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ORIGINAL ARTICLE

Preoperative serum inflammation-based scores in medullary thyroid cancer

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KEYWORDS
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Abstract
Introduction: Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII) are prognostic factors in several tumours, though little is known in medullary thyroid cancer (MTC).
Objective: To evaluate the association between preoperative NLR, PLR and SII with MTC clinicopathological and molecular features, and their predictive value for lymph node and distant metastasis.
Methods: We retrospectively analysed 75 patients with MTC who underwent surgery at our institution. The familial form of MTC was found in 12% of patients.
Results: In our cohort, 56% were females, the median age at diagnosis was 57 years (44–69), the median tumour diameter was 25 mm (15–50); 21.3% were multifocal and 34.7% had extrathyroidal extension. Lymph node and distant metastasis were observed in 36 (48.0%) and 8 (10.7%) patients, respectively. Higher NLR was associated with preoperative calcitonin, angioinvasion, extrathyroidal extension, moderate/severe fibrosis; higher PLR was associated with extrathyroidal extension and advanced T stages; lower SII and NLR were associated with biochemical cure after surgery. Increased PLR, NLR and SII were associated with advanced MTC stages. In the univariate analysis, only NLR was associated with lymph node metastasis (odds ratio

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(OR) = 2.69, 95% confidence interval (CI): 1.50–5.84; $p = 0.004$); however, in the multivariate model, NLR was no longer a predictive factor for lymph node metastasis. None of these serum inflammatory markers predicted the occurrence of distant metastasis.
Conclusion: In conclusion, NLR, PLR and SII are associated with aggressive MTC, but do not predict lymph node or distant metastasis.

PALABRAS CLAVE
Cáncer medular de tiroides;
Índice neutrófilo-linfocito;
Índice plaqueta-linfocito;
Índice de inmunidad-inflamación sistémica

Marcadores inflamatorios preoperatorios en el cáncer medular de tiroides

Resumen
Introducción: El índice neutrófilo-linfocito (INL), el índice plaqueta-linfocito (IPL) y el índice de inmunidad-inflamación sistémica (IIS) son factores pronósticos en varios tumores, aunque poco se conoce en el cáncer medular de tiroides (CMT).
Objetivo: Evaluar la asociación entre INL, IPL e IIS preoperatorios con las características clínico-patológicas y moleculares del CMT y su valor predictivo de metástasis ganglionares y a distancia.
Métodos: Analizamos retrospectivamente 75 pacientes con CMT operados en nuestra institución. La forma familiar de CMT se encontró en el 12% de los pacientes.
Resultados: Un 56% eran mujeres, con una mediana de edad de 57 años (44-69). La mediana del diámetro del tumor fue de 25 mm (15-50); el 21,3% eran multifocales y el 34,7% tenían extensión extratiroidea. Se observaron metástasis ganglionares y a distancia en 36 (48,0%) y 8 (10,7%), respectivamente. Un INL más alto se asoció con calcitonina preoperatoria, angioinvasión, extensión extratiroidea y fibrosis moderada/grave; mayor IPL se asoció con extensión extratiroidea y estadios T avanzados; IIS y INL más bajos se relacionaron con la curación bioquímica después de la cirugía. IPL, INL e IIS más altos se asociaron con estadios más avanzados de CMT. En el análisis univariante solo el INL se asoció con metástasis en los ganglios linfáticos (OR = 2,69, IC 95%: 1,50-5,84; p = 0,004); sin embargo, en el modelo multivariante INL ya no fue un predictor de metástasis en los ganglios linfáticos. Ninguno de estos marcadores inflamatorios séricos predijo la aparición de metástasis a distancia.
Conclusión: En conclusión, INL, IPL e IIS se asocian con datos de mayor agresividad en CMT, pero no predicen metástasis a distancia o en ganglios linfáticos.

Introduction

Medullary thyroid cancer (MTC) arises from the parafollicular cells of the thyroid parenchyma, and it can occur sporadically or be hereditary in case of germline *RET* proto-oncogene mutations.[1] MTC accounts for less than 5% of thyroid malignancies, but is responsible for 13.4% of thyroid cancer-related deaths.[2] MTC is more often associated with lymph node and distant metastasis in comparison to differentiated thyroid cancer, and as many as 70% and 10% of patients with MTC present, respectively, with nodal or distant metastasis at diagnosis.[3] Surgery is the treatment of choice for loco-regional disease, consisting of at least total thyroidectomy with central lymph node dissection.[4]

Tumourigenesis results from the imbalance between cancer-promoting and cancer-inhibiting molecular pathways. Inflammation plays an important role in tumour biology, not only in the local tumour microenvironment, but also systemically, influencing tumour progression or recurrence, and promoting tumour cell proliferation, angiogenesis, invasion and metastasis.[5] Responses to systemic inflammation include alterations in haematopoiesis and in the secretion of acute-phase proteins, cytokines, growth factors and hormones. Different serum inflammation-based scores, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII) can reflect the degree of systemic inflammation and predict clinical outcomes and prognosis of patients with cancer.[6]

Several studies have reported a critical role for neutrophils in terms of tumour progression, through the release of cytokines and angiogenic factors. In addition, lymphocytes can secrete large amounts of cytokines, which can inhibit the cancer cell proliferation.[6] Granulocyte-colony stimulating factor and other cytokines, secreted by the tumour cells or non-neoplastic cells within the tumour microenvironment, induce neutrophil proliferation and myeloid-derived suppressor cell production in the bone marrow and inhibit lymphocyte proliferation, which result in an elevation of NLR, PLR and SII.[7] Hence, in general, high NLR, PLR and SII are associated with poorer cancer outcomes. There are a large number of studies analysing the clinical usefulness of NLR and PLR in different cancers,[7] including in endocrine-related cancers,[8,9] but little is known in MTC.[10–12]

Recently, the biomarker SII has been also shown to predict clinical outcomes in a variety of cancers,[13,14] with some studies highlighting its superiority over other inflammatory markers, including PLR and NLR, as it combines lymphocyte, neutrophil and platelet counts, and therefore better reflects the balance between the inflammatory and immune status.[13,15] There are no studies investigating the role of SII in patients with MTC.

Thus, we aimed to evaluate the association of preoperative serum NLR, PLR and SII with MTC's clinicopathological and molecular features at diagnosis and to determine their usefulness in predicting lymph node and distant metastasis.

Methods

Study population

Patients diagnosed with MTC and who underwent surgery between 1990 and 2016 at our institution were retrospectively analysed. Patients whose first surgery was performed at another hospital, with an unresectable tumour at the time of referral and those who received any other form of treatment before the operation (such as radiotherapy, chemotherapy or targeted therapy with tyrosine kinase inhibitors) were excluded from the study. Patients with chronic medical disorders affecting complete blood count, Hashimoto's thyroiditis, ectopic Cushing's syndrome, history of other active malignancy and infectious/inflammatory diseases or patients with acute myocardial infarction in the past 6 months, as well as patients having immunosuppressive therapy or corticosteroids were also excluded. The study population consisted of a total of 75 MTC patients.

Clinicopathological features and definition of the study subgroups

Patients' demographic data, preoperative levels of calcitonin, histological characteristics of the tumour, such as size, multifocality, fibrosis, angioinvasion, microscopic extrathyroidal extension, as well lymph node and distant metastasis at diagnosis were collected; the somatic mutation status of *RET* exons 5, 8, 10–16 were also checked. Biochemical cure of the disease was defined as undetectable postoperative serum calcitonin levels during follow-up. The fibrosis grade was recorded as being negative (absent), low (+), moderate (++), or severe (+++).[16] Patients were divided into two groups: group 1 (absent and mild fibrosis) and group 2 (moderate and severe fibrosis). *RET* molecular characterisation of the series has been previously reported.[17]

The Tumour-Node-Metastasis (TNM) classification of all tumour specimens and stage grouping were performed according to the criteria described in the American Joint Committee on Cancer (AJCC) TNM classification of MTC,[18] and two subgroups including T1/T2 patients and T3/T4 patients were formed and subject to comparative analysis. Regarding the AJCC stage, two subgroups were also formed, one including stage I and II patients and the other including patients staged III and IV.

Preoperative haematological data collection and calculation of serum inflammatory ratios

Blood samples were routinely taken three days prior to surgery and analysed at our institution's certified laboratory in a standardised manner on automated counters. The preoperative NLR was calculated dividing the absolute neutrophil count by the absolute lymphocyte count. PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. SII was defined as the absolute neutrophil count multiplied by the absolute platelet count divided by the absolute lymphocyte count.

Statistical analysis

Categorical variables are shown as the absolute number and percentage, while data from non-normally distributed continuous variables (as determined by Gaussian distribution with the Shapiro–Wilk test) are shown as median and interquartile range (IQR). Non-parametric data were further analysed with the Mann–Whitney *U* test. Correlations between continuous variables were determined by Spearman's correlation coefficient (rho) for non-normally distributed variables. To evaluate if NLR, PLR and SII represent independent risk factors for lymph node and distant metastasis, we used multivariate linear regression analysis. A 95% confidence interval (CI) was used to estimate the precision of the odds ratio (OR). Statistical analyses were carried out using the SPSS software version 25.0 (IBM, USA). A p-value <0.05 was considered statistically significant.

Results

The study cohort included 75 patients; 42 were women (56%), with a median age at MTC diagnosis of 57 years (44–69). Median NLR was 2.2 (1.7–3.3), median PLR was 141.5 (108.8–192.6) and median SII was 615.4 (384.0–931.2). The main characteristics of our cohort of MTC patients, including their clinicopathological features and TNM classification, are shown in Table 1. The presence of fibrosis was assessed in 37 samples: fibrosis was absent in 7 (18.9%), mild in 12 (32.4%), moderate in 11 (29.7%) and severe in 7 (18.9%). Hereditary forms of MTC were found in 9 (12%) patients, all of them with multiple endocrine neoplasia type 2 (MEN2) syndrome. *RET* somatic status was analysed in 35 patients without germline mutation: 21 cases harboured a *RET* somatic mutation, ten in codon 918 (Supplemental Table 1).

At diagnosis, lymph node metastasis was observed in 36 (48.0%) patients, 31 (86.1%) of whom had lateral and central compartment and 5 (13.9%) had only central compartment lymph node metastasis (Table 1). Regarding distant metastasis, it was only observed in 8 (10.7%) patients at diagnosis. Biochemical cure after surgery was observed in 28 (37.3%) patients, with a median follow-up of 72 months (36–180).

The associations between the inflammation-based scores NLR, PLR and SII and MTC clinicopathological features are shown in Tables 2 and 3. An increased NLR was associated with the presence of angioinvasion (2.7 (1.8–4.2) vs 2.1 (1.6–2.7); $p = 0.024$), extrathyroidal extension (2.8 (2.1–4.5) vs 2.1 (1.7–2.9); $p = 0.020$), higher grades of

Table 1 Baseline clinicopathological characteristics of the studied population.

Age (years), median (IQR)	57 (44–69)
Female, n (%)	42 (56.0)
Serum calcitonin at diagnosis (pg/mL), median (IQR)	1699 (7232)
Familial form of MTC, n (%)	9 (12)
Largest tumour diameter (mm), median (IQR)	25 (15–50)
Multifocality, n (%)	16 (21.3)
Extrathyroidal extension, n (%)	26 (34.7)
Angioinvasion, n (%)	43 (57.3)
TNM classification – primary tumour (T), n (%)	
T1	22 (29.3)
T2	13 (17.3)
T3	18 (24.0)
T4a	17 (22.7)
T4b	5 (6.7)
Lymph node metastasis at diagnosis, n (%)	36 (48.0)
Central	5 (13.9)
Lateral and central	31 (86.1)
Distant metastasis at diagnosis, n (%)	8 (10.7)
Bone	3 (4.0)
Lung	3 (4.0)
Liver	2 (2.7)
AJCC staging, n (%)	
I	18 (24.0)
II	15 (20.0)
III	5 (6.7)
IVA	25 (33.3
IVB	4 (5.3)
IVC	8 (10.7)
Biochemical cure after surgery, n (%)	28 (37.3)
Follow-up (months), median (IQR)	72 (36–180)
NLR, median (IQR)	2.2 (1.7–3.3)
PLR, median (IQR)	141.5 (108.8–192.6)
SII, median (IQR)	615.4 (384.0–931.2)

AJCC: American Joint Committee on Cancer; CEA: carcinoembryonic antigen; IQR: interquartile range; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammatory index; TNM: Tumour-Node-Metastasis.

fibrosis (group 1: 2.1 (1.8–2.9) vs group 2: 3.7 (2.3–4.9); $p = 0.019$) and advanced AJCC stages (stages I + II: 1.9 (1.6–3.0) vs stages III + IV: 2.8 (2.0–4.5); $p < 0.001$). Conversely, a low NLR was associated with biochemical cure after surgery (1.8 (1.5–2.2) vs 2.8 (2.1–4.3); $p < 0.001$) (Table 3). There was also a positive correlation between NLR and both serum calcitonin levels at diagnosis (rho = 0.283; $p = 0.027$) and number of lymph node metastasis (rho = 0.409; $p = 0.003$) (Table 2).

MTC patients with extrathyroidal extension had higher median PLR than those without (156.4 (125.5–210.7) vs 134.2 (98.9–172.8); $p = 0.040$), and the median PLR significantly differed between the TNM subgroups and MTC stages (Table 3).

Regarding SII, there was a significant association between higher SII and advanced AJCC stages (stage I + II: 477.7 (323.4–798.0) vs stage III + IV: 689.3 (496.3–1240.9); $p = 0.012$) and lower SII and biochemical cure after surgery (481.8 (317.9–777.6) vs 690.0 (419.1–1155.5); $p = 0.019$) (Tables 2 and 3). A positive correlation was found between SII and tumour diameter (rho = 0.411; $p < 0.001$) and between SII and number of lymph node metastases (rho = 0.346; $p = 0.013$) (Table 2).

On the univariate analysis, only NLR was a predictor of lymph node metastasis (OR = 2.69, 95% CI: 1.50–5.84; $p = 0.004$). However, in the multivariate model, when adjusted for the other clinicopathological variables (variables included in Table 3), NLR no longer predicted lymph node metastasis at diagnosis (OR = 1.14, 95% CI: 0.65–2.01; $p = 0.649$) (Table 4). None of the three serum inflammation-based scores had a statistically significant association with the presence of distant metastasis at diagnosis (data not shown).

Discussion

In our cohort of MTC patients, we evaluated the association of clinicopathological characteristics with the serum inflammation-based scores NLR, PLR and SII. Several studies have been carried out to investigate the role of NLR and PLR on thyroid cancer,[19-21] however there are only three studies focused on MTC[10–12] (summarised in Table 5); none of these studies assessed the usefulness of SII.

In two of these studies, PLR was found to be an independent predictor of outcomes among MTC patients, with higher preoperative PLR correlating with presence of lymph node metastasis, higher postoperative recurrence rates and lower disease-free survival.[10,11] The optimal PLR cut-off values in predicting recurrence were estimated at 129.8[10] or 128.9,[11] values above which recurrence was more likely; PLR > 105.3 was also found to be an independent predictor for lymph node metastasis.[10] On the other hand, NLR was not associated with recurrence or clinical outcomes in the setting of MTC.[11] Such findings suggest that PLR may be superior than other serum inflammation-based scores in MTC patients, and may well be an useful tool in identifying high-risk patients and perhaps in guiding clinicians towards a more intensive follow-up and/or treatment approach.[10,11] However, a more recent study from Xu and colleagues described an association between preoperative NLR and lymph node and distant metastasis, with an NLR > 1.784 predicting the occurrence of metastasis.[12] The potential usefulness of another inflammatory score in MTC, the Prognostic Nutrition Index, has also been reported.[11]

Taking into consideration these conflicting observations regarding NLR and PLR from previous studies[10–12] and the lack of data about SII in patients with MTC, we further investigated the usefulness of NLR and PLR, as well as SII, in predicting more aggressive disease and clinical outcomes in this patient cohort. We observed an association between high NLR and aggressive histological characteristics of the tumour such as angioinvasion, extrathyroidal extension and number of lymph node metastasis, features with recognised prognostic value in MTC.[22] PLR was associated only with extrathyroidal extension and the SII correlated positively

Table 2 Correlation between.

	NLR	PLR	SII
Serum calcitonin levels at diagnosis	rho = 0.283; p = **0.027**	rho = 0.127; p = 0.330	rho = 0.114; p = 0.383
Number of lymph node metastasis	rho = 0.409; p = **0.003**	rho = 0.251; p = 0.075	rho = 0.346; p = **0.013**
Largest tumour diameter	rho = 0.194; p = 0.073	rho = 0.213; p = 0.082	rho = 0.411; p < **0.001**

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammatory index. Bold values indicate p values that are significant (p < 0.05)

Table 3 Association between NLR, PLR and SII and MTC clinicopathological features.

	NLR Median (IQR)	PLR Median (IQR)	SII Median (IQR)
Multifocality			
No	2.3 (1.8–3.6)	141.5 (107.1–209.2)	615.4 (422.1–1236.3)
Yes	1.7 (1.8–2.9)	143.3 (114.7–178.9)	450.9 (360.1–869.0)
	p = 0.643	p = 0.593	p = 0.245
Angioinvasion			
No	2.1 (1.6–2.7)	133.1 (104.9–162.1)	515.9 (352.6–883.0)
Yes	2.7 (1.8–4.2)	152.4 (122.5–209.2)	678.6 (422.1–1236.3)
	p = **0.024**	p = 0.090	p = 0.161
Extrathyroidal extension			
No	2.1 (1.7–2.9)	134.2 (98.9–172.8)	540.8 (366.8–909.1)
Yes	2.8 (2.1–4.5)	156.4 (125.5–210.7)	689.3 (491.6–1267.7)
	p = **0.020**	p = **0.040**	p = 0.161
Primary tumour (T)			
Groups T1 + T2	2.1 (1.6–2.7)	122.6 (91.1–154.9)	511.0 (373.3–914.7)
Groups T3 + T4	2.5 (1.8–3.7)	152.6 (123.4–209.4)	650.3 (406.9–1029.9)
	p = 0.100	p = **0.016**	p = 0.486
AJCC staging			
Stages I + II	1.9 (1.6–3.0)	131.9 (99.4–153.2)	477.7 (323.4–798.0)
Stages III + IV	2.8 (2.0–4.5)	155.9 (121.1–210.7)	689.3 (496.3–1240.9)
	p < **0.001**	p = **0.032**	p = **0.012**
Fibrosis			
Group 1 (absent + mild)	2.1 (1.8–2.9)	141.5 (109.4–184.0)	566.4 (379.6–919.8)
Group 2 (moderate + severe)	3.7 (2.3–4.9)	154.2 (125.2–213.2)	920.1 (530.4–1319.1)
	p = **0.019**	p = 0.627	p = 0.145
Somatic RET 918 or 883 codon mutation			
No	2.5 (1.9–4.5)	144.8 (119.2–182.7)	724.8 (518.2–1266.8)
Yes	3.6 (2.1–4.4)	149.7 (104.9–214.3)	714.1 (389.3–1280.5)
	p = 0.432	p = 0.864	p = 0.785
Distant metastases			
No	2.2 (1.7–3.0)	136.7 (107.8–184.0)	566.4 (364.8–1605.7)
Yes	3.2 (1.8–6.6)	169.7 (142.8–218.6)	817.4 (535.5–2102.7)
	p = 0.159	p = 0.127	p = 0.099
Biochemical cure after surgery			
No	2.8 (2.1–4.3)	151.1 (113.6–207.3)	690.0 (419.1–1155.5)
Yes	1.8 (1.5–2.2)	129.1 (102.2–153.0)	481.8 (317.9–777.6)
	p < **0.001**	p = 0.095	p = **0.019**

AJCC: American Joint Committee on Cancer; IQR: interquartile range; MTC: medullary thyroid cancer; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; RET: rearranged during transfection; SII: systemic immune-inflammatory index. Bold values indicate p values that are significant (p < 0.05)

Table 4 Univariate and multivariate analysis assessing the roles of NLR, PLR and SII in predicting lymph node metastasis.

	Univariate analysis	Multivariate analysis[a]
NLR	OR = 2.69, 95% CI: 1.5–5.84; p = **0.004**	OR = 1.14, 95% CI: 0.65–2.01; p = 0.649
PLR	OR = 1.00, 95% CI: 0.99–1.01; p = 0.204	OR = 1.00, 95% CI: 0.99–1.01; p = 0.628
SII	OR = 1.00, 95% CI: 1.000–1.001; p = 0.630	OR = 1.00, 95% CI: 0.99–1.00; p = 0.501

CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammatory index.
[a] The variables included in the multivariate model were those considered in Table 3.

Table 5 Summary of the main findings from published studies investigating the role of serum inflammation-based scores in patients with medullary thyroid cancer.

Study	Number of patients	Preoperative NLR or PLR as predicting lymph node metastasis?	Association of NLR or PLR with other prognostic factors?
Jiang et al., 2016	70	- NLR was not an independent predictive factor for lymph node involvement - PLR > 142.1 (OR = 3.452, 95% CI 1.0–11.8) was an independent predictor for lateral lymph node metastasis by univariate and multivariate analysis	- PLR > 102.5 associated with larger tumours (p = 0.031), higher number of lymph node metastasis (p = 0.019) and tended to recur more often (p = 0.088) - NLR > 1.9 was associated with multifocality (p = 0.001) and bilaterality (p = 0.001)
Jiang et al., 2017	78	- PLR was predictive of lymph node metastasis (AUC of 0.644; p = 0.022) by univariate analysis	- PLR was predictive of capsule invasion (AUC of 0.666; p = 0.007) and advanced tumour stages (AUC of 0.657; p = 0.011) - PLR was predictive of recurrence on Kaplan–Meier and Cox regression analysis, with an AUC of 0.703 (95%CI 0.589–0.801; p = 0.002) - NLR showed no significant associations with other prognostic factors
Xu et al., 2018	61	- NLR was associated with lymph node and distant metastasis (OR = 5.918, 95% CI 1.147–30.541; p = 0.034) by univariate and multivariate analysis - Best predictive cut-off NLR value estimated at 1.784 (AUC of 0.717, sensitivity 68.3%, specificity 80%) - PLR was not evaluated in the study	- Not evaluated in the study

AUC: area under the curve; CI: confidence interval; MTC: medullary thyroid carcinoma; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; PLR: platelet-to-lymphocyte ratio.

with the tumour size and number of lymph node metastasis. Ceylan et al. also studied the correlation of NLR and PLR with clinicopathological features in 201 PTC patients and found that higher NLR was correlated with tumour size and extrathyroidal extension, whereas PLR was not associated with any of the clinicopathological characteristics studied.[23] Concerning the TNM classification, higher PLR, but not NLR, was significantly associated with advanced T stages, which may potentially reflect a poorer overall survival and cancer-specific survival.[24] NLR, PLR and SII were associated with advanced AJCC staging, but neither of them were found as independent predictive markers for lymph node or distant metastasis. A high NLR was associated with lymph node metastasis at diagnosis, but significance was lost in the multivariate analysis model, probably because histological findings, such as angioinvasion, may be more determinant for metastasis (whether regional or distant) than the inflammation itself. For this reason, we did not perform a Receiver Operating Characteristic curve analysis for lymph node metastasis. Also, none of the inflammatory markers showed a significant association with the presence of distant metastasis at diagnosis.

Low preoperative NLR and low SII were associated with biochemical cure after surgery, which emphasizes the value of these markers as potential tools to predict clinical outcomes in MTC patients who undergo surgery. We also found

a significant positive correlation between NLR and serum levels of calcitonin at diagnosis.

The median NLR was higher in the group of patients with moderate and severe fibrosis, a factor that has been considered to be correlated with poor prognosis in several cancers,[25] including in PTC.[26] Somatic *RET* mutations involving codons 918 or 883, which may confer increased aggressiveness,[17] were not associated with NLR, PLR or SII. The mutational status was assessed in a small number of patients which can explain, at least in part, this lack of association.

As such, in our study, we were only able to show an association between increased values of NLR, PLR and SII and MTC clinicopathological characteristics of aggressiveness, but it was not possible to determine a cut-off point for these predictive markers that is useful for clinical practice. Nevertheless, we consider this to be an important finding since we managed to show an association between inflammation and MTC aggressiveness. Several lines of evidence support a role for inflammation in the development and progression of thyroid malignancies: (i) altered expression of immune-related genes in PTC[27]; (ii) activation of oncogenes involved in PTC (such as *RET*/*PTC*, *RAS*, *BRAF*) upregulates a pro-inflammatory profile in normal thyrocytes and results in malignant behaviour[28]; (iii) thyroid tumour cells are an active source of cytokines and chemokines that may modulate the local tumour microenvironment and may have systemic pro-inflammatory implications.[29]

There are some limitations to this study that are mainly inherent to its retrospective nature. Other limitations of our study include: (i) single-centre study, mainly including a population of Portuguese patients, hence limiting the generalisation of our findings to other populations or ethnicities; (ii) we also cannot exclude that some patients would have unknown/unreported concomitant diseases or medications capable of influencing haematopoiesis or systemic inflammation; (iii) *RET* genetic analysis was only available for approximately half of the patients; (iv) our study population is relatively small which limits the assessment of the studied serum inflammation-based scores as it is based on small subgroups of patients and provides insufficient statistical power to detect significant differences, particularly after applying a multivariate analytical model and especially if taking into consideration that such haematological parameters have substantial inter- and intra-individual variability. Nevertheless, this is the second largest study evaluating the role of NLR and PLR in patients with MTC, as well as the first study assessing the usefulness of SII in MTC patients.

In conclusion, NLR, PLR and SII may be useful biomarkers to indicate increased clinicopathological aggressiveness in the MTC setting, but their usefulness in independently predicting lymph node or distant metastasis appears to be limited. Further studies involving larger cohorts of patients, ideally multi-centre and involving multi-ethnic populations, are needed to confirm some of the observations from this exploratory study.

Ethical approval

The research was carried out according to the principles of the Declaration of Helsinki. The local Ethics Review Committee of the Instituto Português de Oncologia de Lisboa approved the study protocol.

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Authors' contributions

A.A.F., J.S.-P., P.M. and V.L.: conceptualization. A.A.F., J.S.-P. and M.M.M.: data processing. A.A.F., J.S.-P. and S.E.: statistics. A.A.F.: writing of the original draft. J.S.-P., P.M., M.M.M. and V.L.: writing, review, and editing. V.L.: supervision.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.endinu.2022.06.007.

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