Thyroid

Clinical significance of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio and prognostic nutritional index in low-risk differentiated thyroid carcinoma

Significato clinico del rapporto neutrofili/linfociti, rapporto linfociti/monociti, rapporto piastrine/linfociti e indice prognostico nutrizionale nei carcinomi differenziati della tiroide a basso rischio

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SUMMARY

Objective. Inflammation and nutritional status play an important role in the prognosis of cancer. Lymphocyte-to monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and prognostic nutritional index (PNI) are independent prognostic scores in numerous cancers. However, any study showed their prognostic role in low-risk differentiated thyroid carcinoma (DTC). We aimed to clarify and identify the prognostic value of inflammation indices in low-risk DTC patients.

Methods. We analysed data from 116 patients, dividing the population into two groups, according to AJCC staging system (8th edition). The LMR, NLR, PLR and PNI cut-off value were determined using receiver operating characteristic (ROC) curve. Disease-free survival (DFS) was calculated with Kaplan-Meyer and Log-Rank tests and the risk of recurrence was calculated with univariate and multivariate Cox regression. Statistical significance was $p < 0.05$.

Results. We found a baseline NLR value ≥ 1.750 (75% sensitivity, 40.2% specificity) and a baseline LMR value of 3.83 (66.7% sensitivity, 48.9% specificity). Overall DFS was 74.995 ± 3.236 with a p value of 0.678. NLR showed a hazard ratio for recurrence with almost twice the risk of recurrence (Adjusted Hazard Ratio /HR[A]): 1.828, p-value = 0.019).

Conclusions. NLR can be considered a prognostic score with twice the risk of recurrence in low-risk DTC patients with NLR < 1.750.

KEY WORDS: thyroid carcinoma, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelet-to-lymphoctye ratio, prognostic nutritional index

RIASSUNTO

Oggetto. L'infiammazione e lo stato nutrizionale giocano un ruolo fondamentale nella prognosi del cancro. LMR, NLR, PLR, e PNI sono considerati fattori prognostici indipendenti in numerosi carcinomi. Tuttavia, nessuno studio ha dimostrato il loro ruolo nella prognosi dei DTC-basso rischio. L'obiettivo del nostro studio è chiarire e indentificare il valore prognostico di tali valori nei pazienti con DTC-basso rischio.

Metodi. Abbiamo analizzato 116 pazienti, dividendo la popolazione in due gruppi secondo la stadiazione AJCC. Il valore di LMR, NLR, PLR e di PNI è stato determinato con la curva ROC. La DFS è stata calcolata con il test di Kaplan-Meyer e con il test Log-Rank, mentre il rischio di recidiva è stato calcolato con la regressione univariata e multivariata di Cox. La significatività statistica è stata considerata con valori di p-value < 0,05.

Risultati. Abbiamo trovato un valore di NLR ≥ 1,750 (75% sensibilità, 40,2% specificità)

e di LMR di 3,83 (66,7% sensibilità, 48,9% specificità). La DFS è di 74,995 ± 3,236 con p-value di 0,678. NLR ha mostrato un Hazard Ratio con un rischio di recidiva doppio (HR[A] 1,828, p-value = 0,019).
Conclusioni. NLR può essere considerato un fattore prognostico con un rischio di recidiva duplicato nei pazienti con DTC-basso rischio con valori di NLR < 1,750.

PAROLE CHIAVE: *carcinoma tiroideo, rapporto neutrofili/linfociti, rapporto linfociti/monociti, rapporto piastrine/linfociti, indice prognostico nutrizionale*

Introduction

Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) account for 85% and 12%, respectively, of all thyroid cancers and are defined as differentiated thyroid carcinomas (DTC) [1]. The incidence of DTC has doubled (28.2/100,000 new cases per year in women and 10.1/100,000 new cases in men) in the past decade and the increase is more marked than any other cancer [2]. DTC is more frequent in women, but the mortality is similar between genders (1 death per year per 100,000 people) [3]. The clinical presentation of DTC varies from an indolent tumour with very low mortality to a very aggressive malignancy [3]. PTC has a predominantly lymphatic spread, while FTC shows haematic spreading [2]. Diagnostic suspicion is confirmed with ultrasonography imaging and echo-guided fine needle cytology (FNC) [3]. According to the American Thyroid Association (ATA), the recurrence rate in low-risk DTC is less 1-2% [3]. The treatment of choice in DTCs is surgery followed or not by radioactive iodine (RAI) therapy [3]. Pathological tumour-node-metastases (TNM) stage is the major prognostic factor in DTC [3]. The lymph node recurrence rate is variable in low-risk DTC changes according to histotype of the neoplasm and response to surgical treatment and RAI therapy [1]. Therefore, finding indices that can predict the presence of lymph node metastases at diagnosis or the rate of lymph node recurrence in low-risk DTCs can be a valid help in planning tailored treatment (thyroidectomy versus hemithyroidectomy and postoperative RAI therapy).

The immune system is potentially able to eradicate tumours; the inflammatory response is associated with initiation, progression, metastasis and prognosis [4]. Neutrophils, lymphocytes, monocytes and platelets are inflammatory mediators. Neutrophils and platelets product pro-inflammatory cytokines such as endothelial growth factor (VEGF), tumour necrosis factor-α (TNF-α), interleukin-2 (IL-2), interleukin-6 (IL-6) and interleukin-10 (IL-10), which contribute to tumourigenesis. Monocytes and lymphocytes, on the other hand, have anti-tumoural effects [4]. The literature confirms that the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) are independent prognostic factors in many solid cancers, including colorectal cancer, lung cancer, oesophagus cancer and laryngeal squamous cell carcinoma [5-7]. Prognostic nutritional index (PNI) is a new prognostic score that reflects inflammatory and nutritional status of patient [8]. The recent literature shows that PNI is a predictive and prognostic index in many solid tumours, such as colorectal cancer, gastric cancer, malignant pleural mesothelioma, hepatocellular carcinoma, pancreatic cancer and breast cancer [9-11]. All these indices can be calculated on routine preoperative blood samples and biochemical tests, with no additional costs.

NLR, LMR, PLR and PNI, to our knowledge, have never been investigated in patients with low-risk DTC. Therefore, the routine use of these inflammatory prognostic indices might add prognostic stratification in low-risk DTC patients.

According to the 2015 ATA guidelines, low-risk DTC is defined as: PTC without local or distant metastases; PTC with R0 after surgery; PTC without invasion of locoregional tissues; PTC without an aggressive histology; PTC without metastatic foci outside thyroid bed after RAI therapy; PTC without vascular invasion; PTC with clinical N0 or with ≤ 5 pathological micrometastases (N1c); intrathyroidal follicular variant of PTC; intrathyroidal FTC with capsular invasion and no or < 4 foci of vascular invasion and intrathyroidal papillary unifocal or multifocal microcarcinoma with or without BRAF[V600E] mutations [1]. We have investigated the association between preoperative NLR, PLR, LMR, PNI and the presence of lymph node metastasis and overall survival (OS) and disease-free survival (DFS) in patients with low-risk DTC undergoing or not RAI therapy. Therefore, the aim of this study was to understand the prognostic value of inflammation indices in low-risk DTC patients.

Materials and methods

We have retrospectively collected data on 208 patients who underwent thyroidectomy or hemithyroidectomy at the Department of Thyroid Surgery at the University of Campania "Luigi Vanvitelli". All patients had an anatomopathological diagnosis of DTC and underwent surgery between March 2012 and December 2019. Clinical and pathological TNM staging was performed according to the American Joint Committee on Cancer (AJCC) staging system (8th edition) [12]. We enrolled 116 patients.

We included patients aged over 18 years and not pregnant with: single or multiple thyroid nodule with cytological diagnosis of TIR1c, TIR3a, TIR3b, TIR4 and TIR5 to FNC; characteristic of low-risk DTC, according to 2015 ATA guidelines; complete medical history and complete preoperative blood tests. We excluded patients with: presence of single or multiple thyroid nodule with cytological diagnosis of TIR1 or TIR2; other histopathological thyroid cancer as medullary thyroid cancer (MTC) or anaplastic thyroid cancer (ATC); autoimmune thyroid disease (Hashimoto's thyroiditis or Basedow's disease); neck surgery within 5 years; neck radiation therapy; previous thyroid tumour; previous tumour of the head-neck district; chronic inflammation due to HBV, HCV, chronic gastritis, nephritis or gout; immune or haematological disease; history of chronic anticoagulant drugs use and proliferative haemopoietic disorders. The flow chart (Fig. 1) shows the patients enrolled according to the inclusion and exclusion criteria.

We divided the population into two groups based on age: ≤ 55 years and > 55 years, according to the AJCC thyroid staging system (8th edition). All patients underwent blood and biochemical analyses, FNC, thyroid and laterocervical lymph node ultrasound and fibreoptic-laryngoscopy in the 30 days prior to surgery. Clinical and demographic data as age and sex were obtained from the archive files. Anatomopathological findings suchas histopathological type,

dimension, capsular invasion, vascular invasion, laterality, unifocality, multifocality and stage were obtained from archive files. Laboratory data on white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets were obtained from archive data. NLR, LMR and PLR were obtained from the simple relationship between the two values; PNI was obtained using the following formula: [10 x albumin (g/dL) + (0.005 x total lymphocytes count (10³/μL)]. All surgical procedures were performed by two surgeons. The surgical treatments performed were total thyroidectomy (TT), near total thyroidectomy (NTT) or hemithyroidectomy (HT). TT is the surgical treatment of choice in the treatment of thyroid diseases that requires extracapsular removal of the gland in its entirety. NTT involves the extracapsular removal of the gland leaving a small thyroid residue at the level of the recurrent laryngeal nerve or at the level of the nerve entrance at the laryngeal level where total removal is associated with a sacrifice of the nerve itself. HT involves the removal of the thyroid lobe associated with the removal of the isthmus. These surgical treatments are foreseen in the treatment of DTC by the ATA guidelines [1].

During follow-up we assessed postoperative RAI therapy I^{131}, the rate of lymph node recurrence and DFS. After primary surgery, a follow-up programme was carried out for all patients. During the first years, physical examination, serum thyroglobulin (Tg) and neck ultrasound were performed every 3 months and every 6 months from the second year. In our population we had a follow-up ranging from 3 to 93 months. Recurrence was defined by increased serum Tg (≥ 20 μg/L) and the appearance of suspicious lymph node metastases on neck ultrasound, and then confirmed with FNC and Tg measurement in FNC eluates. DFS was defined as the interval between primary surgery and lymph node recurrence.

This study was approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli" (AOU4588/2020). Written informed consent was obtained from all participants. All procedures performed were in according to Helsinki Declaration.

Statistical analysis
Continuous variables were described as mean and standard deviation (SD), while categorical variables were described as number of cases and percentage. Independent t-tests were performed to compare continuous variables (month of recurrences, maximum diameter of neoplasm and all haematological values with their relatives score), and a test of proportions was applied to categorical variables (number of patients, FNC, RAI, lymph node recurrences and microcarcinoma). The LMR, NLR, PLR and PNI cut-off values
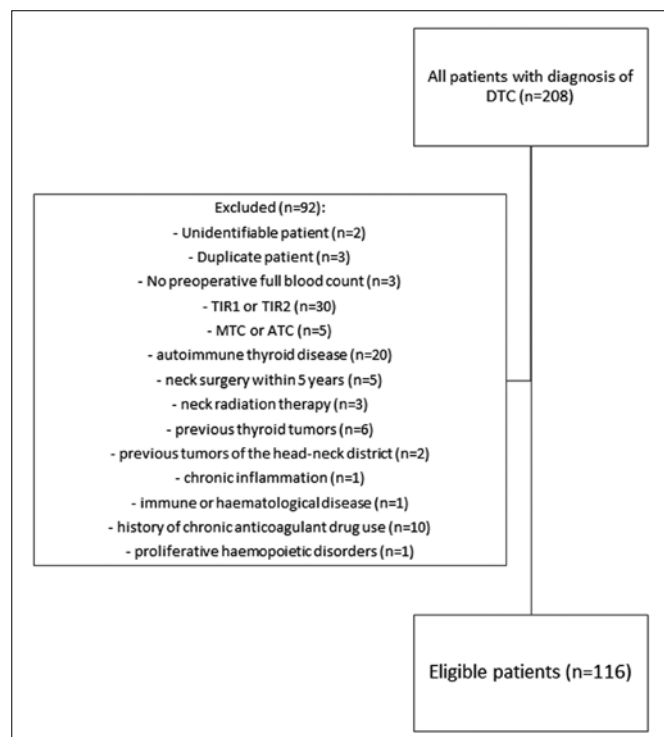
Figure 1. Flow chart of eligible patients.

were determined using a receiver operating characteristic (ROC) curve. Moreover, Fisher's exact test was used to analyse gender, surgical treatment, laterality of neoplasm and histopathological reports. DFS was calculated with the Kaplan-Meyer method and Log-Rank test was used to compare recurrences. The risk of recurrence (Hazard Ratio, HR) was calculated using univariate and multivariate Cox's regression. Statistical significance was considered in case of p value < 0.05. Statistical analysis was performed with SPSS version 23 (SPSS©, Chicago, IL, USA).

Results

We retrospectively enrolled 116 consecutive patients who underwent surgery for a low-risk DTC in our department from March 2012 and December 2019. According to AJCC stage, patients were divided in two groups: low-risk DTC ≤ 55 years and low-risk DTC ≤ 55 years. Baseline demographic characteristics, cytology details, surgical treatment and anatomopathological report are shown in Table I. The study cohort included 80 (68.9%) patients ≤ 55 years and 36 (31.1%) patients > 55 years; the mean age was 43.1 years in the group ≤ 55 years and 63.8 years in the group > 55 years. Female patients were 85.3% without no significant difference (p-value 0.26) between groups. There was no TIR1c in our population. TIR3a, TIR3b, TIR4 and TIR5 in the ≤ 55 year group were 3.75%, 40%, 18.75% and 37.5%, respectively, and 8.34%, 25%, 30.55% and 36.11%, respectively, in the > 55 year group with no significant difference. The principal surgical procedures applied were TT/NTT, and HT was performed in only 5.2% of the cohort (p = 0.08). Tumours were present in 41.4% in the right lobe and in 58.6% in the left lobe (p = 0.06). We analysed only low-risk DTC and recorded 106 cases (91.4%) of PTC and 10 cases (8.6%) of FTC (p = 0.49). We found a microcarcinoma in 50% of the cohort (p = 0.99). In the entire population, we recorded a maximum diameter of neoplasia of 1.37 cm (p = 0.403). In the ≤ 55 year group, 100% of

Table I. Baseline characteristics of patients.

Characteristic	Population	≤ 55 years (according to AJCC stage)	> 55 years (according to AJCC stage)	p-value
Patients (%)	116	80 (68.9)	36 (31.1)	< 0.001
Mean age in years (SD)	49.2 (± 12.45)	43.1 (± 8.45)	63.8 (± 8.58)	< 0.001
Sex (%)				
Male	17 (14.7)	14 (17.5)	3 (8.4)	0.26
Female	99 (85.3)	66 (82.5)	33 (91.6)	
FNC (%)				
TIR1c	0 (0)	0 (0)	0 (0)	0.99
TIR3a	6 (5.2)	3 (3.75)	3 (8.34)	0.56
TIR3b	41 (35.3)	32 (40)	9 (25)	0.17
TIR4	26 (22.4)	15 (18.75)	11 (30.55)	0.24
TIR5	43 (37.1)	30 (37.5)	13 (36.11)	0.72
Surgery (%)				
TT/NTT	110 (94.8)	78 (97.5)	32 (88.9)	0.08
HT	6 (5.2)	2 (2.5)	4 (11.1)	
Laterality of tumour (%)				
Right	48 (41.4)	29 (35)	19 (52.8)	0.06
Left	68 (58.6)	53 (65)	15 (47.2)	
Anatomopathological reports (%)				
PTC	106 (91.4)	74 (92.5)	32 (88.9)	0.49
FTC	10 (8.6)	6 (7.5)	4 (11.1)	
Mean maximum diameter in cm (SD)	1.37 (± 1.89)	1.47 (± 2.2)	1.15 (± 0.8)	0.403
Stage (%)				
I	111 (95.7)	80 (100)	31 (86.1)	0.002
II	5 (4.3)	0 (0)	5 (13.9)	
Microcarcinoma (%)	58 (50)	40 (50)	18 (50)	0.99

SD: standard deviation; PTC: papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; TT: total thyroidectomy; NTT: near total thyroidectomy; HT: hemithyroidectomy.

Table II. Baseline haematological values.

Blood values	Population	≤ 55 years (according to AJCC stage)	> 55 years (according to AJCC stage)	p-value
Mean albumin (SD)	4.49 (± 0.31)	4.51 (± 0.26)	4.45 (± 0.40)	0.356
Mean white blood cells (SD)	6.82 (± 2.17)	7.03 (± 2.18)	6.53 (± 2.09)	0.116
Mean neutrophils (SD)	4.37 (± 1.67)	4.61 (± 1.74)	3.84 (± 1.38)	0.21
Mean lymphocytes (SD)	2.45 (± 4.29)	2.65 (± 5.15)	2.02 (± 0.73)	0.467
Mean monocytes (SD)	0.42 (± 0.14)	0.43 (± 0.14)	0.39 (± 0.13)	0.157
Mean eosinophils (SD)	0.16 (± 0.10)	0.16 (± 0.10)	0.17 (± 0.09)	0.549
Mean basophils (SD)	0.04 (± 0.03)	0.04 (± 0.03)	0.03 (± 0.01)	0.06
Mean platelets (SD)	259.8 (± 52.05)	266.08 (± 51.10)	245.69 (± 52.09)	0.051
Mean LMR (SD)	6.20 (± 8.29)	6.37 (± 9.61)	5.48 (± 4.12)	0.751
Mean NLR (SD)	2.41 (± 1.09)	2.59 (± 1.20)	2.01 (± 0.66)	0.001
Mean PLR (SD)	145.05 (± 48.8)	151.14 (± 51.8)	131.5 (± 38.8)	0.045
Median PNI (SD)	44.94 (± 3.17)	45.13 (± 2.69)	44.53 (± 4.06)	0.354

SD: standard deviation; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index.

Table III. RAI, recurrences and lymph nodes recurrence frequency.

	Population	≤ 55 years (according to AJCC stage)	> 55 years (according to AJCC stage)	p-value
RAI therapy (%)	59 (50.86)	47 (58.8)	12 (33.3)	0.01
Lymph node recurrences (%)	24 (20.68)	18 (22.5)	6 (16.7)	0.63
Mean months of recurrence (SD)	22.45 (± 21.71)	26.44 (± 23.81)	10.50 (± 3.50)	0.13

SD: standard deviation; RAI: radioactive iodine.

patients were in TNM stage I, while in the > 55 year group 13.9% of patients were in TMN stage II, with a significant difference between groups (p = 0.002). This difference is due to staging of the malignancy. The patients in stage II had a T3a, and therefore neoplasm size and age determinate the stage [15].

Table II shows baseline haematological values. Only two values, mean NLR and mean PLR, showed a significant difference between groups. Mean NLR was 2.41 (SD ± 1.09) in entire population, 2.59 (SD ± 1.20) in the ≤ 55 year group and 2.01 (SD ± 0.66) in the > 55 year group (p = 0.001). Mean PLR was 145.05 (SD ± 48.8) in the entire population, 151.14 (SD ± 51.8) in the ≤ 55 year group and 131.5 (SD ± 38.8) in the > 55 year group (p = 0.045).

Table III shows data from patients who underwent RAI therapy, lymph node recurrence and DFS in months. The percentage of lymph node recurrence and DFS in months showed no significant differences between groups. In all, 47 patients underwent RAI therapy (58.8%) in the ≤ 55 year group and 12 patients (33.3%) in the > 55 year group with a significant difference between groups (p = 0.01). Our data showed that the indication to RAI was common in young patients.

Table IV shows prognostic scores to evaluate recurrence risk factors; in particular, adjusted NLR showed a HR of 1.828 (p = 0.019). Other haematological values showed no significant differences in the HR.

We calculated the receiver operating characteristic

Table IV. Univariate and multivariate analysis evaluating risk factors affecting recurrences.

	Unadjusted HR (95% CI)	p-value	Adjusted HR[a] (95% CI)	p-value
PNI	1.110 (0.985-1.252)	0.088	1.088 (0.966-1.225)	0.162
NLR	1.240 (0.873-1.760)	0.229	1.828 (1.103-3.029)	0.019
LMR	1.008 (0.961-1.057)	0.739	1.011 (0.958-1.066)	0.696
PLR	0.997 (0.998-1.005)	0.47	0.988 (0.975-1.001)	0.079

[a]Adjusted for age, full blood count values, procedure and dimension of lesion. HR: hazard ratio; CI: confidential interval; PNI: prognostic nutritional index; NLR: neutrophil-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio; PLR: platelet-to-lymphocyte ratio.
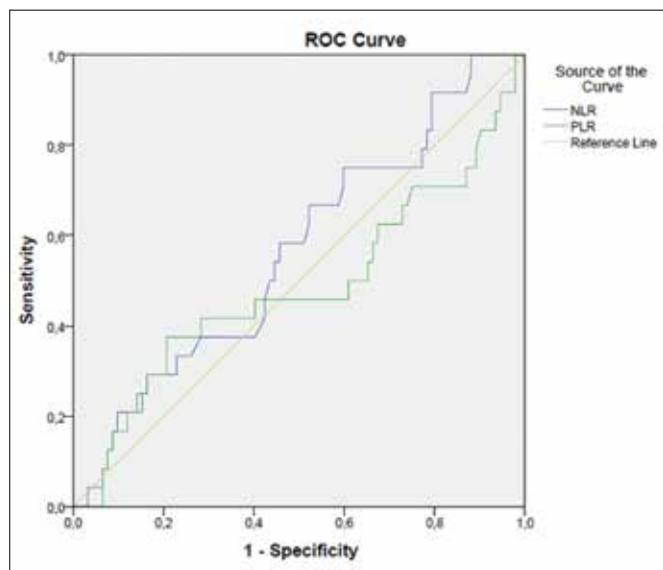
Figure 2. ROC curve of LMR with a cut-off value of 4.635 (AUC 0.540 ± 0.066, 66.7% sensitivity, 48.9% specificity) and PNI (AUC 0.417 ± 0.079). (LMR: lymphocyte-to-monocyte ratio; PNI: prognostic nutritional index; AUC: area under curve).
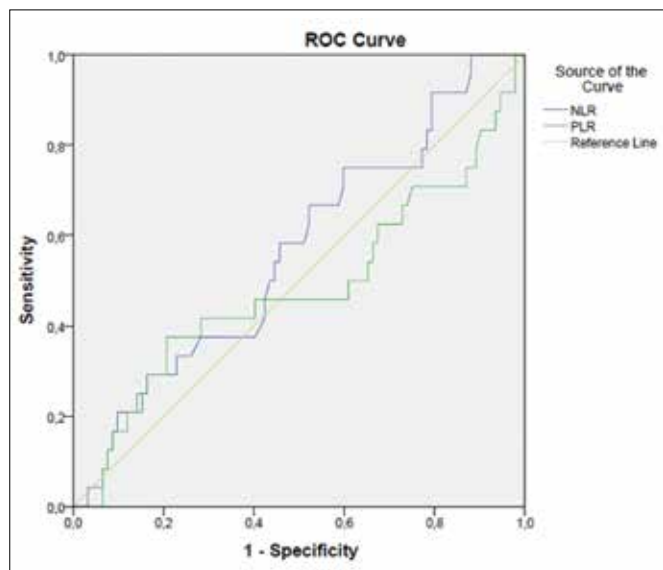

Figure 4. DFS functions distinguished between patients ≤ 55 years and > 55 years. DFS was 74.995 ± 3.236; DFS was 72.249 ± 3.689 in patients ≤ 55 and DFS was 77.514 ± 5.717 in patients >55 years. Log-rank test was used to compare recurrences (p = 0.678). (DFS: disease-free survival).

Figure 3. ROC curve of NLR with a cut-off value of 1.750 (AUC 0.564 ± 0.065, 75% sensitivity, 40.2% specificity) and PLR and (AUC 0.484 ± 0.075). (NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; AUC: area under curve).

(ROC) curves for LMR and PNI values (Fig. 2). We found 4.635 as best cut-off value for LMR with 66.7% sensitivity, 48.9% specificity and an area under the curve (AUC) of 0.540 ± 0.066. We did not find a cut-off value for PNI. All PNI values entered in the ROC curve were below the reference line with an area under the curve of 0.417 ± 0.079.
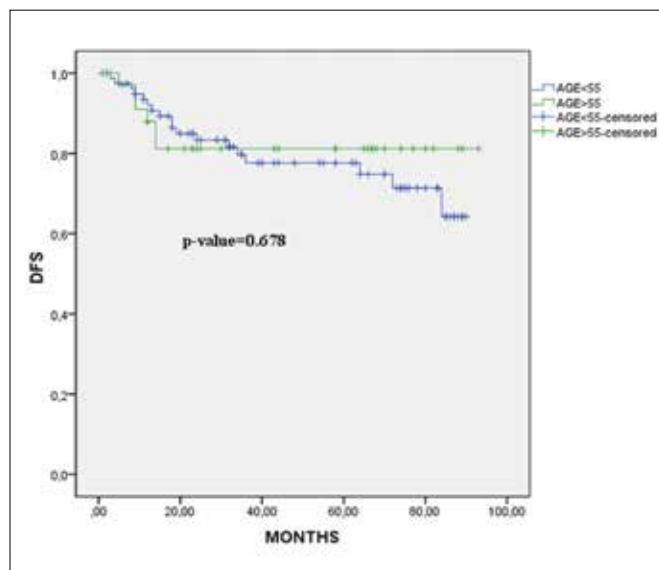
We also calculated a ROC Curve for NLR and PLR (Fig. 3). NLR cut-off values was 1.750 with 75% sensitivity, 40.2% specificity and an AUC of 0.564 ± 0.065. As for the PNI cut-off value, we found no cut-off value for PLR. All PLR values were below the ROC curve reference line with an AUC of 0.484 ± 0.075.

Figure 4 shows DFS curves in the two groups. Overall DFS was 74.995 ± 3.236; DFS in the ≤ 55 year group was 72.249 ± 3.689 and in the > 55 year group was 77.514 ± 5.717 (p = 0.678). There was no significant difference between recurrences based on age, as shown above.

Discussion

Herein, we tried to find a correlation between haematological inflammation indexes and prognosis and risk of recurrence. This is the first study that has examined correlations between LMR, NLR, PLR, PNI and the risk of recurrence in patients with low-risk DTC. The 2015 ATA guidelines suggest undergoing HT in low-risk DTC patients and to undergo NTT/TT in case of expected postoperative RAI therapy, follow-up based on increased serum Tg and patient preference [1]. Various studies have documented a recurrence rate of 1-2% in patients who underwent thyroid surgery without postoperative RAI therapy over a follow-up of 5-10 years [13,14]. Indeed, with a low risk of recurrence, the risk stratification changes during follow-up [1]. The aim of our study was to find an instrument that can identify, at

the time of diagnosis, patients at higher risk of recurrence which would allow improving the follow-up protocols and plan tailored treatment.

Blood inflammatory cells play an important role in initiation, progression, metastasis and prognosis in oncological patients. Inflammatory blood mediators include neutrophils, lymphocytes, monocytes and platelets. Monocytes and lymphocytes play an important role as anti-tumoural mediators. Low levels of lymphocytes and monocytes has been observed in advanced stage neoplasms and are associated with a poor prognosis [15]. Monocytes penetrate the tumour mass, reduce angiogenesis and induce apoptosis of cancerous cells, thus reducing cancer invasion and progression [15,16]. In the literature, low LMR has been associated with poor prognosis in numerous solid cancers and is an independent prognostic factor. This alteration of the immune system promotes angiogenesis, progression and tumour invasion [17,18]. In thyroid carcinoma the low LMR value is associated with worse prognosis, a high risk of recurrence of ATC and high-risk DTC [19,20]. At the moment no study has examined whether a low LMR value in low-risk DTCs can be an indicator of worse prognosis and increased risk of lymph node recurrence. In our study, the LMR cut-off value was 4.635 with 66.7% sensitivity and 48.9% specificity. In the literature, various studies have reported that NLR is an independent prognostic factor in numerous solid tumours [5,21]. However, there are few in DTC. A high ratio is due to an increased neutrophil count compared to lymphocyte count. As mentioned above, neutrophils produce VEGF and inhibit TNF-α, facilitating tumour progression and invasion, and a decreased lymphocyte and monocyte count is associated with reduction in antineoplastic activity [4,15,16]. Moreover, neutrophils promote the secretion of IL-2, IL-6 and IL-8, contributing to tumourigenesis [4]. Despite this, the exact correlation between NLR and cancer prognosis still is not entirely clear. Chen et al. suggested that a low NLR (≤ 1.6) is associated with a high risk of PTC recurrence, but with a follow-up of 12.2 ± 3.8 months it is not possible to have an estimate of DFS and OS at 5 or 10 years [22]. Ceylan et al. suggested an NLR cut-off value of 1.92 and a correlation between a high NLR, large tumour size and positivity of extra-thyroidal spread [23]. Seretis et al. reported that an elevated preoperative mean NLR is present in patients with microcarcinoma and in DTC, and found that elevated mean NLR does not show any significant difference between patients with multifocal or unifocal microcarcinoma. They did not evaluate an NLR cut-off, but only the NLR preoperative mean [24]. In the literature there are no univocal and concordant data, and thus further studies are needed to find possible correlations between inflammatory indexes and risk of DTC lymph node recurrence to validate

them as independent risk factors. In our population, we found an NLR cut-off value of 1.750 with 75% sensitivity and 40.2% specificity. This suggests that we have a good chance of finding unwell patients with NLR values ≥ 1.750, but a poor chance of finding healthy patients. Therefore, only NLR showed a valid HR for recurrence, and indeed it is associated with almost twice the risk of recurrence (Adjusted HR 1.828, p = 0.019), while patient age showed no significant difference in terms of risk of recurrence. Even if patients with > 55 years had higher DFS, there was no significant difference between groups (p = 0.678). This can be explained by the fact that in our cohort there were more patients ≥ 55 years undergoing RAI therapy.

According to the most recent studies, there are few correlations between PLR and prognosis of patients with DTC. Ceylan et al. found no correlation between clinicopathologic features of PTC and PLR [23]. Ozmen et al. reported that PLR and NLR are more successful indexes for diagnosis and recurrence of DTC than C-reactive protein (they included FTC, PTC and microcarcinoma). They found that high NLR and PLR are associated with high levels of thyroglobulin and worse prognosis, but their study did not evaluate cut-off values of these indexes [25]. In our study, we did not find a cut-off value for PLR because the PLR AUC was 0.484 ± 0.075 and all values were under reference line. Therefore, further studies are necessary to correlate PLR with multiple variables.

PNI is a score that assesses the patient's nutritional status and immune status based on evaluation of lymphocyte counts and albumin. PNI is a prognostic independent score in most solid cancers, including colorectal cancer, gastric cancer, malignant pleural mesothelioma, hepatocellular carcinoma, pancreatic cancer and breast cancer. Studies show that a low PNI value is associated with worse prognosis due to the deficiency in the nutritional state and deficits of the immune system [9-11]. In our study, we did not found a cut-off value for PNI. Our hypothesis was that we selected a population without concomitant pathologies and with low-risk DTC, a type of indolent tumour with good prognosis.

This study showed that only NLR was a prognostic score, but further studies are necessary to clarify and validate its specific role.

Conclusions

The correlation between inflammatory indexes and OS and DFS has been established in numerous solid tumours. In our study, NLR emerged as a prognostic factor. Obviously, additional studies are needed to demonstrate this correlation and cannot yet be used to stage and stratify patients

with low-risk DTC. The limitation of our study is its retrospective nature. Follow-up should be extended to 10 years to better assess the risk of long-term recurrence and a larger population should be examined. Our hope is that in the future these scores can be used to predict the risk of recurrence and to identify patients with low-risk DTC to be submitted to RAI therapy to avoid delays in treatment and to avoid overtreatment by implementing tailored therapy.

Acknowledgements

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