



Prognostic and predictive biomarkers in thymic epithelial tumors: beyond traditional staging: a narrative review

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Background and Objective: Thymic epithelial tumors (TETs), encompassing thymomas (TMs) and thymic carcinomas (TCs), are rare and heterogeneous mediastinal malignancies with variable clinical behaviors and prognoses. Current prognostic assessment primarily relies on histological classification (WHO) and anatomical staging systems (Masaoka-Koga, TNM). However, the rarity and complex biology of TETs necessitate the identification of novel prognostic and predictive biomarkers to improve risk stratification and guide personalized treatment strategies. This narrative review aims to summarize and discuss emerging prognostic and predictive biomarkers in TETs beyond traditional staging systems.

Methods: For this narrative review, we searched EMBASE and MEDLINE up to 4 September 2025. The terms used in the search included TM, TC, TETs, prognosis and predictive biomarkers.

Key Content and Findings: Traditional staging systems (Masaoka-Koga, TNM) and histological classification retain strong prognostic value. Clinical factors (including age, resection status, and lymph node involvement) further refine risk stratification. Molecular markers such as programmed death-ligand 1 (PD-L1) expression, tumor mutational burden (TMB), DNA methylation profiles, Hippo pathway components, and Ki-67 show promise as prognostic and/or predictive biomarkers, although prospective validation remains limited. Predictive biomarkers for immunotherapy and targeted agents are under active investigation, with preliminary evidence supporting the role of TMB, PD-L1 expression, and c-kit mutations.

Conclusions: Prognosis in TETs relies primarily on histology and staging, whereas molecular and immunological biomarkers represent emerging tools for risk stratification and treatment selection. Multiparametric models integrating clinical, pathological, and molecular data may pave the way for precision oncology in TETs.

Keywords: Thymic epithelial tumors (TETs); thymoma (TM); thymic carcinoma (TC); prognosis; predictive biomarkers and molecular alterations

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Introduction

Thymic epithelial tumors (TETs) are a rare and heterogeneous group of primary mediastinal neoplasms arising from thymic epithelial cells, comprising thymomas (TMs), thymic carcinomas (TCs). The annual incidence of TETs is approximately 0.15 cases per 100,000 individuals, with TCs accounting for only 10–20% of these cases (1). Despite their rarity, TETs present a unique spectrum of malignancies, with TMs being specific to the thymus, while carcinomas often resemble those found in other organs (2).

The clinical behavior of TETs varies widely, from indolent growth patterns in some TMs, to highly aggressive and metastatic tendencies in TCs, leading to significant differences in overall survival (OS) and disease-free survival (DFS) (3). TMs can be associated with paraneoplastic autoimmune diseases, most notably myasthenia gravis (MG), which is present in about 30% of patients (4).

Diagnosis and classification of TETs have evolved, primarily relying on histopathological features. The World Health Organization (WHO) classification system categorizes TETs into types A, AB, B1, B2, B3 TMs, and TCs, based on tumor cell morphology, degree of atypia, and the extent of the lymphocytic component (5). Types A and AB TMs typically have low malignant potential, whereas B1, B2, and B3 TMs show increasing aggressiveness, with B3 having the greatest tendency for intrathoracic spread (6). TCs are highly aggressive and often present with advanced stages and frequent lymphatic and hematogenous metastases, resulting in a poorer prognosis compared to TMs (6). Staging is commonly performed using the Masaoka-Koga system, which classifies tumors based on invasiveness, and the more

recently proposed TNM staging system (7,8).

Despite these classification and staging systems, there remains a critical need for more accurate and comprehensive prognostic and predictive biomarkers. Even with complete surgical resection (the primary treatment modality), 10–30% of TMs can recur, sometimes decades after initial surgery (9,10). Furthermore, responses to standard chemotherapy in advanced or recurrent non-resectable TETs are modest (11). The rarity and heterogeneity of TETs hinder large-scale investigations and the development of targeted therapies (12). Therefore, identifying novel biomarkers is essential for better patient stratification, guiding adjuvant therapies, and improving the long-term management of TETs (13). This review aims to discuss the various prognostic factors and genetic markers available in the literature to date, highlighting their potential to advance personalized medicine for TET patients. We present this article in accordance with the Narrative Review reporting checklist (available at <https://med.amegroups.com/article/view/10.21037/med-25-44/rc>).

Methods

A comprehensive literature search was performed in EMBASE and MEDLINE databases to identify relevant studies published up to September 4, 2025. The complete search strategy is provided in Table 1. The search terms included *thymoma*, *thymic carcinoma*, *thymic epithelial tumors*, *prognosis*, and *predictive biomarkers*.

The initial search yielded 176 articles. After screening titles and abstracts, 115 studies were excluded for the following reasons: 65 did not address prognostic or

Table 1 The search strategy summary

Items	Specification
Date of search	4 th September 2025
Databases searched	MEDLINE, EMBASE
Search terms used	Thymic epithelial tumors, thymoma, thymic carcinoma, prognosis, predictive biomarkers and molecular alterations
Timeframe	January 1, 1950 to September 4, 2025
Inclusion and exclusion criteria	Inclusion: (I) English and Spanish language; (II) case reports, case series, retrospective cohort series, prospective studies; (III) studies addressing prognostic or/and predictive biomarkers in thymic epithelial tumors Exclusion: studies not focused on thymic epithelial tumors
Selection process	L.C.G., V.P.B. and B.C.O. selected literature, all authors chose those for inclusion

Table 2 Molecular and immunological biomarkers with prognostic *vs.* predictive roles

Biomarker/parameter	Prognostic role	Predictive role	Evidence level	Clinical applicability
PD-L1 expression	Conflicting results for OS, DFS	ICI response prediction	Moderate	Needs standardization
TMB	High TMB → worse prognosis	ICI response prediction	Emerging	Prospective trials needed
DNA methylation signatures	OS and RFS prediction	–	Moderate	Research stage
Hippo pathway (YAP, TAZ, TEAD4)	Correlation with aggressiveness	–	Low	Experimental
Ki-67 index	Higher values → worse OS, DFS	–	High	Routine histopathology
c-kit mutations	Poor prognosis in TC	Targeted therapy response	Low	Selected cases

DFS, disease-free survival; ICI, immune checkpoint inhibitor; OS, overall survival; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival; TC, thymic carcinoma; TMB, tumor mutational burden.

predictive factors, 31 evaluated other neoplasms, and 19 were duplicate publications.

The full texts of the remaining 61 articles were critically appraised for methodological quality, scientific rigor, and relevance to the review objectives. Studies were assessed according to commonly accepted criteria for observational research, including clarity of study design, adequacy of sample size, transparency of statistical analyses, and clinical applicability of the findings. Only studies meeting these predefined quality standards were included in the final synthesis.

Definitions

In the management of TETs, it is critical to distinguish between prognostic and predictive factors. Prognostic factors are those that inherently influence the overall natural course of the disease and a patient’s survival outcome, independent of the specific treatment received. The most well-established prognostic variables for TETs consistently include the Masaoka-Koga clinical staging system, the WHO histological subtype, and the completeness of surgical resection (14,15). Conversely, predictive factors are those utilized to forecast the likelihood of clinical benefit from a particular systemic therapy. Examples of predictive biomarkers in TETs include genomic alterations such as KIT mutations in TC, which predict response to tyrosine kinase inhibitors (12), and the expression of programmed death-ligand 1 (PD-L1) or tumor mutational burden (TMB), which are evaluated to predict the efficacy of immune checkpoint inhibitors (ICIs) (16). Therefore, while prognostic factors inform the overall aggressiveness of the tumor, predictive factors guide the selection of

individualized treatment strategies. Selected prognostic and predictive factors are detailed in *Table 2*.

Prognostic factors

Prognostic factors for TETs are detailed below. The most important are summarized in *Figure 1*.

Anatomical and histological factors

WHO histological classification

The WHO histological classification and the Masaoka-Koga staging system are the most commonly adopted and reliable prognostic factors for TETs. The WHO classification categorizes TMs into types A, AB, B1, B2, and B3 based on tumor cell morphology, degree of atypia, and extent of the thymocyte component (17). TCs (type C in older classifications) are distinguished by overt malignant features. Overall, the WHO histological classification correlates with the oncological behavior of TM. In general, TMs have a better prognosis than TCs (14,18).

Masaoka-Koga stage

The Masaoka-Koga staging system classifies TETs based on the degree of tumor invasiveness and presence of metastasis, and its usefulness has been widely validated (17). An advanced Masaoka stage (III–IV) is consistently associated with worse outcomes, including shorter OS and DFS (18,19). Survival analysis across distinct cohorts underscores the substantial variability in patient outcomes, particularly by disease stage. In one series, 5-year OS rates for stages II, III, and IV were reported as 88%, 100%, and 80%, respectively, with corresponding 5-year DFS rates of 88%, 75%, and

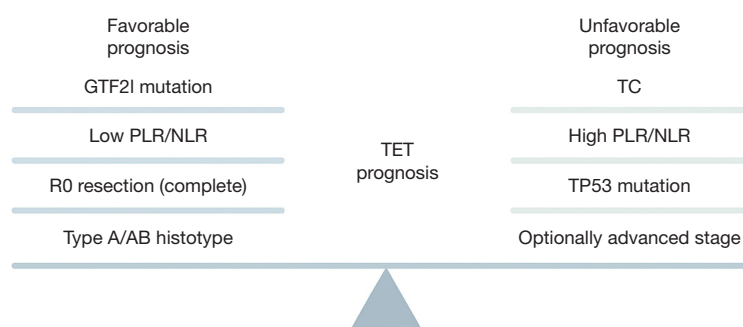


Figure 1 Prognostic factors in TETs: a risk-stratification scale. The prognostic outcome in TETs is determined by the cumulative “weight” of traditional clinicopathological, molecular, and systemic inflammatory factors. The scale tips toward a favorable prognosis when molecular drivers such as the *GTF2I* mutation, low systemic inflammation (low PLR/NLR), and complete tumor excision (R0 resection) are present. Conversely, the scale tips toward an unfavorable prognosis due to the presence of high-risk histological subtypes (TC), aggressive molecular aberrations (*TP53* mutation), and pronounced systemic inflammation (high PLR/NLR). NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TC, thymic carcinoma; TETs, thymic epithelial tumors.

55% (18). However, another study highlighted a poorer prognosis in advanced disease, showing 5-year OS rates of 100% for stages I and II, 80% for stage III, and 0% for stage IV (19). This divergence emphasizes the need for consistent reporting and potentially different management strategies based on staging and institutional experience; there is a clear correlation between advanced stages and worse prognosis.

TNM staging (8th–9th editions)

The updated TNM staging system (8th and 9th editions) also provides reliable prognostic information, with higher TNM stages associated with impaired survival. The updated ninth edition of the TNM staging system for TETs maintains the validated N (nodal) and M (metastasis) components from the eighth edition but incorporates minor structural adjustments, notably the inclusion of tumor size and redefinitions for T2/T3 categories, based on a vast global dataset (20). Achieving precise clinical staging, informed by systems like the thymic lymph node map remains fundamental for effective treatment and prognosis. Future system refinements will rely heavily on continued high-quality data collection, specifically for lymph node assessment and advanced non-surgical cases.

The strong relationship between staging, histology, and prognosis in TETs has been consistently reported. A retrospective analysis of 245 resected TM patients established a correlation between the TNM classification system and the WHO histological grade (21). This association was reflected in the median survival time (MST):

Masaoka-Koga staging yielded MSTs of 187, 166, and 158 months for stages I, IIa, and IIb, respectively, and 107 months (stage III) and 53 months (stage IVa). Similarly, the TNM system correlated with MSTs of 166 months (stage I), 107 months (stage II), 108 months (stage IIIA), 22 months (stage IIIB), and 98 months (stage IVa), with advanced TNM stages corresponding to more aggressive histologies (21). Moreover, the prognostic capacity of the classification system was validated in a retrospective cohort of 154 patients, which demonstrated a significant, stage-dependent reduction in recurrence-free survival (RFS) (22). The hazard ratio (HR) for recurrence increased markedly with progression, ranging from 2.68 (stage II) to 6.84 (stage IIIA), and reaching 24.62 (stage IVB). Conversely, some studies indicate that tumor size is an influential prognostic factor only for TM, and not for TC (23).

Histology

TMs

- ❖ Less aggressive TM (types A, AB, B1) generally have a favorable prognosis, with type A and AB TMs often having low malignant potential. The 5-year survival rate for patients with TM is about 90% (18).
- ❖ More aggressive TMs (types B2, B3) are associated with a poorer prognosis and a greater tendency for intrathoracic spread. The 20-year survival rate after surgical resection for type A, AB, B1, B2, and B3 tumors was reported as 100%, 87%, 91%, 59%, and 36%, respectively, indicating a tendency towards worse survival in type B3 compared to type A tumors (24).

TCs

These are highly malignant and invasive, often presenting with advanced tumor stages and consequently worse OS and DFS compared to TMs. TC is generally characterized by obvious malignant biological behavior and frequent lymphatic and hematogenous metastasis. The 5-year survival rate for TCs ranges from 30% to 55% (25).

Clinical and patient-related factors

Age (>60 or ≥65 years)

Older patients (e.g., >60 or ≥65 years) are frequently associated with a poorer prognosis (26,27). Higher TMB has been significantly associated with older age (28). However, multivariate analysis sometimes shows age as the only independent prognostic factor, overriding other factors like WHO classification and BMP-7 expression (29). These studies fail to distinguish whether the observed increase in mortality is primarily due to tumor-related factors or is a consequence of the comorbidities prevalent in the geriatric population.

Completeness of resection (R0 vs. R1/R2)

The completeness of resection is standardly classified as R0 (complete resection), R1 (microscopic residual disease infiltrating resection margins), and R2 (macroscopic residual disease). R0 resection is considered the only curative strategy for localized disease and is a crucial prognostic factor (5,7,26,30). Incomplete resection (R1 or R2) is a significant independent prognostic factor for worse cause-specific survival (CSS) and is associated with impaired OS (13). In multivariable analyses involving TET patients, the incomplete resection status (R1 + R2) maintained statistical significance as a predictor of worse CSS (HR =13.5; P=0.018) (13).

Tumor size

Tumor size is an independent prognostic factor for OS in patients with TETs after R0 resection (15,31,32). Increased tumor size is also associated with higher preoperative C-reactive protein (CRP) levels (33). However, some studies have found no prognostic significance of tumor size in thymic malignancies, or that it does not improve the predictive power of TNM staging (31). Some studies suggest a worse OS for TETs originating in the upper mediastinum (34), partly attributable to the increased risk of great vessel infiltration and hematogenous dissemination associated with this specific location (35).

Lymph node metastasis

Nodal involvement is associated with worse OS and is more frequent in TCs compared to TMs (36). Complete lymphadenectomy may be beneficial in surgical treatment, especially in higher-risk cases (36). Overall, nodal involvement is more frequent in TCs than in TMs (36). A retrospective analysis of a Chinese database including 1,617 patients reported a nodal involvement rate of 2.2%, which was associated with reduced OS (37). Among 1,310 patients with TM, nodal metastases occurred in only 0.5%, compared with 7.9% in TC (37). In the study by Kondo and Monden involving 1,320 patients, nodal metastases were observed in 1.8% of TMs and 27% of TC (38). For TM, a significant difference in 5-year survival was reported between node-negative and node-positive cases, although no survival differences were noted between N1 and N2 stages among node-positive patients. In contrast, in TC, 5-year survival decreased progressively with increasing nodal stage (N0: 56.0%, N1: 42.1%, N2: 29.3%, N3: 18.8%) (36,38). Similarly, Fang *et al.* reported lymph node metastases in 2.1% of TMs and 25% of TC (39). Predictors of nodal involvement included WHO B3 histology, TC, advanced T stage (T3–T4), and N2 node dissection, leading the authors to recommend lymphadenectomy including ipsilateral N2 nodes in such cases (39).

Paraneoplastic syndromes (e.g., MG)

The presence of paraneoplastic syndromes, such as MG, is not consistently correlated with prognosis (15). However, MG is more frequently associated with TM than TC (40). In clinical cohorts of TET patients, a history of MG has been reported in approximately 28.1% of cases (41). Notably, MG was associated with TM in one study at a rate of 18%, compared to 9% in TC cases (40). Moreover, in a large series analysis, all patients presenting with MG were diagnosed with TM, and corresponding autoimmune disorders were generally not observed in TC (40,42).

Drinking history

Drinking history may be an independent predictive factor for postoperative recurrence (31,43). In one cohort analysis (31), drinking history showed a significant independent association with RFS [HR =4.227, 95% confidence interval (CI): 1.431–12.484, P=0.007]. Furthermore, drinking history has also been identified as an important independent prognostic factor for OS (43). Despite these initial findings, the precise relationship between drinking history and TETs prognosis requires further investigation, as the rarity of these tumors has

Table 3 Preoperative systemic inflammatory, nutritional, and tumor marker prognostic indicators in TETs

Marker	Prognostic value and association	Outcome measured	References
CRP	Elevated CRP (>0.6 or >1.0 mg/dL) is an independent negative prognosticator for OS (HR 1.77, P=0.006). High pretreatment CRP is associated with significantly worse FFR in univariable analysis (HR 3.30; P=0.015). CRP concentrations are highest in TCs and metastatic TETs. CRP often lacks independent prognostic significance for CSS (P=0.150)	OS, FFR, CSS	(33,40,45)
NLR	High baseline NLR (>3.76 or >4.35) is associated with impaired OS outcomes in univariable models (P=0.008). NLR is significantly higher in TCs than in thymomas (P=0.002). NLR typically lacks independent prognostic significance for OS (P=0.113) or CSS (P=0.310) in multivariate analyses	OS, CSS, FFR	(33,46)
PLR	Elevated PLR (>201.66) is a significant independent negative prognosticator for OS (HR 1.93, P=0.002) and CSS (HR 2.51, P=0.001). High baseline PLR is an independent risk factor for worse OS and DFS. PLR is significantly higher in TCs than in thymomas (P<0.001). A greater absolute change in PLR after treatment is identified as a risk factor for poor OS (HR 3.31, P<0.05)	OS, CSS, DFS	(33,46)
MLR	High pretreatment MLR (>0.22) is an independent predictor of poor DFS in completely resected TETs (HR =3.337, P=0.0264). High MLR is associated with significantly lower DFS rates in Kaplan-Meier analysis (P=0.0001). MLR did not predict OS after surgery in this cohort	DFS, OS	(46)
CAR	Elevated preoperative CAR (>0.17) is an independent predictor of poor OS and RFS after thymectomy. CAR provides comparable predictive accuracy for OS (AUC 0.734) and RFS (AUC 0.680)	OS, RFS	(43)
PNI	Low PNI (<44.02) reflects poor nutritional and immunological status and is associated with significantly lower DFS rates in univariable analysis (HR =2.7766, P=0.0398). PNI was not an independent predictor of DFS (P=0.5366) in multivariate analysis and did not predict OS after surgery	DFS, OS	(47)
CK	Low preoperative serum CK (<62 IU/L for men) is an independent negative prognostic factor for shorter OS (P=0.005) and DFS (P=0.03). Low CK reflects poor host nutritional status and is significantly associated with sarcopenia (lower Th12 muscle index, P=0.03) and lower serum albumin/cholesterol. CK level was not associated with WHO histological type or Masaoka-Koga stage	OS, DFS	(48)
CEA	High preoperative serum CEA levels serve as an independent predictor of OS (HR 5.421, P=0.018). CEA levels were not significantly associated with RFS in multivariate analysis (P=0.321). CEA is often used as a tumor marker	OS, RFS	(31)

AUC, area under the curve; CAR, C-reactive protein to albumin ratio; CEA, carcinoembryonic antigen; CK, creatine kinase; CRP, C-reactive protein; CSS, cause-specific survival; DFS, disease-free survival; FFR, freedom from recurrence; HR, hazard ratio; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; RFS, recurrence-free survival; TCs, thymic carcinomas; TETs, thymic epithelial tumors; WHO, World Health Organization.

limited comprehensive studies on this topic (31). Notably, the prognostic significance of this factor is not uniform across all analyses, with some studies finding no statistical significance in the univariate analysis of its effect on RFS (P=0.128) (44).

Inflammatory and nutritional markers

Systemic inflammatory markers and nutritional status have emerged as valuable prognostic indicators in various cancers, including TETs. The most relevant factors are

summarized in *Table 3*.

- (I) C-reactive protein (CRP): elevated preoperative CRP levels are associated with increased tumor size and negatively impact OS (33,40,45). High pretreatment CRP concentrations are prognostic for worse freedom from recurrence (FFR) and are found highest in patients with metastatic tumors and TCs (45).
- (II) Neutrophil-to-lymphocyte ratio (NLR): a high NLR is associated with impaired prognosis,

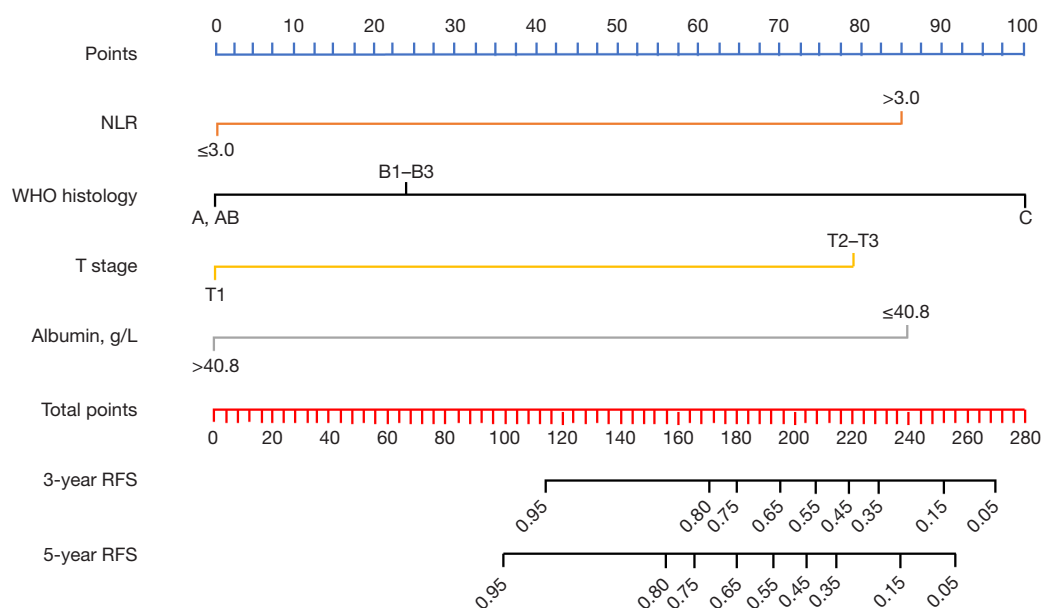


Figure 2 Nomogram predicting 3- and 5-year RFS after thymectomy for thymic epithelial tumor patients. Reproduced and modified from Huang *et al.*, 2022 under CC BY 4.0. (44). NLR, neutrophil-to-lymphocyte ratio; RFS, relapse-free survival.

including reduced OS and FFR in many solid tumors. Higher baseline NLR is related to inferior DFS and OS in TETs (33,46).

- (III) Platelet-to-lymphocyte ratio (PLR): elevated PLR significantly influences OS and CSS independently (33,46).
- (IV) Monocyte-to-lymphocyte ratio (MLR): a high MLR is an independent predictor of poor DFS in patients with completely resected TETs (46).
- (V) C-reactive protein to albumin ratio (CAR): an elevated preoperative CAR is associated with poor prognosis in TETs (43).
- (VI) Prognostic nutritional index (PNI): is a readily available, objective, and cost-effective hematological score designed to reflect the patient's systemic nutritional and immunological status. The PNI is calculated using a standard formula that incorporates two routinely measured blood parameters: $PNI = 10 \times \text{serum albumin value (g/dL)} + 0.005 \times \text{peripheral lymphocyte count (cells/}\mu\text{L)}$. A low PNI is a significant predictor of poor DFS in TET patients (47).
- (VII) Serum creatine kinase (CK): preoperative serum CK concentration may be a prognostic factor in TETs (48).
- (VIII) Serum carcinoembryonic antigen (CEA):

preoperative serum CEA levels can independently predict OS in patients with TETs after R0 resection. Higher preoperative CEA levels are observed in advanced stage (T4) and TCs (31).

- (IX) Nomogram models integrating hematological and clinical factors: nomogram models integrating hematological and clinical factors have emerged as a robust, multi-dimensional approach to refine prognosis prediction in TETs (44). These predictive tools move beyond conventional staging by combining tumor-related, host-related, and environment-related variables (13). For instance, a validated nomogram constructed to predict RFS successfully integrated independent factors such as the pathological T stage, WHO histological type, preoperative albumin levels, and the NLR (44) (Figure 2). This model exhibited strong prognostic capability (C-index: 0.902 in the training cohort) and demonstrated accuracy superior to the Masaoka-Koga staging system in predicting RFS (44). Furthermore, models developed for predicting OS and DFS have integrated variables including age, Masaoka stage, metastasis, and both baseline and absolute changes in inflammatory markers like the PLR and the platelet-to-monocyte ratio (PMR) (46).

These integrated nomograms offer a convenient method for physicians to assess personalized postoperative prognosis and identify high-risk patients earlier.

Molecular and genetic biomarkers

Protein expression and mutations

c-kit (CD117)

Overexpression of c-kit is strongly, but not exclusively, related to TC histological type (at a frequency of approximately 9% of sequenced cases) (49). c-kit expression is significantly higher in TC (reported between 46% and 88%) compared to TM, where expression is rare (0–5%) (49). C-kit expression is of prognostic value, demonstrating decreased DFS and progression-free survival (PFS) observed in c-kit positive tumors. For instance, one study reported that the 10-year disease-related survival (DRS) was 71% for c-kit-positive patients versus 90% for c-kit-negative patients (49). C-kit is also part of an immunohistochemical panel, along with markers like EZH2 and CD205, used to distinguish thymic squamous cell carcinoma from type B3 TM (50).

Epidermal growth factor receptor (EGFR)

Overexpression is widely reported in TETs, with reported frequencies reaching up to 70% in TMs and 53% in TCs (49,51). High EGFR staining is significantly associated with advanced tumor stages, particularly stage III–IV tumors (51). Moreover, immunohistochemical analysis shows that EGFR immunoreactivity of 2+ or 3+ is associated with more aggressive thymic tumors, specifically WHO types B2 and B3 (49). Despite this association with aggressive phenotypes, some studies analyzing advanced or recurrent TETs found that the presence of EGFR immunoreactivity (1+, 2+, and 3+) correlated with significantly improved PFS (52). However, EGFR generally failed to maintain independent prognostic significance for OS in multivariate analyses (52). Crucially, EGFR gene mutations are rare in thymic malignancies. Studies sequencing large cohorts have found only a very low frequency of mutations, such as missense mutations in exon 21 (e.g., L858R), and no mutations were detected in exons 18 and 19 in sampled tumors (51). The limited efficacy observed in phase II clinical trials using EGFR inhibitors, such as gefitinib and erlotinib, is likely attributable to this low frequency of activating EGFR mutations in TETs (51).

Insulin-like growth factor-1 receptor (IGF1R)

IGF1R is a transmembrane receptor implicated in the regulation of cell metabolism, growth, and survival (53).

Overexpression of IGF1R protein is frequently reported in TETs (51). Specifically, moderate to high IGF1R staining has been observed in a majority of thymic malignancies, showing a significantly higher frequency in TCs (reported at 86%) compared to TMs (reported at 43%) (53). This moderate to high expression is also significantly associated with high EGFR staining (53). IGF1R overexpression has been reported to carry poor prognostic value for OS, as well as for PFS (51). However, the prognostic value of IGF1R expression remains controversial in multivariate analyses; for example, one study found no association between IGF1R expression and time to progression (HR =3.07, P=0.291), failing to demonstrate independent prognostic significance after adjusting for factors like tumor stage and histological type (53).

Programmed death-1 (PD-1) and PD-L1

The prognostic significance of PD-L1 expression in TETs remains highly controversial (54). Although PD-1 and/or PD-L1 are expressed in up to 82% of TETs, supporting their role as potential therapeutic targets, studies evaluating their independent prognostic value have yielded conflicting results (54). In TMs, high PD-L1 expression ($\geq 50\%$) has frequently been linked to worse outcomes, including reduced DFS ($P < 0.001$) and higher recurrence rates (54). In the largest cohort to date, PD-L1 positivity was identified as an independent predictor of poor OS (HR 2.087, 95% CI: 1.009–4.318, $P = 0.047$) (55). However, some studies reported improved OS/PFS in B3 TMs with high PD-L1 expression, while others found no prognostic impact (54). In TC, results are equally contradictory. Some investigations demonstrated associations between high PD-L1 expression and worse DFS ($P = 0.0037$) and OS ($P = 0.004$) (56), as well as increased recurrence following induction therapy ($P = 0.03$) (56). Conversely, other studies linked PD-L1 overexpression to prolonged OS/DFS or found no significant correlation with survival (54). Notably, high PD-L1 expression combined with PD-1⁺ tumor-infiltrating lymphocytes (TILs) correlates with worse prognosis in TC (54), and PD-L1 upregulation in epithelial-mesenchymal transition (EMT)-positive tumors has been associated with shorter DFS (42). Regarding PD-1, most studies (including large cohort analyses) found no significant association between its expression and OS in either TM or TC (32), although higher PD-1 levels have occasionally been observed in lower-grade TMs without survival implications (32).

TMB

TETs exhibit the lowest TMB among solid adult malignancies (49). Nonetheless, higher TMB correlates

with advanced Masaoka-Koga stage, more aggressive histological subtypes, and older age (28). Patients with low TMB consistently demonstrate superior OS, whereas high-TMB status is associated with significantly worse long-term outcomes ($P<0.001$) (28). Notably, a subset of TCs displays elevated TMB, potentially predicting responsiveness to ICIs (12). Given its established role as a predictive biomarker in other malignancies, TMB assessment may aid in selecting TET patients most likely to benefit from anti-PD-1 therapy (12,28).

DNA methylation markers

Specific methylation patterns at cg05784862 (KSR1), cg07154254 (ELF3), cg02543462 (ILRN), and cg06288355 (RAG1) loci have been linked to TET progression and may represent novel biomarkers for predicting OS (15,41). A prognostic model incorporating these four methylation sites demonstrated superior accuracy for OS prediction compared with the Masaoka staging system (41). Additionally, methylation β -values at cg20068620 in MAPK4 correlate significantly with RFS (57), and combining this marker with the WHO classification improves prognostic accuracy for recurrence beyond the WHO system alone.

Moreover, GAD1 expression and methylation serve as indicators of aggressive tumor biology in TETs (33). High GAD1 DNA hypermethylation, coupled with elevated mRNA and protein expression, has been associated with an unfavorable clinical course and significantly shorter RFS (33,57).

Hippo pathway components

Components of the Hippo signaling pathway, including TAZ, TEAD4, and YAP, demonstrate distinct expression patterns related to tumor aggressiveness (58). Cytoplasmic H-scores for TAZ and TEAD4 are significantly higher in epithelial-rich, high-grade TETs (WHO type B3, TC) and in tumors with advanced Masaoka-Koga stages (58). Specifically, TAZ cytoplasmic expression was elevated in B3/TC tumors compared with other subtypes ($P=0.0001$) and in stage III/IV disease ($P=0.0308$). Similarly, TEAD4 cytoplasmic expression was higher in B3/TC tumors ($P=0.002$) and marginally increased in stage II–IV tumors ($P=0.05$) (58).

In contrast, nuclear YAP expression was greater in less aggressive tumors, showing higher levels in type A and early-stage (I–II) TETs compared with B3/TC subtypes ($P=0.0042$) and advanced-stage disease ($P=0.042$) (58). Despite these associations with histology and stage, no

significant correlations between YAP, TAZ, TEAD4, or LATS1 expression and overall or DFS were observed ($P<0.10$) (58).

Cathepsins

Cathepsin K (CTK) expression is predominantly observed in TCs, with 76.9% of TCs showing CTK positivity compared with TMs ($P<0.05$) (50). Absent in normal thymic tissue, aberrant CTK expression may therefore serve as a potential diagnostic marker for TCs (50). Moreover, CTK expression correlates with poor outcomes, as patients who died from the disease exhibited significantly higher mean H-scores (170.0) compared with survivors (101.2; $P<0.01$ or $P=0.0038$), supporting its role as a prognostic biomarker in TCs (50).

In contrast, cathepsin B (CTB) and cathepsin D (CTD) are more frequently expressed in type A and type AB TMs (50). CTB was detected in 100% of type A TMs and in 56.4% of type AB cases, whereas CTD was expressed in 90.0% and 92.3%, respectively (50). In type AB TMs, CTB expression correlated with histologic features, being predominantly localized to the type A component ($P<0.01$ versus type B component) (50).

BMP-7

High expression of BMP-7 has been associated with poor prognosis in TETs (29). Across all patients, BMP-7 positivity correlated with significantly reduced OS ($P=0.006$) (29). BMP-7 expression was most frequent in type B3 TMs (70%) and TC (80%), contrasting with markedly lower rates in type B2 (29.1%), AB (26%), B1 (3.7%), and A (31%) TMs (29). The BMP-7 positive ratio increased proportionally with WHO-defined tumor malignancy ($P<0.001$) (29). However, in multivariate Cox regression analyses adjusting for other prognostic variables, age, but not BMP-7, emerged as the only independent predictor of OS ($P=0.033$) (29).

Ki-67

The Ki-67 labeling index (LI) is a well-established diagnostic and prognostic marker in TETs, correlating significantly with OS ($P=0.007$) and WHO histological subtypes ($P<0.0005$) (29). Higher Ki-67 LI values consistently characterize more aggressive tumors, with mean levels of 10.1% in TC versus 4.9% in type B3 TMs ($P=0.037$) (59). Ki-67 expression also correlates with metabolic and proliferative activity, demonstrating a strong association with the FDG PET-CT SUV T/M

ratio, described as a “metabolic biopsy” reflecting tumor proliferation (59). Moreover, elevated Ki-67 levels are significantly linked to BMP-7 positivity in type B3 TMs and TCs ($P=0.026$) (29).

Metabolic scores

Dysregulated cellular proliferation in TETs induces profound metabolic reprogramming, suggesting that metabolic profiling may uncover key aspects of tumor biology (60). Using LASSO Cox regression, a metabolic score derived from differential metabolism-related genes (DMRGs) was developed, with high scores correlating with significantly worse OS in both Kaplan-Meier ($P=0.015$) and multivariate Cox analyses, identifying it as an independent prognostic factor (60).

High metabolic scores were also linked to an immunosuppressive tumor microenvironment, predominantly the immune-desert phenotype, characterized by minimal T-cell infiltration and poor response to PD-1/PD-L1 blockade (60). These tumors exhibited reduced stromal and immune infiltration scores but upregulated CTLA-4 expression (60).

Moreover, elevated expression of asparagine synthetase (ASNS) and biliverdin reductase A (BLVRA) (both key metabolic enzymes) was associated with unfavorable outcomes, although neither emerged as an independent prognostic factor in multivariate analyses (60).

Immune-related lncRNAs (IRLs)

A robust IRL-based predictive model has recently been developed to improve prognostic assessment and prediction of immunotherapy response in TET patients (61). This IRL classifier was constructed using six prognosis-associated lncRNAs (AC004466.3, AC138207.2, AC148477.2, AL450270.1, HOXB-AS1, and SNHG8) identified through univariate Cox regression and LASSO regression analyses (61). By integrating the expression profiles of these markers, the model enables effective stratification of TET patients into low- and high-risk groups with significantly different survival outcomes (61). Characteristic expression patterns were validated in tumor samples, showing upregulation of AC138207.2, AC148477.2, AL450270.1, and SNHG8, and downregulation of AC004466.3 and HOXB-AS1, compared with normal controls (61). Importantly, in terms of predictive accuracy and clinical applicability, this IRL-based classifier demonstrated superior prognostic performance compared with the conventional Masaoka staging system (61).

Genomic alterations

The genomic landscape of TC is distinct from that of TM, generally featuring a significantly higher frequency of genomic alterations (12). Comprehensive genomic profiling of advanced, refractory TCs has revealed several recurrently mutated genes, many of which serve as crucial prognostic biomarkers that reflect the aggressive biological behavior of these tumors (12). The most frequently mutated genes in TC include (62):

- ❖ *TP53*: the *TP53* tumor suppressor gene is among the most frequently altered genes in TC (62). Immunohistochemical detection of p53 protein shows a strong correlation with underlying TP53 mutations in TC patients (62). Elevated p53 expression is commonly observed in TMs, with staining intensity increasing in more advanced stages of disease (15). Moreover, the p53 LI has been shown to correlate significantly with histological subtypes ($P<0.0005$) (63). Consistently, TP53 mutations have been confirmed as markers of poor prognosis in TC (62).
- ❖ *CDKN2A* and *CDKN2B*: recurrent mutations in *CDKN2A* and *CDKN2B* are frequently reported in TC and are linked to deregulation of cell cycle control pathways (12,62). Loss of p16INK4A expression (encoded by *CDKN2A*) has been associated with significantly worse recurrence- and metastasis-free survival ($P=0.01$), and in multivariate analysis it emerged as an independent predictor of poor outcome ($P=0.007$) (64). Homozygous deletion of *CDKN2A*, present in approximately 18.2% of analyzed TCs, is strongly correlated with loss of p16 expression ($P=0.02$) and confers adverse prognostic implications (62,64). In the squamous cell carcinoma subtype—the most common histological type of TC—loss of p16 expression was specifically associated with poorer OS ($P=0.0009$) as well as reduced recurrence- and metastasis-free survival ($P=0.006$) (64). Interestingly, homozygous *CDKN2A* deletion has also been linked to younger age at diagnosis in TC patients (62).
- ❖ *TET2*, *SETD2*, *BAP1*, and *ASXL1*: these genes are among the most frequently reported recurrently mutated genes in TC and are categorized as epigenetic regulatory genes (16,62). Mutations affecting these regulators underscore the importance of disrupted epigenetic control in TC pathogenesis (62). In particular, *TET2* mutations impair DNA demethylation by altering the conversion of 5-methylcytosine, ultimately contributing to abnormal genomic hypermethylation (62).

Alterations in DNA methylation have also been validated as prognostic factors in TETs. For example, hypermethylation of the cg05784862 site, which regulates the oncogene KSR1, is associated with improved prognosis, whereas patients with poor outcomes show reduced methylation at this site, leading to increased KSR1 expression (41). Additional methylation sites—including cg05784862 (KSR1), cg07154254 (ELF3), cg02543462 (ILRN), and cg06288355 (RAG1)—have been identified as independent prognostic markers for OS in TET patients, even after adjustment for Masaoka staging (41).

Proteomic markers

Proteomic markers such as CNOT2/9 (carbon catabolite repressor 4-NOT complex subunits 2 and 9) and SHMT1 (serine hydroxymethyltransferase 1) have been identified through systematic quantitative proteomic profiling of TETs, showing strong potential for both subtype differentiation and prognostic assessment (6). These proteins were expressed at markedly low levels in the thymic epithelia of the more aggressive subtype, thymic squamous cell carcinoma (TSCC), with SHMT1 in particular exhibiting very low abundance in TSCC samples (6). By contrast, both CNOT2/9 and SHMT1 were detected at high levels in type B3 TM (6). Immunohistochemical analyses confirmed high expression of these proteins in TM epithelia (6). At the transcriptional level, mRNA expression of CNOT2, CNOT9, and SHMT1 correlated closely with clinical outcomes, as patients with lower expression of these genes demonstrated significantly reduced RFS probabilities (6).

Imaging and other biomarkers

18F-2-fluoro-2-deoxy-D-glucose (18F-FDG) PET/CT
Pretreatment 18F-FDG PET/CT has demonstrated diagnostic value for predicting histological grade and provides prognostic information on recurrence and survival in resectable TET patients (65). The maximum standardized uptake value (SUV_{max}) shows excellent diagnostic performance for identifying TC and has been validated as an independent prognostic factor for FFR and as a significant predictor of OS in multivariable analyses (65). Elevated SUV_{max} values are also associated with markers of tumor aggressiveness, being significantly higher in BMP-7-positive tumors ($P=0.038$) (29). Furthermore, the ratio of tumor SUV to aortic arch SUV (SUV T/M) correlates significantly with WHO histological classification (65).

Notably, SUV T/M is markedly higher in samples with high Ki-67 LI, showing a strong correlation between SUV T/M and Ki-67 LI [Spearman rank non-linear correlation coefficient (ρ) =0.8] (59). These findings support the concept of FDG PET/CT as a “metabolic biopsy”, capable of reflecting tumor proliferative activity and stratifying TETs into high- and low-risk groups (65). In addition, metabolic tumor volume (MTV) and total glycolytic volume (TGV) have been reported as complementary prognostic imaging biomarkers (66).

TILs

The density and composition of TILs within the tumor microenvironment provide important prognostic information, particularly in aggressive TET subtypes. In patients with TC, reduced stromal infiltration by CD4⁺ lymphocytes ($P=0.037$) and CD20⁺ lymphocytes ($P=0.045$) has been associated with poor survival outcomes (67). Prognosis is further worsened when combinations of low CD4⁺ and CD20⁺ ($P=0.014$), CD8⁺ and CD20⁺ ($P=0.025$), or CD4⁺, CD8⁺, and CD20⁺ lymphocyte levels ($P=0.025$) are observed in the tumor stroma, suggesting a cooperative role of these subsets in suppressing tumor progression (67). The presence of PD-1–positive TILs (PD-1⁺ TILs) also carries prognostic relevance, correlating with significantly shorter DFS ($P=0.001$) (56). Interestingly, one study reported that abundant PD-1⁺ TILs, when combined with low PD-L1 expression, were strong predictors of poor survival (68). More broadly, TC is characterized by reduced overall lymphocyte infiltration, which contributes to elevated systemic inflammatory markers such as the NLR and PLR (33).

Matrix metalloproteinases (MMPs) and TIMP-2 expression

MMPs are proteolytic enzymes that mediate degradation of the extracellular matrix, a critical step facilitating tumor invasion and metastasis (15). In TETs, activation of matrix metalloproteinase-2 (MMP-2) has been directly linked to invasive behavior (69). Elevated expression of MMP-2 and its inhibitor, TIMP-2, correlates with adverse prognostic features in TET patients (15), and both MMP-2 positivity and TIMP-2 expression increase with advancing clinical stage (70). Expression patterns of MMP family members also vary by histological subtype: MMP-2 and MMP-7 expression in tumor cells correlate with WHO classification and clinical stage, with MMP-2 predominantly observed in type B3 TMs, MMP-7 in TCs, and MMP-9 in type B2 TMs (70).

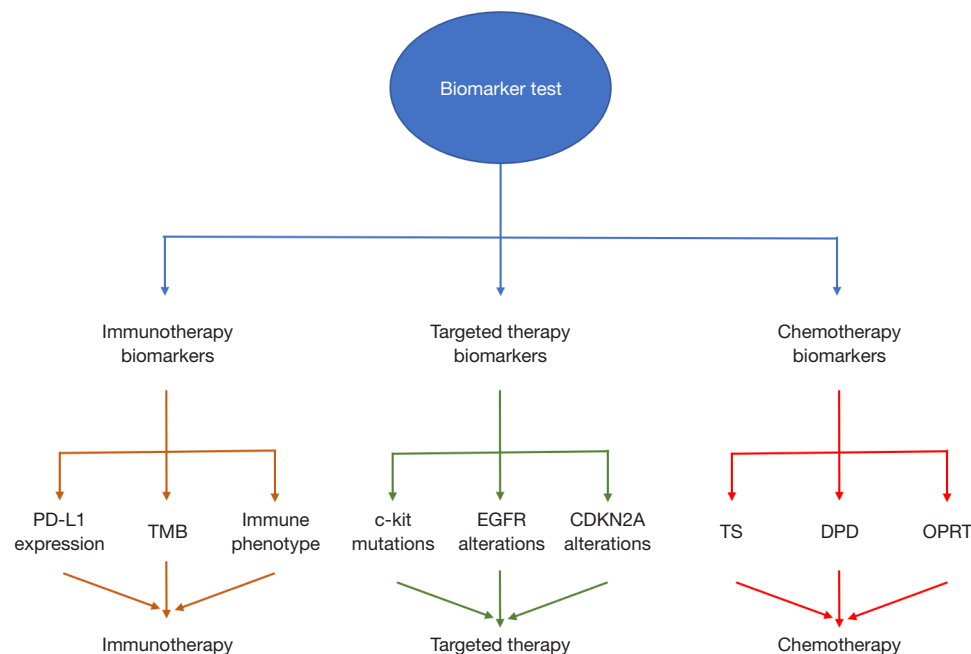


Figure 3 Predictive factors in TETs. DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; OPRT, orotate phosphoribosyltransferase; TET, thymic epithelial tumor; TMB, tumor mutational burden; TS, thymidylate synthase.

Predictive factors

The identification of predictive biomarkers, factors that forecast the likelihood of a patient responding to a specific treatment, is critical for advancing personalized medicine in rare and biologically heterogeneous TETs (12,16). Predictive factors in TETs primarily concern response to novel ICIs, molecularly targeted therapies, and, to a lesser extent, chemotherapy. Key predictive factors are summarized in *Figure 3*.

Predictive biomarkers for immunotherapy response

Immunotherapy using ICIs has demonstrated encouraging clinical activity in relapsed and refractory TETs (16,32). The necessity of investigating robust biomarkers predictive of response is heightened by the risk of severe immune-related adverse events associated with ICI administration in this patient group (16).

PD-L1 expression

PD-L1 expression is the most extensively studied predictive biomarker for ICI therapy. PD-L1 is detected in a high proportion of TETs, ranging from 61% to 82% (54). This elevated prevalence supports the rationale for targeting

the PD-1/PD-L1 axis as a potential therapeutic strategy in these tumors (16,54,71). However, clinical evidence remains mixed. A phase II trial of pembrolizumab in TC reported an objective response rate (ORR) of 22.5% (16). In one study, use of the 22C3 antibody with a cutoff of $\geq 50\%$ PD-L1 expression identified a subgroup with better treatment responses compared with tumors showing lower expression (42). Nonetheless, this predictive association has not been consistently validated across cohorts (16,42). Establishing a standardized, reproducible protocol for PD-L1 assessment is therefore essential to optimize its role as a biomarker and to advance personalized ICI-based therapy in TETs (16).

Genomic and molecular predictors

- ❖ **TMB:** TMB analysis is emerging as a key predictive parameter for evaluating the benefit-risk balance of ICI therapy in advanced TETs (12). Evidence from other malignancies indicates that higher TMB correlates with improved ORR and PFS following anti-PD-1/PD-L1 immunotherapy (28). Although data in TETs remain limited, TMB assessment may provide valuable guidance for clinical decision-making regarding ICI use (12).
- ❖ **CYLD mutations:** loss-of-function alterations in *CYLD*, a recurrently mutated gene in TC, may modulate response to ICIs (62). Preliminary findings from a

small phase II trial of pembrolizumab reported a higher prevalence of CYLD mutations among responders compared with non-responders, suggesting a potential predictive role (72).

- ❖ **IRL classifier:** the IRL classifier has been proposed as an innovative biomarker that captures the immune landscape of TETs and may guide personalized immunotherapy strategies (61,73). This model is significantly associated with immune cell infiltration (particularly dendritic cells, activated CD4 memory T cells, and TILs) as well as broader immune microenvironmental features, including immune score and checkpoint molecule expression. It also correlates with markers of tumor immunogenicity, such as TMB (61). Analyses using the TIDE algorithm revealed that the low-risk IRL subgroup contained a higher proportion of predicted ICI responders, while the IRL score was strongly and inversely associated with therapeutic benefit (61). Collectively, these findings highlight the IRL classifier as an integrative biomarker with the potential to predict prognosis, immune infiltration, and immunotherapy responsiveness in TET patients, ultimately supporting more individualized treatment approaches (61).

Predictive biomarkers for targeted therapy

Insights into the molecular biology of TETs have largely derived from anecdotal clinical responses to targeted therapies (51). Agents directed against receptor tyrosine kinases and other oncogenic pathways are being explored as potential biological treatments (51), and the identification of recurrent mutations provides a strong rationale for their clinical development (12).

KIT mutations (SCFR/CD117)

KIT (stem cell factor receptor, SCFR) is frequently overexpressed in TC (51,52). Importantly, KIT mutations represent a predictive biomarker, as they may confer sensitivity to c-kit tyrosine kinase inhibitors, including imatinib, sunitinib, and sorafenib (62,72). Anecdotal case reports have described notable responses to KIT inhibitors in mutation-positive patients (52). In particular, activating mutations such as V560del and L576P are known to be sensitive to imatinib, with impressive clinical responses documented in individual cases (52).

CDKN2A alterations

Loss of p16INK4A expression, encoded by CDKN2A,

or homozygous CDKN2A deletion, suggests a potential therapeutic role for CDK4/6 inhibitors in TETs. However, this strategy remains investigational and requires further functional validation (64).

EGFR overexpression

EGFR is overexpressed in up to 70% of TMs and 53% of TCs, with higher levels associated with advanced-stage disease (51). Although EGFR mutations are rare in TETs (51), case reports have documented clinical activity of the EGFR inhibitor cetuximab (52). Given the established role of EGFR as a therapeutic target in other cancers, continued investigation of anti-EGFR therapies in TETs is warranted (15).

Other potential targets

Additional molecular pathways of interest include the IGF1R, VEGF receptor (VEGFR), somatostatin (SST) receptors, histone deacetylases (HDACs), the mammalian target of rapamycin (mTOR), and cyclin-dependent kinases (CDKs) (51). The observation that most thymic malignancies exhibit moderate to high IGF1R expression provides a rationale for evaluating anti-IGF1R therapies (51,74). Clinical trials of the IGF1R monoclonal antibody cixutumumab (IMC-A12) have demonstrated disease control in both TMs and TCs (75). However, a significant limitation of this approach is the risk of severe immune-related adverse events; in one trial, 24% of TM patients developed autoimmune complications during treatment (75).

Predictive biomarkers for chemotherapy

Predictive biomarkers for chemotherapy response in TETs are crucial for personalized treatment selection. Enzymes involved in pyrimidine metabolism, specifically thymidylate synthase (TS), orotate phosphoribosyltransferase (OPRT), and dihydropyrimidine dehydrogenase (DPD), may predict the effectiveness of 5-fluorouracil (5-FU) based chemotherapy (76).

Pyrimidine metabolism enzymes (5-FU chemotherapy)

Enzymes of the pyrimidine pathway play a critical role in TET biology, as their expression reflects proliferative capacity, correlates with tumor grade, and may predict sensitivity to 5-FU-based chemotherapy (76). The key enzymes TS, OPRT, and DPD show expression patterns closely linked to tumor aggressiveness (76). In a study of

56 TET patients, TS, OPRT, and DPD were expressed in 61%, 48%, and 41% of cases, respectively, with higher-grade malignancies displaying significantly greater expression of all three markers (76). *In vitro* analyses further demonstrated marked overexpression of TS and OPRT in TC cells compared with thymic tumor or fibroblast cells, consistent with the poor chemosensitivity typically observed in this histological subtype (51,76). Expression of these enzymes has also been associated with p53 status and microvessel density, underscoring their integration into broader pathways of tumor progression (76).

Given that 5-FU specifically targets the pyrimidine pathway, the expression levels of TS, OPRT, and DPD are particularly relevant for predicting treatment response or resistance. High expression of these biomarkers may therefore serve as a valuable predictor of the effectiveness of 5-FU-based chemotherapy in TETs (76).

Systemic inflammation markers (combined modality therapy)

Preoperative assessment of host-related systemic inflammation markers has demonstrated value in identifying patient subgroups that may significantly benefit from combined treatment approaches in TETs (33,46). Focusing specifically on TC patients, analysis revealed that low preoperative levels of PLR and thrombocytes possess a clear predictive role for the efficacy of adjuvant therapy (33). Patients with low preoperative PLR values and low thrombocyte levels showed a statistically significant improvement in OS when receiving adjuvant combination chemo-radiotherapy compared to those receiving chemotherapy alone (PLR: $P=0.001$; thrombocytes: $P=0.007$) (33). This observation is hypothesis-generating, suggesting that TC patients exhibiting these low preoperative inflammatory markers may represent a specific subgroup that could significantly benefit from combined modality treatment after surgery, thus guiding individualized adjuvant therapeutic planning (33).

Discussion

The management of TETs has long relied on conventional histopathological classification and staging systems such as Masaoka-Koga and TNM. While these remain indispensable for initial treatment planning and prognostication, they fail to fully capture the biological complexity and clinical heterogeneity of these neoplasms.

Indeed, outcomes in patients with similar stage or histological subtype can diverge substantially, underscoring the limitations of purely morphological and anatomical criteria (7,21). This review highlights the growing body of evidence that molecular, immunological, and systemic host-related biomarkers can refine risk assessment and guide personalized therapeutic strategies in TETs.

From a molecular perspective, recurrent genetic alterations such as GTF2I mutations in indolent TMs or TP53 and CDKN2A aberrations in aggressive TCs represent robust indicators of divergent clinical trajectories (12). The favorable prognostic profile associated with GTF2I-mutated TMs suggests that a subset of patients may be candidates for de-escalated therapeutic approaches or surveillance-based strategies, while alterations in TP53 and CDKN2A consistently portend inferior survival and warrant closer monitoring or intensified treatment. Beyond prognosis, genomic findings are beginning to shape therapeutic selection. For instance, KIT mutations (though infrequent) have clear predictive implications for tyrosine kinase inhibitor responsiveness (12). Similarly, the relevance of PD-L1 expression and TMB as predictive biomarkers for ICIs continues to evolve. Despite conflicting data regarding PD-L1 as a prognostic marker (33,42), its widespread expression and correlation with immunotherapy response in subsets of patients underscore its clinical importance.

Equally noteworthy is the role of systemic inflammatory and nutritional indices such as NLR, PLR, and CAR, which mirror the host-tumor interaction and have emerged as independent predictors of survival across multiple malignancies, including TETs (33). Their accessibility and cost-effectiveness make them attractive adjuncts to molecular profiling, and early evidence suggests that specific inflammatory profiles may even predict benefit from combined modality treatment in TC. Incorporating such host-derived biomarkers into prognostic models can provide a more comprehensive picture of disease biology, moving beyond tumor-centric assessments.

Imaging-derived markers also hold promise. For example, FDG PET/CT parameters, particularly SUVmax and MTV, correlate strongly with proliferative activity, histological subtype, and outcomes (8). These tools provide a non-invasive “metabolic biopsy” and could be integrated with molecular and clinical markers to enhance real-time patient stratification.

Despite these advances, several challenges persist. The rarity of TETs has limited the generation of large, prospective datasets, leading to inconsistent cutoff values,

heterogeneous study designs, and variable methodologies across published series. Moreover, while multiple candidate biomarkers have been identified, few have undergone prospective validation or achieved standardized implementation in clinical practice. Collaborative international efforts, such as those coordinated by International Thymic Malignancy Interest Group (ITMIG) and International Association for the Study of Lung Cancer (IASLC), are crucial to harmonize research efforts, establish reproducible biomarker assays, and validate multiparametric prognostic models. Ultimately, such integrative approaches (incorporating clinical, molecular, immunological, and host-derived parameters) will be critical to achieving precision oncology in TETs.

Conclusions

Prognosis in TETs is primarily driven by histological classification, staging systems, and surgical outcomes. Molecular and immunological biomarkers hold promise but lack standardized implementation and prospective validation. Predictive biomarkers for immunotherapy and targeted treatments represent an emerging research frontier. The path forward requires the prospective validation of candidate biomarkers and the development of multiparametric models that integrate clinical, pathological, molecular, and systemic data. Such models have the potential to surpass traditional staging systems, enabling a more individualized therapeutic approach and ultimately improving outcomes for patients with these rare and heterogeneous tumors.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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