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Research Paper

Diagnostic and prognostic relevance of inflammatory markers in surgically treated thymic epithelial tumors: An international multicenter study

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ABSTRACT

Background: Complementary prognostic markers are needed in thymic epithelial tumors (TETs) to aid patient stratification and determine the most appropriate follow-up strategies. This study aimed to assess the diagnostic and prognostic relevance of blood-based inflammatory markers in a large cohort of surgically treated TET patients.

Material and Methods: A total of 743 TET patients who underwent surgical resection between 1999–2021 were included in this multicenter study. Inflammatory markers were recorded from the most recent preoperative blood cell count prior to surgery. Measured variables were rescaled and harmonized to obtain comparable values across the participating centers.

Results: Preoperative CRP was significantly higher in TET patients with increased tumor size (vs. those with T1 tumors, $p = 0.035$). Likewise, neutrophil-to-lymphocyte ratio (NLR) ($p = 0.002$) and platelet-to-lymphocyte ratio (PLR) ($p < 0.001$) were both significantly higher in thymic carcinomas than in thymomas. Notably, increased NLR and PLR were mainly attributed to significantly decreased lymphocyte levels in thymic carcinoma patients. Concerning survival outcomes, we found that elevated PLR and fibrinogen influenced overall survival (OS) ($p = 0.002$ and $p = 0.018$, respectively) and cause-specific survival (CSS) ($p = 0.002$ and $p = 0.009$, respectively) independently of other variables in our multivariate models, and they constituted negative prognosticators in TETs. Elevated CRP had an independent negative impact only on OS. Although elevated NLR was linked with impaired prognosis in our univariate model ($p = 0.008$), its independent prognostic significance could not be validated.

Conclusions: Using the so-far largest cohort of surgically treated TET patients, our study demonstrates that CRP, PLR, and NLR have diagnostic significance in TETs, while elevated PLR and fibrinogen constitute independent negative prognosticators for OS and CSS. Accordingly, the current multicenter study offers additional guidance in developing personalized surveillance protocols in thymoma and thymic carcinoma.

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1. Introduction

Thymic epithelial tumors (TETs) are relatively rare (0.2–1.5 % of all malignant tumors), yet they represent the most frequent neoplasms in the anterior mediastinum [1,2]. With regard to histological characteristics, TETs constitute a unique spectrum of malignancies, with thymomas being specific to the thymus, while neuroendocrine neoplasms and carcinomas are often similar to those seen in other organs [1]. Due to this remarkable histological heterogeneity [3], the classification of TETs has been controversial and elusive for decades.

According to the WHO classification (that is primarily based on organotypic features and cellular composition), TETs include thymomas (types A, AB, B1, B2, B3) and thymic carcinomas (type C) [4]. Thymomas arise from thymic epithelial cells and are characterized as low or intermediate-grade malignancies with favorable survival outcomes [1,5]. Autoimmune and paraneoplastic manifestations, such as neuromuscular disorders like myasthenia gravis (MG), are frequently linked with these less aggressive histological types [6]. Meanwhile, thymic carcinomas exhibit increased invasiveness, metastatic capacity, and a higher propensity for recurrence [5]. Like other carcinomas, they tend to occur in a slightly higher age group and are associated with worse prognosis than thymomas [1,7]. At present, Masaoka–Koga and TNM stagings are also used to stratify thymomas and thymic carcinomas [8,9]. Moreover, the classification of TETs was strongly reinforced recently by new molecular findings.

The molecular landscape of TETs started delineating when a TCGA study revealed four molecularly distinct spectrums of tumors within TETs [3,5,10]. These subtypes mirror the WHO histological classification and are defined by specific genomic hallmarks. Subtype 1 is primarily represented by type B thymomas and is heavily enriched with cases presenting with MG. Meanwhile, subtype 2 corresponds to thymic carcinoma and is characterized by a high tumor mutation burden and frequent chromosome 16q loss. Tumor suppressors such as *p53* are frequently downregulated in this subtype, whereas oncogenic alterations are upregulated. Subtype 3 consists of AB thymomas, with a high prevalence of *GTF2I* mutations and abundant lymphocytic infiltration. Lastly, subtype 4 is a mix of types A and AB and has a high incidence of *GTF2I* and *HRAS* somatic mutations [10]. Of note, another TCGA-based study has compellingly demonstrated the feasibility of classifying TETs into separate groups based on *GTF2I* mutation and chromosomal stability [11].

Although the WHO classification of TETs has revealed prognostic relevance [4,12], it is currently debatable which of the abovementioned molecular findings should have an impact on clinical management. Indeed, the biological complexity of TETs can result in heterogeneous and widely divergent clinical outcomes even amongst patients of similar stage or histology [13]. Therefore, complementary prognostic markers are needed to aid in patient stratification and determine the most appropriate follow-up strategies. Concerning genomic alterations, the expression of cancer-testis antigens like *SAGE* and *GAGE7* is associated with impaired prognosis in type B2 and B3 thymomas [14]. In thymic carcinomas, high *GAD1* DNA hypermethylation and high mRNA and protein expression levels are suggestive of an adverse clinical course [15]. Similar to small cell lung cancer (SCLC) [16] and non-SCLC [17], some POU2F3-positive thymic carcinomas share a unique gene expression profile with normal chemosensory tuft cells and have tuft cell–like phenotype. However, POU2F3 expression is not associated with prognosis in TETs [17]. Given the potent immunogenicity of thymic tumors, it is assumed that blood-based inflammatory markers might serve as prognostic markers in TETs [18]. In fact, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have already been demonstrated to represent robust prognostic factors in various solid malignancies, along with other markers of inflammation such as fibrinogen [19–21]. Regarding the role of inflammatory markers in TETs, elevated pre-treatment NLR and PLR have been shown to be consistently associated with higher tumor stages and more advanced Masaoka Koga stages [22,23]. Nevertheless, due to the moderate cohort size, studies evaluating the independent prognostic relevance of these markers in thymomas and thymic carcinomas yielded conflicting results [22,23]. Therefore, in this study, we aimed to determine the diagnostic and prognostic relevance of blood-based inflammatory markers in a large multicenter cohort of surgically treated TET patients.

2. Material and methods

2.1. Study population and treatment

This multicenter study included histologically confirmed TET patients who underwent surgical resection in the following European medical centers: National Koranyi Institute of Pulmonology and National Institute of Oncology, Budapest, Hungary (cohort #1, n = 329); Medical University of Vienna, Vienna, Austria (cohort #2, n = 162); and Ruhrlandklinik – University Duisburg-Essen, Essen, Germany (cohort #3, n = 252). All patients underwent open or video-assisted thymectomy between January 1999 and December 2021. The diagnosis of TET was histologically confirmed from resected specimens, using specific antibodies when needed. Adjuvant therapeutic approaches were conducted according to the contemporary National Comprehensive Cancer Network guidelines [24], with no differences across the host institutes. Staging was performed according to both the TNM and Masaoka-Koga systems, and the WHO classification was also considered. Clinical and follow-up data were collected from the available medical records and/or records from the Central Statistical Office of the given country. Meanwhile, laboratory parameters were recorded from the most recent preoperative blood cell count prior to surgery. Inflammatory ratios such as PLR and NLR were calculated by dividing the absolute platelet and neutrophil counts by the total count of lymphocytes. Since specific comorbidities might significantly impact the absolute value of inflammatory laboratory parameters, patients with acute or chronic inflammatory diseases such as rheumatoid arthritis were excluded from the study.

2.2. Data harmonization across multiple patient cohorts

Given the multicenter nature of the study, certain laboratory parameters were determined by different methods and/or equipment. Thus, in order to obtain comparable values across the participating centers, it was essential to rescale and harmonize the measured variables. For a given laboratory parameter p, with normal reference range $(N_{p,c}^{min}, N_{p,c}^{max})$ in patient cohort treated at center c, the harmonized $\overline{M}_{p,i}$ values were calculated with the following formula, given the originally measured value of $M_{p,i}$ for patient i:

$$\overline{M}_{p,i} = \frac{M_{p,i} - N_{p,i\in c}^{min}}{N_{p,i\in c}^{max} - N_{p,i\in c}^{min}} \bullet \frac{1}{n_p}\left(\sum_{c=1}^{n_p} N_{p,c}^{max} - \sum_{c=1}^{n_p} N_{p,c}^{min}\right) + \frac{1}{n_p}\sum_{c=1}^{n_p} N_{p,c}^{min}$$

where n_p is the number of treatment centers with available data for laboratory parameter p. Essentially, values were rescaled to harmonized reference ranges defined by the mean reference range of various treatment centers. Supplementary Fig. 1 shows the distribution of the harmonized laboratory parameter values across all patients. Further data harmonization steps are detailed in Supplementary material

2.3. Statistical analyses

All statistical analyses were performed in R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The diagnostic relevance of laboratory parameters and inflammatory ratios were assessed by Mann-Whitney U tests performed in a pairwise manner. Resulting p-values were adjusted for multiple testing with the Bonferroni-correction. Correlations of laboratory parameters and disease stage (as numeric

variable) were calculated using Pearson correlation. The value of linear correlation coefficient (r) varied from − 1 to 1 both values inclusive. Of note, in case of correlation analysis, the Holm-method was used as correction for multiple comparisons. Clinicopathological characteristics were statistically analyzed by $\chi 2$ test and Kruskal-Wallis rank sum test. Concerning WHO classification, patients with type B thymomas were primarily grouped together to prevent overcategorization, which could reduce statistical power and increase the likelihood of quasi- or complete separation in survival model fitting. Survival curves of different patient groups were estimated by Kaplan–Meier plots and the differences between the groups were compared using the log-rank test. Overall survival (OS) was defined as the elapsed time in months between surgery and the last available follow-up or death of any cause. Meanwhile, cause-specific survival (CSS) represents the interval (expressed in months) between surgery and the last available follow-up or death from TET. The cause of death was determined by reviewing the patients' final death certificates. Of note, individuals with unknown causes of death were not included in CSS-related measurements. Median follow-up time was calculated using the reverse-censored Kaplan–Meier approach. Multivariate analysis was performed using a Cox regression model. To avoid non-convergence of the likelihood function in traditional Cox-regression, the coxphf function of the corresponding R package

Table 1
Patient characteristics according to clinicopathological variables and disease stage.

	Total (n = 743)	Cohort #1 (n = 329)	Cohort #2 (n = 162)	Cohort #3 (n = 252)	p value
Gender					
female	391 (52.6 %)	188 (57.4 %)	87 (53.7 %)	115 (45.6 %)	0.026[a]
male	352 (47.4 %)	141 (42.6 %)	75 (46.3 %)	137 (54.4 %)	
Age (years)					
Median (Range)	59.0 (15.0, 86.0)	58.0 (20.0, 82.0)	57.0 (16.7, 86.0)	61.0 (15.0, 83.0)	0.017[b]
Diabetes					
NA	234	72	162	0	
no	456 (89.6 %)	225 (87.5 %)	0	231 (91.7 %)	0.128[a,c]
yes	53 (10.4 %)	32 (12.5 %)	0	21 (8.3 %)	
Hypertension					
NA	233	71	162	0	
no	300 (58.8 %)	134 (51.9 %)	0	166 (65.9 %)	0.001[a,c]
yes	210 (41.2 %)	124 (48.1 %)	0	86 (34.1 %)	
COPD					
NA	233	70	162	1	
no	451 (88.4 %)	236 (91.1 %)	0	215 (85.7 %)	0.053[a,c]
yes	59 (11.6 %)	23 (8.9 %)	0	36 (14.3 %)	
Myasthenia gravis					
NA	0	0	0	0	
no	598 (80.5 %)	266 (80.9 %)	120 (74.1 %)	212 (84.1 %)	0.04[a]
yes	145 (19.5 %)	63 (19.1 %)	42 (25.9 %)	40 (15.9 %)	
Other malignancy					
NA	163	1	162	0	
no	487 (84.0 %)	274 (83.5 %)	0	213 (84.5 %)	0.748[a,c]
yes	93 (16.0 %)	54 (16.5 %)	0	39 (15.5 %)	
WHO classification					
NA	31	16	14	1	
A	78 (11.0 %)	34 (10.9 %)	16 (10.8 %)	28 (11.2 %)	0.016[a]
AB	155 (21.8 %)	66 (21.1 %)	23 (15.5 %)	66 (26.3 %)	
B	376 (52.8 %)	179 (57.2 %)	75 (50.7 %)	122 (48.6 %)	
C	103 (14.4 %)	34 (10.8 %)	34 (23.0 %)	35 (13.9 %)	
Masaoka-Koga stage					
NA	139	139	0	0	
I	235 (38.9 %)	60 (31.6 %)	44 (27.2 %)	131 (52.0 %)	<0.001[a]
II	228 (37.7 %)	98 (51.6 %)	75 (46.3 %)	55 (21.8 %)	
III	68 (11.3 %)	15 (7.9 %)	20 (12.3 %)	33 (13.1 %)	
IV	73 (12.1 %)	17 (8.9 %)	23 (14.2 %)	33 (13.1 %)	
TNM stage					
NA	61	61	0	0	
I	462 (67.7 %)	229 (85.5 %)	95 (58.6 %)	138 (54.8 %)	<0.001[a]
II	92 (13.5 %)	19 (7.1 %)	28 (17.4 %)	45 (17.9 %)	
III	57 (8.4 %)	2 (0.7 %)	20 (12.3 %)	35 (13.9 %)	
IV	71 (10.4 %)	18 (6.7 %)	19 (11.7 %)	34 (13.4 %)	

[a] Pearson's Chi-squared test (adjusted for multiple comparisons); [b]Kruskal-Wallis rank sum test (adjusted for multiple comparisons); [c]concerning cohorts #1 and #3; NA, not available; COPD, chronic obstructive pulmonary disease; Cohort #1, National Koranyi Institute of Pulmonology and National Institute of Oncology, Budapest, Hungary; Cohort #2, Medical University of Vienna, Vienna, Austria; Cohort #3, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany.

(version 1.13.4) was utilized, which implements the Firth's penalized maximum likelihood bias reduction method to get finite confidence intervals. Model performance was assessed by calculating the concordance value. See Supplementary material for additional details concerning statistical analyses.

2.4. Ethics statement

The study was conducted in accordance with the guidelines of the Helsinki Declaration of the World Medical Association and with the approval of the national or local Ethics Committees of participating countries (approval numbers: Medical Research Council of Hungary – IV/5198–1/2021/EKU for cohort #1, The Ethic Committee of the Medical University of Vienna – EC#1053/2016 for cohort #2 and The Ethic Committee of the Medical Faculty of University Duisburg-Essen – 17–7775-BO for cohort #3). Data sharing, synchronization and pooled analysis were coordinated by the Medical University of Vienna (cooperation agreement number: 020622, DC-number: 2022–047). Due to the retrospective nature of the study, the requirement for written informed consent was waived. Tissue and data collection were approved in all institutions. After clinical information was collected, patient identifiers were removed, and subsequently, patients could not be identified either directly or indirectly.

3. Results

3.1. Characteristics of the study population

A total of 743 surgically treated TET patients were included in the study, whose clinicopathological characteristics are summarized in Table 1. The total patient pool comprised 609 (85.5 %) thymoma and 103 (14.4 %) thymic carcinoma cases, as per the WHO classification. Concerning thymic carcinoma, all tumors exhibited classical squamous cell carcinoma histology except for two cases of thymic adenocarcinoma and one case of thymic mucoepidermoid carcinoma. No detailed information on WHO classification was available in 31 cases. The median age of included patients was 59 years (range: 15–86). All individuals had a Caucasian background, and 391 of them were female (52.6 %). 19.5 % of individuals had symptoms of MG at presentation. At pathological diagnosis, 76.6 % and 23.4 % of patients had Masaoka-Koga stage I-II and III-IV, respectively. 10.4 % of all TET patients had stage IV disease based on the TNM classification. With regards to comorbidities, 41.2 % and 11.6 % of patients had coexisting hypertension and COPD, respectively, and individuals originating from patient cohort #1 presented with hypertension more frequently than those from cohort #3.

3.2. Diagnostic relevance of inflammatory markers

The diagnostic relevance of each marker was assessed by using the full cohort after data harmonization, whenever possible. In cases where a marker was unavailable in one or more cohorts, the reduced dataset was used. As shown in Fig. 1, elevated CRP levels were characteristic of increased tumor size. Accordingly, CRP was significantly higher in TET patients with T3 tumors (vs. T1 tumors, $p = 0.035$, Fig. 1A) and mean CRP levels were constantly rising with the tumor size. As for the WHO classification, inflammatory ratios were diagnostic for histological patterns. Namely, both NLR ($p = 0.002$) and PLR ($p < 0.001$) were significantly higher in thymic carcinoma than in type B thymoma (median

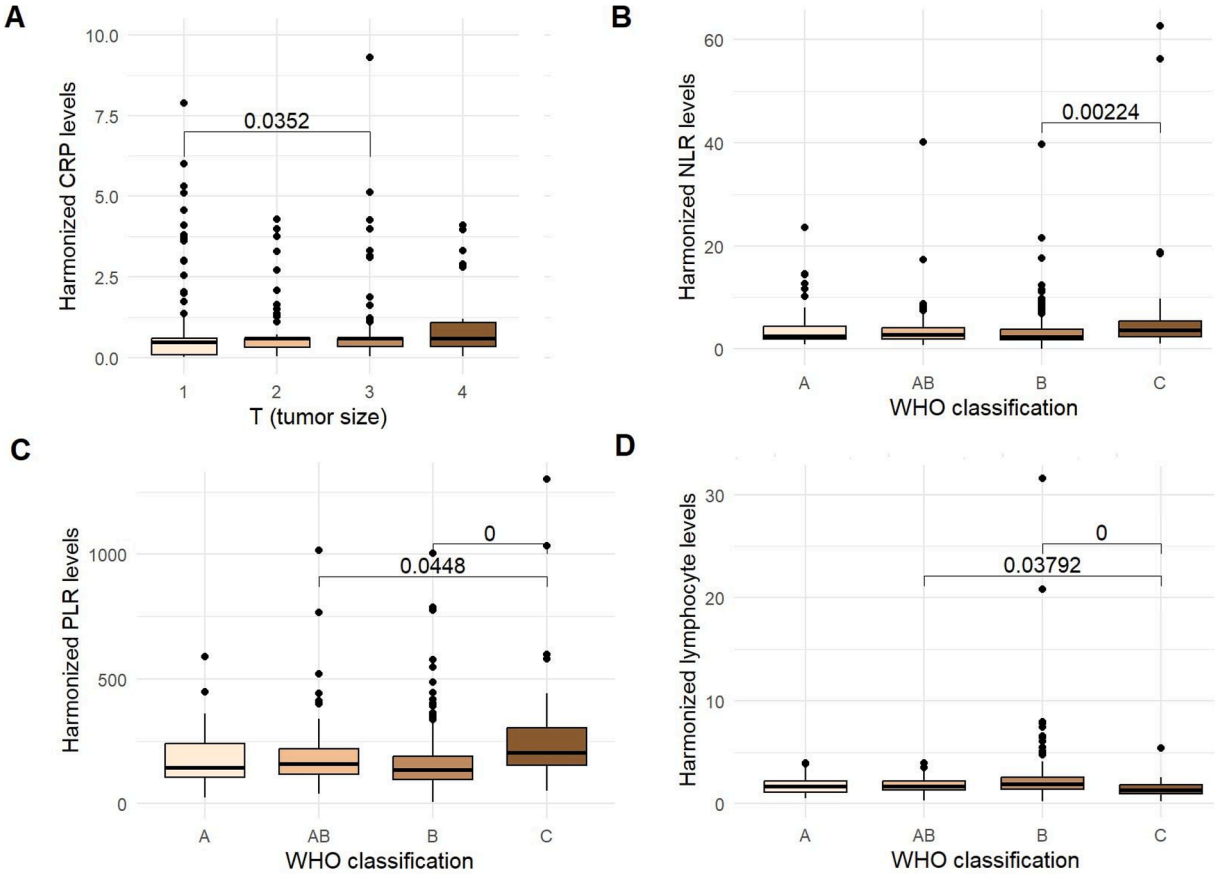

Fig. 1. Diagnostic relevance of blood-based inflammatory markers in TETs. (***A***) High preoperative CRP levels are significantly associated with increased tumor size. Elevated NLR (***B***) and PLR (***C***) are characteristic of thymic carcinomas (type C TETs). (***D***) Lymphocyte level is significantly lower in patients with type C tumors than in those with type B or AB thymomas (medians: 1.32, 1.93 and 1.72 g/L, respectively). Abbreviations: TET, thymic epithelial tumor; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

values were 3.62 vs. 2.34 and 209.18 vs. 136.65 for NLR and PLR, respectively). Decreased lymphocyte levels were as well associated with thymic carcinoma ($p = 0.037$ and $p < 0.001$). NLR and PLR did not differ significantly between B thymoma subgroups; however, both inflammatory ratios increased progressively from type B1 to B3 thymomas (Supplementary Fig. 2A-B). Meanwhile, lymphocyte levels consistently decreased across type B thymomas, with the highest levels detected in B1 thymomas and the lowest in type B3 (Supplementary Fig. 2C). Notably, inflammatory markers were diagnostic neither for the overall TNM stage nor for the Masaoka-Koga stage. Correlations between inflammatory parameters and the extent of TETs according to each study cohort are shown in Supplementary Fig. 3. Next, we assessed whether the investigated immune biomarkers are associated with the occurrence of MG among TET patients. Although the presence of MG had no statistically significant impact on the preoperative level of inflammatory markers after multiple correction testing, the average level of CRP, WBC, neutrophils, fibrinogen, NLR, and PLR was higher in MG patients (vs. those without known MG, Supplementary Fig. 4). The preoperative level of blood-based markers did not predict the type of recurrence in our cohort (Supplementary Fig. 5).

3.3. PLR and fibrinogen level are independent negative prognosticators in surgically treated TETs

The median follow-up time for patients in the full cohort was 69.7 months, whereas the median OS was 226 months. First, we performed a

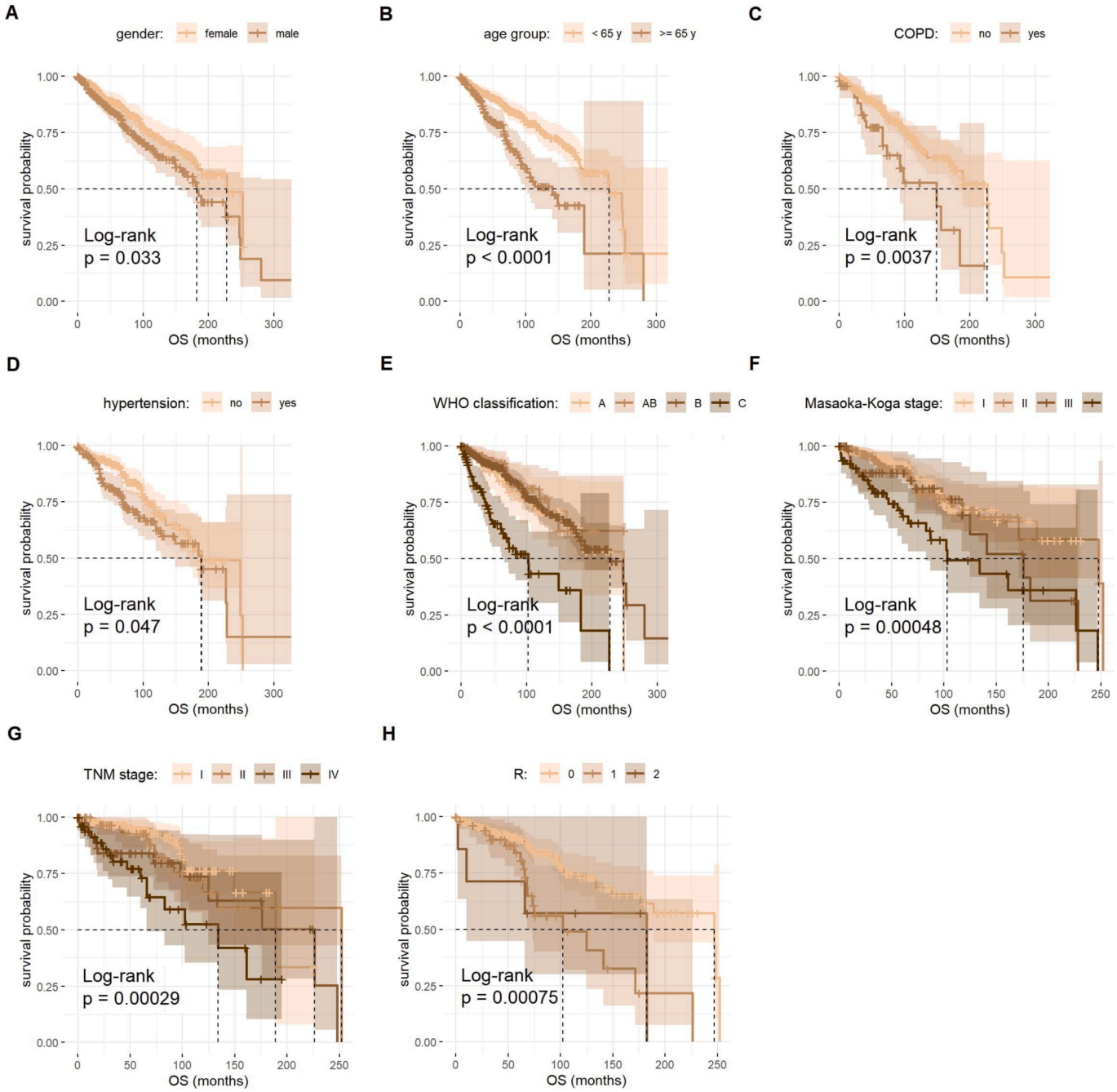

Fig. 2. Kaplan-Meier estimates for OS according to clinicopathological characteristics associated with statistical significance. Kaplan-Meier curves comparing OS of TET patients with regards to (***A***) gender, (***B***) age, (***C***) COPD, as comorbidity, (***D***) hypertension, as comorbidity, (***E***) WHO classification, (***F***) Masaoka–Koga stage, (***G***) TNM stage, and (***H***) resection margins (R). Differences between different groups were compared using the log-rank test. Abbreviations: OS, overall survival;

univariate survival analysis in order to identify clinical prognostic factors for OS (Fig. 2). Female gender (vs. males, p = 0.033, Fig. 2A) and younger age (<65 vs. ≥ 65 years, p < 0.001, Fig. 2B) were both associated with improved survival outcomes. Concerning the comorbidities, we found that patients with COPD exhibited significantly impaired OS compared to those without this lung disease (median OSs were 149 vs. 226 months, respectively; HR 0.64, p = 0.003, Fig. 2C). Likewise, diagnosed hypertension was linked with poor survival outcomes (p = 0.047, Fig. 2D). As expected, the WHO classification, the Masaoka-Koga stage, and the TNM stage of the TET had a significant impact on prognosis. Accordingly, higher Masaoka Koga and TNM stages (p < 0.001 and p < 0.001, respectively), as well as thymic carcinoma (p < 0.001), were all associated with impaired survival (Fig. 2E-G). With regards to type B thymomas, although the median OS was shorter in patients with B3 tumors (vs. B2 and B1), the survival outcomes did not differ significantly across these patients (Supplementary Fig. 6). Incomplete histological margins (tumor cells at the surgical margin) had a negative impact on OS (p < 0.001, Fig. 2H). We found no significant associations between OS and other clinicopathological variables such as MG, diabetes, or adjuvant therapy.

Next, we examined the prognostic value of inflammatory markers and other preoperative lab values. We grouped patients into low and high categories as shown in the Supplementary materialbased on their preoperative lab parameters and found that high CRP (≥0.6 mg/dL), neutrophil (≥3.82 g/L), thrombocyte (≥322.38 g/L), fibrinogen (≥506.2 mg/dL), and TSH (≥ 1.72 mIU/L) levels were all suggestive of worse OS compared to those with low levels (Fig. 3A-E). In contrast, in our univariate models, high lymphocyte (≥ 1.98 g/L), RBC (≥4.85 g/L), Hgb (≥13.9 g/dL) and albumin (≥43 g/L) values were significantly associated with improved OS (vs. low levels; Fig. 3F-I). We could not gain prognostic information from the preoperative WBC and LDH levels. With regards to the inflammatory ratios, we found that high (≥3.76) NLR values were associated with impaired survival outcomes in surgically resected patients (versus low NLR; median OSs were 171 vs. 247 months, respectively, p = 0.008; Fig. 3 J). Importantly, TET patients with high (≥201.66) preoperative PLR levels also had significantly shorter OS (versus those with low PLR; median OSs were 171 vs. 247 months, respectively; p < 0.001, Fig. 3 K).

In order to assess if the prognostic value of inflammatory markers was independent of other clinically relevant variables, we performed multivariate Cox-regression analyses. The models were adjusted for factors such as age, gender, WHO classification (type A, AB, B and C) and

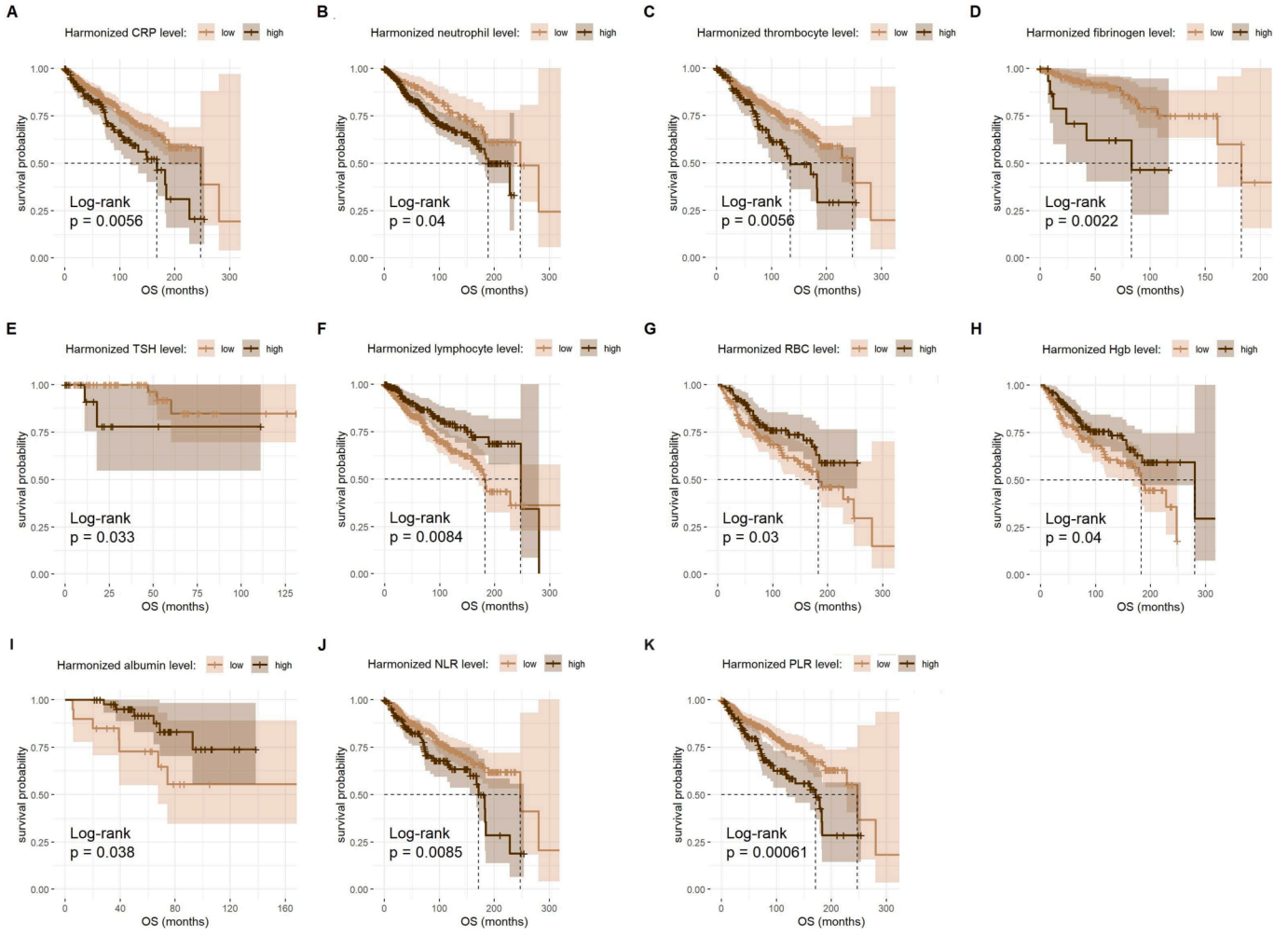

Fig. 3. Kaplan-Meier estimates for OS in surgically treated TET patients according to the preoperative values of blood-based inflammatory makers. Patients with high (***A***) CRP (p = 0.005), (***B***) neutrophil (p = 0.04), (***C***) thrombocyte (p = 0.005), (***D***) fibrinogen (p = 0.002), and (***E***) TSH (p = 0.033) levels exhibit significantly worse median OS than those with low values of the given parameter. TET patients with high preoperative (***F***) lymphocyte (p = 0.008), (***G***) RBC (p = 0.03), (***H***) Hgb (p = 0.04), and (***I***) albumin (p = 0.038) levels have significantly improved OS (vs. those with high levels concerning each parameter). Increased NLR (***J***) and PLR (***K***) are associated with impaired OS according to univariate survival analysis (p = 0.008 and p < 0.001, respectively). Differences between groups were compared using the log-rank test. Abbreviations: OS, overall survival; TET, thymic epithelial tumor; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TSH, thyroid stimulating hormone; RBC, red blood cell; Hgb, hemoglobin.

patient cohort. We found that high CRP and fibrinogen levels, along with high PLR values all remained significant negative prognosticators for OS ($p = 0.006$, $p = 0.018$ and $p = 0.002$, respectively; Fig. 4A-C). Accordingly, hazard ratios associated with increased (vs. low) CRP, fibrinogen and PLR were 1.77, 3.63 and 1.93, respectively. Despite its elevated hazard ratio, high NLR values did not influence the survival outcomes independently of other clinicopathological variables ($p = 0.113$, Fig. 4D). As expected, increased age ($p < 0.001$) and thymic carcinoma ($p < 0.001$) had an independent negative impact on OS. Of note, Cox regression analysis adjusted for the detailed WHO classification also including the individual type B subgroups yielded similar results (Supplementary Fig. 7). Conversely, according to our multivariate models, individuals from patient cohorts #2 and #3 had improved survival (vs. those in cohort #1). Given that the cause of death was most likely not always TET-related in the current patient pool, we performed additional Cox regression analyses to assess the CSS (Fig. 5). Importantly, both fibrinogen ($p = 0.009$) and PLR ($p = 0.001$) influenced CSS independently of other variables. In this context, the CSS-related hazard ratios of increased (vs. low) fibrinogen and PLR values were 7.09 and 2.51, respectively. CRP ($p = 0.150$) and NLR ($p = 0.310$) were not related to CSS in our multivariate models.

Lastly, we assessed the impact of different adjuvant therapeutic approaches on the survival of thymic carcinoma patients according to the preoperative level (low vs. high) of blood-based parameters (Supplementary Fig. 8). Of note, these analyses were applied solely to thymic carcinoma patients to overcome selection bias. We found that patients with low preoperative PLR values and thrombocyte levels had significantly improved OS when receiving adjuvant combination chemoradiotherapy (vs. receiving chemotherapy only; $p = 0.001$ and $p = 0.007$, respectively). Importantly, in case of the other investigated markers, therapeutic approaches also had different effects on OS for patients with high vs. low levels of the respective biomarkers; however, these divergent survival trends were not statistically significant.

4. Discussion

Traditionally, TETs constitute a histologically and molecularly heterogeneous group of tumors where additional prognostic markers are constantly needed. In this context, deciphering the complex inflammatory processes could steer the development of personalized follow-up strategies, potentially improving patient prognosis. In the current multicenter study, we evaluated the clinical significance of preoperative blood-based inflammatory markers in the so far largest cohort of Caucasian TET patients.

The role of the systemic inflammatory response in tumorigenesis and cancer progression has been highlighted in various malignancies [25,26]. Indeed, given that TETs arise from epithelial cells of the thymus, which plays a critical role in adaptive immunity, associations between inflammatory markers and clinical outcomes might be even more pronounced in thymomas and thymic carcinomas [3]. In our cohort, elevated preoperative CRP levels were associated with increased tumor size, whereas high PLR and NLR values were both characteristic of thymic carcinomas. CRP is an acute-phase protein associated with tissue injury and advanced disease stage in numerous cancer types [27]. One possible explanation for this common increase of CRP in sizeable tumors is that the tumor cells themselves cause tissue inflammation through cytokine (e.g. IL-6) production [27]. Nevertheless, in contrast to lung [28] and breast cancer [29], no significant correlation has been reported between CRP and IL-6 levels in TETs [30]. CRP might as well be secreted by tumor cells themselves [31,32], yet the origin and concept of "tumor-CRP" in TET patients have not been validated so far either [30]. With this regard, we also examined the tissue expression of fibrinogen and CRP in our previous studies to determine whether the elevated levels of these immune biomarkers are a bystander effect resulting from an enhanced immune response to a higher tumor burden in TETs or if they actively contribute to tumor progression by promoting tumor growth, angiogenesis, and metastasis. In these studies, we demonstrated by immunohistochemistry that both fibrinogen and CRP staining were

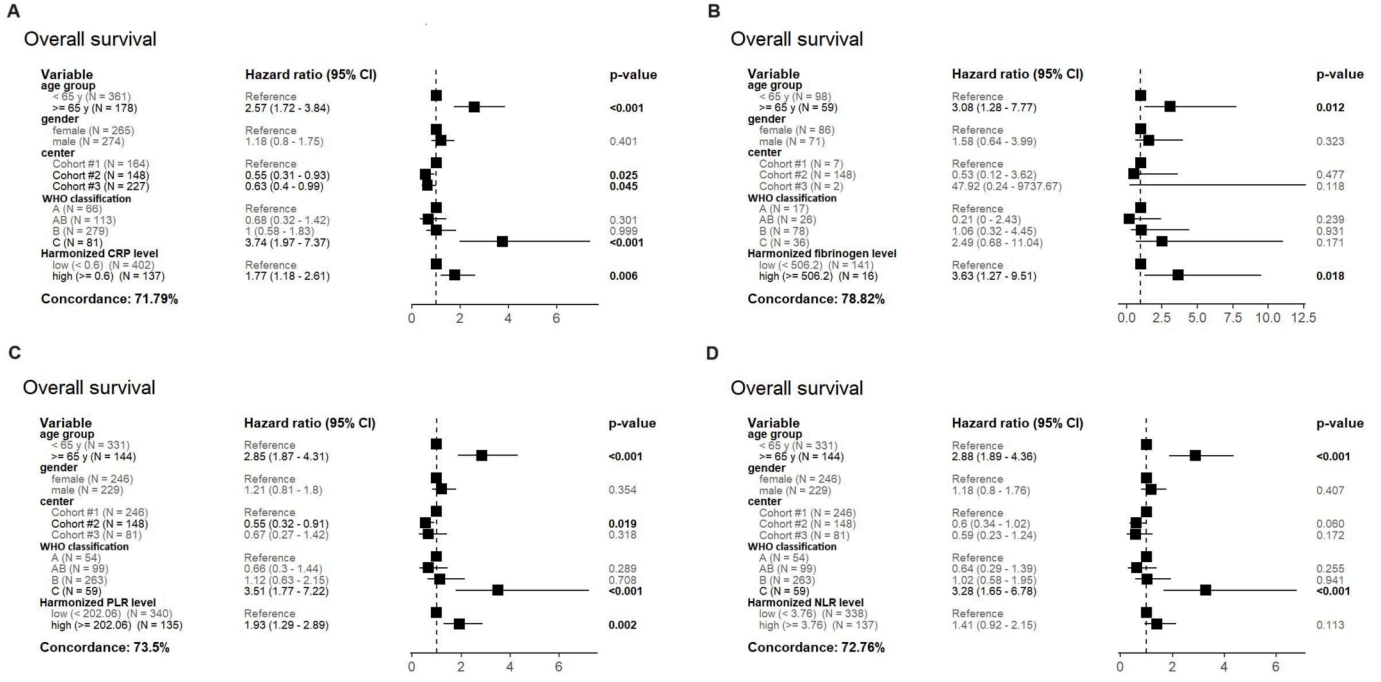

Fig. 4. Multivariate Cox regression model for clinicopathological variables and blood-based inflammatory markers influencing the OS in surgically treated TET patients. Concerning the clinicopathological variables, older age, and type C TET (as per WHO definition) are statistically significant negative prognostic factors for OS. Cox regression analysis revealed that increased (***A***) CRP ($p = 0.006$), (***B***) fibrinogen ($p = 0.018$) and (***C***) PLR ($p = 0.002$) values were also negative prognosticators in surgically treated TET patients. Notably, patients with elevated (***D***) NLR levels have non-significantly ($p = 0.113$) increased hazard ratios towards poor survival. The concordance of the models is in the reasonable range (60–80 %) for survival data. Abbreviations: OS, overall survival; TET, thymic epithelial tumor; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

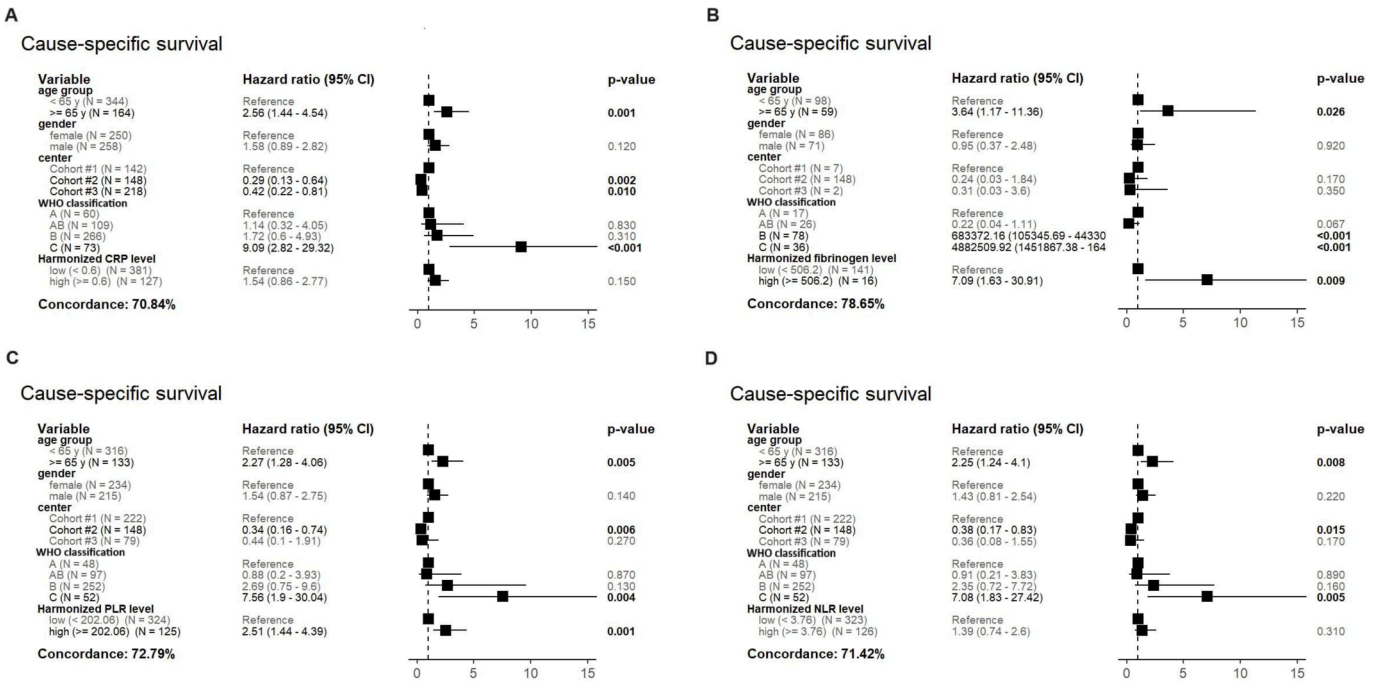

Fig. 5. Multivariate Cox regression model for clinicopathological variables and blood-based inflammatory markers influencing the CSS in surgically treated TET patients. Older age and type C TET (as per WHO definition) were significant negative prognosticators for CSS (***A-D***). As for inflammatory markers and ratios, Cox regression analysis revealed that patients with increased (***B***) fibrinogen ($p = 0.009$) and (***C***) PLR ($p = 0.001$) values had significantly impaired CSS. Neither the (***A***) CRP nor the (***D***) NLR had an independent impact on CSS ($p = 0.150$ and $p = 0.310$, respectively). The concordance of the models is in the reasonable range (60–80 %) for survival data. Abbreviations: CSS, cause-specific survival; TET, thymic epithelial tumor; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

absent in malignant thymic epithelial cells [23,30]. Accordingly, despite various elucidating attempts [30,33,34], the linkage between elevated CRP and increased tumor size remains elusive in TETs. Interestingly, the average level of most inflammatory markers examined within the framework of the study was higher in patients presenting symptoms of MG (vs. non-MG patients), albeit the differences were not statistically significant. This may primarily be due to the underlying immune dysregulation and chronic inflammation associated with TET-related myasthenia gravis [35]. Additionally, persistent muscle weakness and repeated neuromuscular strain can lead to localized inflammation in the muscle tissue, which may also contribute to elevated levels of systemic inflammatory markers [35].

In this study, elevated PLR and NLR values in thymic carcinomas were primarily attributed to the significantly decreased lymphocyte levels seen in these invasive tumors. Although it is evident that the thymus is critical for the normal development of the immune system in infants [36,37], its function in human adults remains unclear. Once thymus atrophy begins in childhood, an exponential decline in new T-cell generation occurs [38,39]. Under these circumstances, normal T-cell count is primarily maintained through the peripheral clonal proliferation of T-cell populations [40]. Nevertheless, previous studies suggest that also the thymus continues to produce T cells in adults, even after atrophy [41,42]. Indeed, a recent large-scale study found that patients who underwent thymectomy had an increased risk of developing autoimmune diseases throughout their lifetime, and the all-cause mortality and the risk of cancer were also higher among these individuals (vs. matched controls) [43]. Importantly, thymus removal also has been reported to induce a consistent proinflammatory state and decreased production of CD4 + and CD8 + lymphocytes, supporting the presumption that the thymus contributes to new T-cell production even in adulthood [43]. Structural and histological rearrangement, as well as cell destruction, impairs the ability of the thymus to develop T-cells. Since thymic carcinomas disrupt the normal functioning of the thymus more aggressively than other TETs, lymphocyte counts might be lower in these tumors than in less-malignant thymomas. In fact, even histologically, thymomas show a higher proportion of lymphocytic infiltrate than thymic carcinomas [44]. Altogether, low lymphocyte levels (and consequently high PLR and NLR values) in thymic carcinomas might be a consequence of damaging the T-cell-producing function of the thymus rather than the result of the generalized lymphocyte count depletion seen during cancer progression and metastasis [45].

The current multicenter study did not include postoperative assessment of blood-based inflammatory markers due to their high variability in the recovery phase after surgery. Indeed, thoracic surgery, like other major surgical procedures, can significantly impact postoperative inflammatory markers in the blood count due to the body's immune response to tissue injury, anesthesia, and potential complications such as infection [46–48]. In this context, our primary aim was to offer clinicians preoperative prognostic markers that might aid surgical decision-making, pathological diagnosis, and long-term follow-up. Nevertheless, in our previous investigation [23] conducted on a smaller subset of cohort #2 of the current study, we assessed early (3 to 7 days after surgery) and late (6 to 12 months after surgery) postoperative measurements of fibrinogen serum concentration, NLR, and PLR to evaluate their reliability as tumor markers within oncologic follow-up of TET patients. As expected, inflammatory markers in the immediate postoperative period were not informative as all investigated markers significantly increased because of surgical stress. Meanwhile, analysis of these markers within 6–12 months post-resection revealed that patients with tumor recurrence had significantly higher NLR and PLR values during follow-up (2.5-fold and 1.8-fold higher than in patients without recurrence, respectively). More specifically, NLR and PLR measured during oncologic follow-up predicted tumor recurrence with sensitivities of 80 % and 100 % and negative predictive values of 96 % and 100 %, respectively. This increase in NLR and PLR in patients with tumor recurrence is likely due to the resurgence of tumor-related inflammation in the relapsed patients.

Inflammation-based scores, such as PLR and NLR, have been linked

with unfavorable prognosis in various types of solid tumors, including colorectal [49], breast [50], liver [51], and lung cancer [21]. Here, we report that PLR represents an independent negative prognosticator in surgically treated TET patients concerning both OS and CSS, whereas increased NLR is associated with impaired prognosis in a univariate model. Along with other markers of inflammation, platelets are part of the tumor-associated inflammatory response, and thrombocytosis is relatively common in patients with malignant tumors [52]. Platelets interact with the tumor cells directly, and besides augmenting tumor growth via angiogenesis, they also endow tumor cells with mechanical and physical support to evade the immune system [52,53]. Moreover, platelets protect malignant cells from natural killer cell-mediated lysis, thereby facilitating tumor cell extravasation and metastasis [54]. In contrast to PLR, our multivariate model could not demonstrate the independent prognostic relevance of NLR despite the elevated hazard ratios. In light of this, NLR is rather a diagnostic marker for thymus carcinoma than an individual prognostic biomarker in TET patients.

Similar to PLR, elevated blood-based preoperative fibrinogen levels constituted an independent negative prognosticator in our study. Fibrinogen is a glycoprotein involved in blood clotting and inflammatory response, and its increase in cancer patients can be attributed to various factors. Increased serum fibrinogen may indicate fibrinogen deposits in tumor tissue that serve as an extracellular matrix for tumor cell adhesion and migration, and promote tumor growth, angiogenesis, and metastasis [55]. Nevertheless, in our previous study, immunohistochemical fibrinogen staining was absent in TETs [23]. Therefore, elevated fibrinogen plasma levels, as indirect indicators of tumor aggressiveness, are more likely bystander effects of an enhanced immune response against higher tumor load [23]. Notably, fibrinogen might also act as a bridging factor between host and tumor cells, thus enhancing endothelial adhesion of malignant cells during metastatic spread [56]. Notably, hazard ratios of increased fibrinogen and PLR values were considerably higher when assessing CSS than OS, thus supporting the cause-specificity of these markers.

Concerning clinicopathological variables, thymic carcinoma and increased age were both independently associated with impaired prognosis, as expected. Gender failed to influence survival to a significant degree. It's also worth mentioning that patients in cohort #1 tended to have impaired survival outcomes according to some of our multivariate models. Given the standardized diagnostic and treatment protocols across the study centers, these slightly divergent survival outcomes might result from the different incidences of underlying chronic conditions in each participating country.

Since TETs are characterized by relatively high tumor recurrence rates even decades after initial treatment, it is recommended that patients receive life-long oncologic follow-up. Nevertheless, there are no established serum biomarkers currently that can aid in optimizing the surveillance protocols in these patients. Given that some inflammatory markers examined in our current multicenter study have both diagnostic and prognostic relevance, we hypothesize that patients with high preoperative CRP, fibrinogen, PLR, and NLR values should be followed up more frequently than those with lower values, and, moreover, that these patients should be classified as high-risk individuals concerning tumor recurrence. However, even after further validation, inflammatory markers should only be used as complementary tools in decision-making, not outweighing the standard predictors of tumor aggressiveness and recurrences (such as stage or resection margins). As for their therapeutic relevance, our results suggest that thymic carcinoma patients with low preoperative PLR values and/or thrombocyte levels may constitute a specific subgroup that could significantly benefit from combination chemo-radiotherapy after surgery. Nevertheless, this observation is rather hypothesis-generating and a larger dataset would be needed for a more comprehensive analysis of how preoperative levels of individual blood-based markers (and their combination) could help tailor adjuvant therapy for patients with TETs.

The present study has some limitations that need to be acknowledged. Because of the study's multicenter and large-scale nature, the cause of death was not available in all cases. Patients lacking this data were not included in analyses related to CSS. Thus, the patient pool used for assessing CSS was smaller than that used in the OS-related measurements. Another limitation is that most of our results refer to the harmonized values of inflammatory parameters rather than their actual values used in everyday practice. Accordingly, while our results demonstrate that specific markers of inflammation have diagnostic and prognostic relevance in TETs, defining widely applicable cut-offs for these markers warrants further prospective studies.

Given the high degree of tumoral heterogeneity, developing biomarkers to predict clinical outcomes is of paramount importance in TETs. Here, we demonstrate that elevated preoperative CRP is associated with increased TET size, whereas high PLR and NLR are characteristic of thymic carcinoma. Notably, elevated PLR and NLR are primarily due to a significant decrease in lymphocyte levels. Concerning patient survival, increased PLR and fibrinogen constitute independent negative prognosticators both for OS and CSS. Altogether, by investigating the diagnostic and prognostic relevance of blood-based inflammatory markers in the so-far largest cohort of surgically treated TET patients, the current multicenter study offers additional guidance in developing personalized surveillance protocols in these rare, but highly variable tumor types.

CRediT authorship contribution statement

Evelyn Megyesfalvi: Writing – original draft, Methodology, Conceptualization. **Aron Ghimessy:** Investigation, Formal analysis. **Jonas Bauer:** Investigation, Data curation. **Orsolya Pipek:** Visualization, Software, Formal analysis. **Kevin Saghi:** Investigation, Data curation. **Aron Gellert:** Investigation, Formal analysis. **Janos Fillinger:** Resources. **Ozlem Okumus:** Investigation, Data curation. **Vivien Teglas:** Data curation. **Erna Ganofszky:** Data curation. **Krisztina Bogos:** Resources. **Ferenc Renyi-Vamos:** Resources. **Zsolt Megyesfalvi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Conceptualization. **Clemens Aigner:** Resources. **Balazs Hegedus:** Writing – review & editing, Writing – original draft, Conceptualization. **Balazs Dome:** Writing – review & editing, Writing – original draft, Conceptualization. **Bernhard Moser:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and materials.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

(I) Study conception and design: Evelyn Megyesfalvi, Aron Ghimessy, Zsolt Megyesfalvi, Balazs Hegedus, Balazs Dome, Bernhard Moser; (II) Administrative support: All authors; (III) Provision of study materials: Krisztina Bogos, Ferenc Renyi-Vamos, Janos Fillinger, Clemens Aigner, Bernhard Moser; (IV) Collection and assembly of data: Jonas Bauer, Kevin Saghi, Aron Gellert, Ozlem Okumus, Vivien Teglas, Erna Ganofszky; (V) Data analysis and interpretation: Orsolya Pipek, Evelyn Megyesfalvi, Zsolt Megyesfalvi; (VI) Manuscript writing: Evelyn Megyesfalvi, Zsolt Megyesfalvi, Balazs Hegedus, Balazs Dome, Bernhard Moser; (VII) Final approval of manuscript: All authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2025.108111.

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