes (*P* value of log rank test=0.74).

Correlation of histomorphology with stage: Of the 138 resection specimens, stage could not be determined in 13 cases as the tumour in these cases was either received in multiple fragments or was operated in a different hospital, with only a few representative slides received for review. Seventy of the remaining 125 resection cases (56%) were Stage I disease. Stage II, III and IV disease were seen in 39 (31.2%), 14 (11.2%) and 2 (1.6%) cases, respectively. It was noted that patients with higher stage of tumour were mostly men and patients with Stage I disease were mostly women ($P<0.01$). Type A and AB thymomas were predominantly (33 of 47) lower stage, whereas 41 of 55 cases (74.5%) of higher stage tumours were Type B thymomas (Types B1, B2 and B3) ($P<0.01$).

patients with advanced stage ($P<0.05$) (Fig. 4). It had no significant association with the type of thymoma. Almost 87 per cent (21 of 24) of limited stage, 33 per cent (7 of 21) of advanced stage, 80 per cent (12 of 15) of Type A/AB and 75 per cent (25 of 34) of Type B thymomas were surviving at the end of 40-month follow up period. The remaining 36 patients were disease free till the last follow up. Fisher's exact test for the comparison of survival between resectable and unresectable cases was insignificant hence, further survival analysis was not carried out for them.

Discussion

The worldwide incidence of thymomas is about 1.3-2.5 million per year[10]. Its incidence in the Indian

population has not been defined and in the power analysis carried out by Marchevsky *et al*[11], only 20 cases of thymomas were included from India. Among the Indian studies with more than 10 cases[12-20], Julka *et al*[18] had the largest sample with 71 cases (all thymomas) from the same centre; however, histomorphological spectrum was not described in this study. Except for studies by Vaideeswar *et al*[19] and Sundaram *et al*[20], none of the studies assessed the histomorphology of TET, especially thymic carcinomas. Both these studies used the Marino and Muller-Hermilink classification[21,22]. The distinction between thymic carcinoma and Type B3 thymoma also can be challenging, so it is not clear whether the historic reports from India are dealing with 'true' thymic carcinomas according to the current WHO classification or with 'mixtures' of thymic carcinomas and B3 thymomas. The absence of thymic carcinomas in our surgically resected cases may be because these cases present at an advanced stage of the disease when surgical resection may not be a treatment option. Global data have reported no sex predilection for TETs; however, the Indian studies had shown male predominance similar to the observation in the present series[10,14,15,17,18,23]. Only two studies from India demonstrated a female-predominant population[13,16].

Thymomas are frequent in the age group of 40-60 yr but have a wide age range of <10 yr to >80 yr[23]. The thymoma subtype has been found to have significant association with age where patients with Type A and AB are older than those with Type B, resulting in better survival characteristics of the former subtypes[1]. The mean age of Types A and AB thymomas in our study was significantly higher as compared to Type B.

PNS are known to be associated in 50-60 per cent of thymoma cases, of which MG is the most common type. The other commonly associated PNS are Cushing syndrome, PRCA, rheumatoid arthritis, limbic encephalitis and hypogammaglobulinaemia. We also showed a preponderance of MG among the PNS, with only two other cases of PRCA and Cushing syndrome. It was also observed that PNS were more frequently associated with lower-stage tumours but not with histologic subtype. Their association with stage has not been found in other studies; however, it is found to be significant among the lower-stage tumours[24].

The size of thymomas is also known to have prognostic implication as demonstrated by Roden *et al*[25]. The tumours, in our study, varied in size from 2 cm to up to a maximum size of 18 cm, however, showed no substantial association with either the histomorphological type or stage of the disease.

The morphological classification and staging of thymomas have been extensively debated upon since decades[26], with at least 24 histomorphological classifications and 15 staging systems proposed till date[10]. In our study, the latest modifications of WHO 2015 classification of TETs was applied which also led to the reclassification of 24 cases[2,7,27]. The changes which were attributed to the above modifications affected mainly two categories. First, Type A thymomas were reclassified into Type AB by performing IHC for TdT, leading to the identification of small lymphocytic clusters impossible to count or present in >10 per cent of tumour area which were easily missed on hematoxylin and eosin (H & E) sections. Type A thymomas are strongly positive for AE-1-defined acidic keratins, whereas negative for AE-3-defined basic keratins and are always negative for CK20[4]. However, CK immunostaining was not done in our study. Second, thymomas with mixed histology were diagnosed by mentioning the percentages of the second histologic types along with the primary subtype in 10 per cent of increments. While analyzing the data, these were included in the category of the predominant histology. Atypical features such as hypercellularity and pleomorphic enlarged nuclei with increased mitoses were appreciated in a few cases of Type A and AB histology, which led to reclassifying them as atypical A and 'AB with atypical features', respectively. Such tumours with atypical features, especially with the presence of necrosis, even though necrosis was not a feature in our cases, may be associated with poor prognosis[28]. Among the various other histomorphologic features, focal clear cell change was found in nine cases. This finding corroborated with that of Weissferdt *et al*[29] who have stated that clear cell change may be found in thymomas also and may not necessarily be a morphological indicator of clear cell carcinomas.

Type B thymomas were the predominant population, with Type B2 being the most frequent subtype in our study as also seen in the Indian as well as other Asian studies[30]. Among the Type A and AB thymomas, Type AB was predominant with a few cases of Type A morphology. The ITMIG worldwide database[1] revealed a higher frequency of Types AB and B3 in Asians and lower incidences of Types A and B2, which was contrary to our findings. The power analysis carried out by the International Thymoma Study Group, which included a small subset of

Indian patients suggested a study of a larger cohort to establish the characteristics of thymomas in various subpopulations[11]. The current study of 219 patients, in that respect, might reflect a more realistic picture, at least among Indians. While relating the status of MG, no significant difference was observed in the association of MG in either group of thymomas divided on the basis of their type. These findings were not in concurrence with worldwide database as well as with Indian data reporting higher incidence of MG in the Type B subgroup[1,17,24].

The data evaluating the Masaoka-Koga staging revealed a higher prevalence of Stage I tumours. It was also seen that MG was significantly associated with lower-stage lesions. The Indian literature reviewed has also depicted Stage I disease as the most common Masaoka staging except a few study[12,13,18]. The distribution of different histological types in various stages reveals Type A and AB thymomas to present more commonly in lower stages as compared to Type B thymomas[11]. Higher-stage thymomas in our study population belonged to the Type B subtype, with a significant association, the result being in concordance with the ITMIG database[1].

Modified Masaoka staging has been repeatedly proven to be an independent prognostic parameter of overall survival in various studies[25]. The survival analysis of the various thymoma subtypes and their stages could not be satisfactorily formulated in the present study as follow up was available in only 67 cases. The limitation of this study was the lack of adequate clinical follow up of patients and therefore, the inability to demonstrate the representative survival characteristics for all tumour parameters.

Therefore, in conclusion, the thymomas evaluated in our study were most commonly of B2 and AB histotypes, with Types A and AB being found more commonly in older age groups. Most of these were Stage I tumours with good prognosis, and higher-stage tumours were more commonly seen in Type B thymomas. MG was usually associated with lower-stage thymomas. Although the recent WHO 2015 classification led to reclassification of a substantial percentage of thymomas, the prognostic importance of this aspect could not be elucidated in the present study. The difference of the tumour profile in Indian patients as compared to the Western population suggests the uniqueness of these tumours needing molecular characterization and further evaluation. More pathology-centric and genetic studies are needed from India to determine the exact frequency and biology of malignant TETs from this part of the world.

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***Conflicts of Interest*:** None.

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