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Thyroid

Evaluation of LMR, NLR and PLR as predictors of malignancy in indeterminate thyroid nodules

Valutazione di LMR, NLR e PLR come predittori di malignità in noduli tiroidei indeterminati

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SUMMARY

Objective. Thyroid nodules with indeterminate cytology represent 20% of all thyroid nodules. Inflammation plays an important role in cancer. Lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are independent prognostic scores in numerous cancers, although no study has documented their role in cytology indeterminate nodules. The aim of this study is to evaluate the role of LMR, NLR and PLR values as predictors of malignancy in patients with cytology indeterminate nodules.

Methods. This retrospective study analysed data from 298 patients with indeterminate thyroid nodule. Anatomopathological and haematological data were analysed, dividing the population into two groups. LMR, NLR and PLR values were determined using ROC curve and data were analysed using independent samples t-test, test of proportions, Fisher's exact test and univariate and multivariate logistic regression.

Results. We found that a baseline LMR value ≥ 4.09 was indicative of benignity of indeterminate nodule. The probability of malignancy in patients with LMR < 4.09 was 26 times higher than patients with a LMR value ≥ 4.09.

Conclusions. This study showed that only LMR has shown a concrete probability to find a thyroid cancer in patients with indeterminate nodules. Further studies are necessary to implement tailored treatment.

KEY WORDS: indeterminate thyroid nodule, thyroid cancer, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, platelet-to-lymphocyte ratio

RIASSUNTO

Obiettivo. *I noduli tiroidei a citologia indeterminata rappresentano il 20% di tutti i noduli tiroidei. L'infiammazione gioca un ruolo importante nel cancro. LMR, NLR e PLR sono fattori prognostici indipendenti in numerosi tumori; tuttavia, nessuno studio ha mostrato il loro ruolo nei noduli a citologia indeterminata. Questo studio si propone di valutare il ruolo di LMR, NLR e PLR come predittori di malignità in pazienti con noduli a citologia indeterminata.*

Metodi. *Abbiamo analizzato retrospettivamente i dati di 298 pazienti con nodulo tiroideo indeterminato. Abbiamo analizzato i dati anatomopatologici ed ematologici, dividendo la popolazione in due gruppi. I valori cut-off di LMR, NLR e PLR sono stati determinati con la curva ROC e i dati sono stati esaminati utilizzando il t-test per campioni indipendenti, il test delle proporzioni, il Fisher exact test e la regressione univariata e multivariata.*

Risultati. *Un valore LMR basale ≥ 4,09 è indicativo di benignità. La probabilità di neoplasia nei pazienti con LMR < 4,09 è 26 volte superiore rispetto ai pazienti con valore LMR ≥ 4,09.*

Conclusioni. *Questo studio ha dimostrato che solo un valore di LMR < 4,09 ha una probabilità concreta che un nodulo a citologia indeterminata possa essere un cancro.*

PAROLE CHIAVE: *nodulo tiroideo indeterminato, cancro della tiroide, rapporto neutrofili-linfociti; rapporto linfociti-monociti, rapporto piastrine-linfociti*

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Conflict of interest
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Introduction

Papillary thyroid cancer (PTC) represents 90% of all malignant thyroid neoplasms [1]. Thyroid cancer accounts 3-4% of new cancer diagnoses annually, representing the most common endocrine neoplasm [2]. The incidence of thyroid cancer has increased in past decades due to the increased incidence of PTC [1]. PTC is more frequent in women and has a mortality of 1/100,000 deaths per year [3]. PTCs are indolent tumours, with an incidence of lymph node metastases of 30-90% [4]. Diagnosis is performed with neck ultrasound associated with fine needle cytology (FNC), although non-diagnostic or indeterminate cytology rates are up to 20% [1,3]. Early and accurate diagnosis allow to plan surgery and radiometabolic therapy, considering the high percentage of cytology indeterminate neoformations (Tir3a and Tir3b), it is desirable to identify haematological markers that can identify PTC at an early stage [5].

Genetic mutations play a role in risk assessment in indeterminate cytology. The risk of recurrence in tumours with BRAFV600E mutations versus wild-type BRAFV600E tumours has already been widely evaluated in the literature [1]. The genetic mutation profile in indeterminate nodules is not always valuable in common practice, as this involves the execution of a second FNC, which is not well accepted by the patient. However, a blood sample is a noninvasive, well-tolerated, safe and inexpensive method and can be used in screening, diagnosis and follow-up. The immune system and inflammatory response are associated with initiation, progression, metastasis and prognosis of the cancer [6]. The inflammatory mediators are neutrophils, lymphocytes, monocytes and platelets. Neutrophils and platelets contribute to tumourogenesis, producing 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). On the other hand, monocytes and lymphocytes contribute with anti-tumoural effects [6]. The lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are independent prognostic factors in many solid cancers [7]. All these ratios can be calculated on routine preoperative blood samples with no additional costs and no discomfort to the patient.

In the literature it is established that the various ratios play an important role in prognosis of high-risk differentiated thyroid cancer (DTC) and in anaplastic thyroid cancer (ATC), but there are no studies on the role played in cytology indeterminate nodules [8,9].

The aim of this study is to evaluate the LMR, NLR and PLR values in patients with cytology indeterminate nodules without mutation analysis undergoing total thyroidectomy (TT) and compare these indices with anatomopathological findings. The routine use of these inflammatory indices can add information in cytology indeterminate nodules.

Materials and methods

We retrospectively collected data on 298 adult patients undergoing TT at the Department of Thyroid Surgery of the University of Campania "Luigi Vanvitelli" from March 2012 until December 2019. All patients had a multinodular goiter with a cytological diagnosis of indeterminate thyroid nodule (Tir3a or Tir3b) to FNC, according to the SIAPEC-IAP classification [5]. Clinical and demographics records were reordered in an electronic database. Anatomopathological findings were evaluated and classified with tumour-node-metastases (TNM) staging, according to the American Joint Committee on Cancer (AJCC) staging system (8th edition) [10].

Table I shows the patients enrolled according to the inclusion and exclusion criteria. We included adult patients with: multinodular goiter with cytological diagnosis of Tir3a and Tir3b to FNC, complete medical history and complete preoperative blood tests. We excluded patients with: pregnancy; other histopathological thyroid cancer as medullary thyroid cancer (MTC) or ATC; previous thyroid tumours; distant metastases; autoimmune thyroid disease; previous tumours of the head-neck district; neck surgery within 5 years; neck radiation therapy; chronic inflammation due to HBV, HCV, chronic gastritis, nephritis or gout; immune or haematological disease; proliferative haemopoietic disorders. Moreover, we excluded patients with heart failure, use of anticoagulant drug, hypertension and diabetes mellitus. All excluded patients are shown in Figure 1. These conditions could represent a bias in white blood cell and platelet counts.

We divided the population into two groups based on anatomopathological results: PTC (Group A) and multinodular goiter (Group B). All patients underwent preoperative blood sample, FNC, neck ultrasound and fiberoptic-laryngoscopy tests in the 30 days prior to surgery. Clinical, demographic data and anatomopathological findings such as histopathological type, dimension, capsular invasion, vascular invasion, laterality, unifocality, multifocality and stage were obtained from archive files. Laboratory data, such as 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 respectively values. All surgical procedures were performed by two surgeons (GD and GC). The surgical treatments performed were TT/near total thyroidectomy (NTT).

Table I. Patient demographic and clinicopathological data.

Characteristics	Population	Group A	Group B	*p*-value
Cases (%)	298	59 (19.79)	239 (80.21)	< 0.001
Sex (%)				
Male	63 (21.14)	12 (20.33)	51 (21.33)	0.866
Female	235 (78.46)	47 (79.66)	188 (78.66)	
Age (mean, ± SD)	50.69 (± 14.73)	49.08 (± 12.88)	51.09 (± 15.15)	0.370
TNM stage (8th ed.)				
I (%)	56 (18.8)	56 (94.91)	NA	NA
II (%)	3 (1)	3 (5.09)		
Mean tumour size in cm (mean, ± SD)		1.54 (±0.9)	NA	NA
Laterality of tumour (%)				
Right	24 (8.05)	24 (40.7)	NA	NA
Left	35 (11.75)	35 (59.3)		
Cases (%)	298	59 (19.79)	239 (80.21)	< 0.001

SD: standard deviation; NA: not applicable.

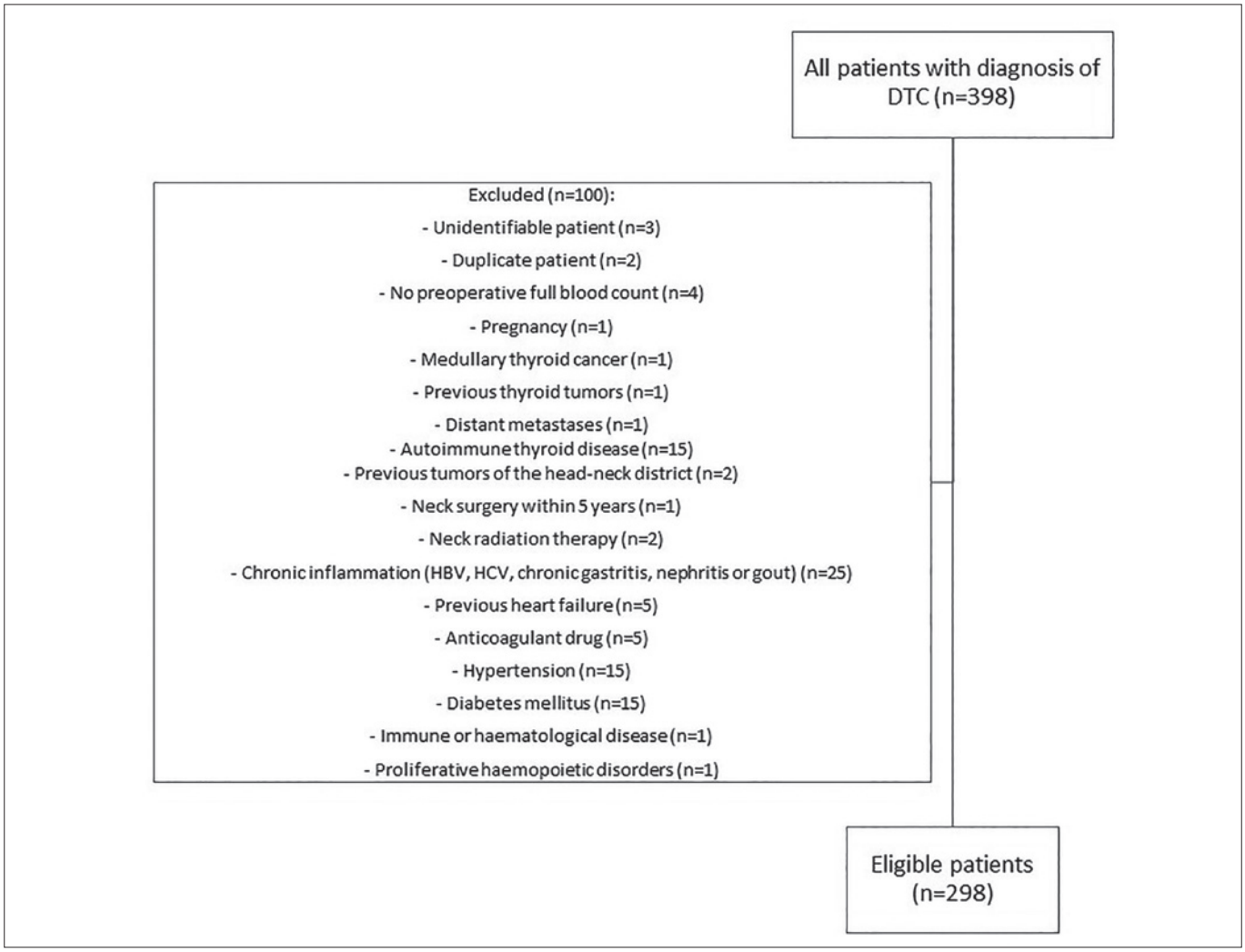

Figure 1. Flow-chart of eligible patients.

Table II. Baseline haematological values.

Blood values	Population	Group A	Group B	*p*-value
Mean white blood cell (± SD)	7.30 (± 1.87)	6.81 (± 1.66)	7.41 (± 1.9)	0.02
Mean neutrophils (± SD)	4.61 (± 1.54)	4.32 (± 1.5)	4.68 (± 1.54)	0.62
Mean lymphocytes (± SD)	2.07 (± 0.55)	1.78 (± 0.36)	2.14 (± 0.57)	< 0.001
Mean monocytes (± SD)	0.41 (± 0.13)	0.50 (± 0.12)	0.39 (± 0.12)	< 0.001
Mean eosinophils (± SD)	0.15 (± 0.1)	0.14 (± 0.10)	0.15 (± 0.11)	0.289
Mean basophils (± SD)	0.04 (± 0.02)	0.04 (± 0.03)	0.38 (± 0.02)	0.784
Mean platelets (± SD)	260.370 (± 63.2)	254.800 (± 53.49)	262.426 (± 65.15)	0.439
Mean LMR (± SD)	5.61 (± 2.82)	3.46 (± 0.64)	6.10 (± 2.94)	< 0.001
Mean NLR (± SD)	2.31 (± 0.82)	2.26 (± 0.80)	2.49 (± 0.87)	0.58
Mean PLR* (± SD)	132.878 (± 43.02)	129.674 (± 43.42)	145.857 (± 39.13)	0.003

*SD: standard deviation; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; *x1000.*

Blood samples were taken preoperatively as part of the routine preoperative tests and were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) to allow study of white blood cell and platelet counts.

The study protocol was approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli" with protocol AOU4588/2020. Written informed consent was obtained from all participants. All procedures performed were in accordance with the Helsinki Declaration.

Statistical analysis

Variables were continuous, described as mean and standard deviation, and categorical, described as number of cases and percentage. The population was divided in those with PTC (Group A) and those with benign goiter (Group B), according to anatomopathological reports. A nonparametric Wilcoxon-Mann-Whitney independent samples test was performed to compare continuous variables (age, blood sample values and LMR, NLR and PLR). Test of Proportions was conducted on categorical variables (number of cases based on anatomopathological reports of PTC or multinodular goiter). Moreover, the chi square test has been used in order to analyse gender. Odds ratio (OR) was calculated using univariate and multivariate Logistic 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

Blood samples, clinical and anatomopathological data of 298 patients with multinodular thyroid goiter with a cytology indeterminate nodule, were analysed retrospectively. Baseline demographic and disease characteristics are reported in Table I. Group A had 57 patients (19.79% with a mean age of 49.08 ± 12.88) and Group B had 239 patients (80.21% with a mean age of 51.09 ± 15.15), without no significant difference between groups. Female patients were 78.46% of the studied population, with a similar percentage in the two groups.

The mean blood count values, LMR, NLR and PLR values are shown in Table II. Mean white blood cells, lymphocytes and monocytes were significantly different between groups with a *p*-values of < 0.001 for lymphocytes and monocytes and *p*-value of 0.018 for white blood cells. Mean LMR and mean PLR were significantly different between groups, with a *p*-value of < 0.001 and 0.009, respectively. NLR showed no significant difference between groups (*p*-value 0.057).

In Table III, prognostic scores were evaluated as odds factors for presence of the disease; in particular, we noticed that univariate LMR factor showed an OR of 0.13 (*p*-value < 0.001). Moreover, we calculated the univariate OR cancer when LMR was less than 4.09, which was 26.058 (*p*-value < 0.001). Other haematological prognostic factors showed no significant difference in OR.

We calculated the receiver operating characteristic (ROC) curves for LMR, PLR and NLR (Figs. 2-4). The ROC curve for LMR had an area under the curve (AUC) of 0.886 ± 0.19 with a cut-off value of 4.09, sensitivity of 84.7% and specificity of 82.4%. The ROC curve for PLR had an AUC of 0.623 ± 0.39 with a cut-off value of 121.665, sensitivity of 69.5% and specificity of 48.1% (Fig. 3). The ROC curve for NLR has an AUC of 0.58 ± 0.4, with no valid cut-off value or significant difference between groups (Fig. 4).

Discussion

Our study attempted to find a correlation between LMR, PLR and NLR and prediction of malignancy or benignity in thyroid nodules with indeterminate cytology (Tir3a and Tir3b). In the literature, various studies have evaluated the values of LMR, PLR and NLR in patients with thyroiditis

Table III. Univariate and multivariate analysis evaluating the odds of PTC.

	Univariate OR (95% CI)	*p*-value	Adjusted OR[a] (95% CI)	*p*-value
NLR	0.712 (0.440-1.152)	0.166	0.513 (0.61-4.326)	0.539
LMR	0.130 (0.071-0.238)	< 0.001	0.216 (0.028-1.671)	0.142
PLR	1.001 (0.991-1.012)	0.825	1.012 (0.969-1.057)	0.590
Cancer when LMR < 4.09	26.058 (11.898-57.072)	< 0.001	2.960 (0.787-11.136)	0.109

[a] *Adjusted for full blood count values (OR: odds ratio; CI: confidential interval; LMR: lymphocytes-to-monocytes ratio; NLR: neutrophil-to-lymphocytes ratio; PLR: platelet-to-lymphocytes ratio.*

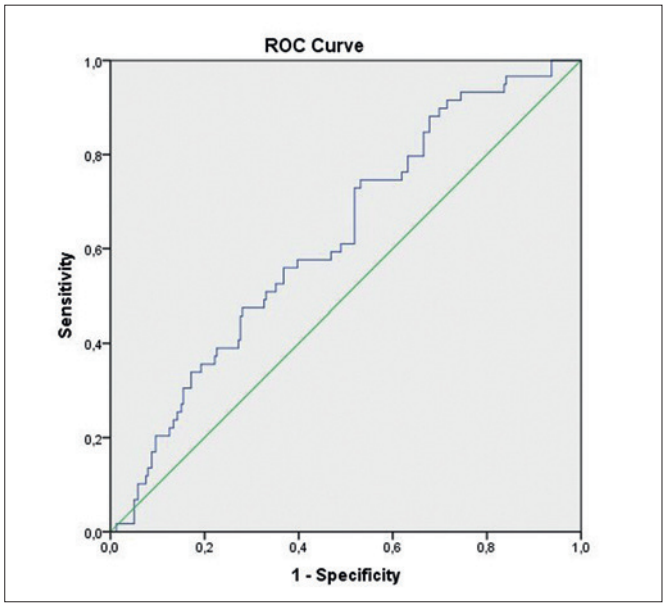

Figure 2. ROC curves of LMR (cut-off value 4.09, AUC 0.886 ± 0.1, sensitivity of 84.7% and a specificity of 82.4%. For LMR < 4.09, univariate OR is 26.058 with a *p*-value < 0.001).

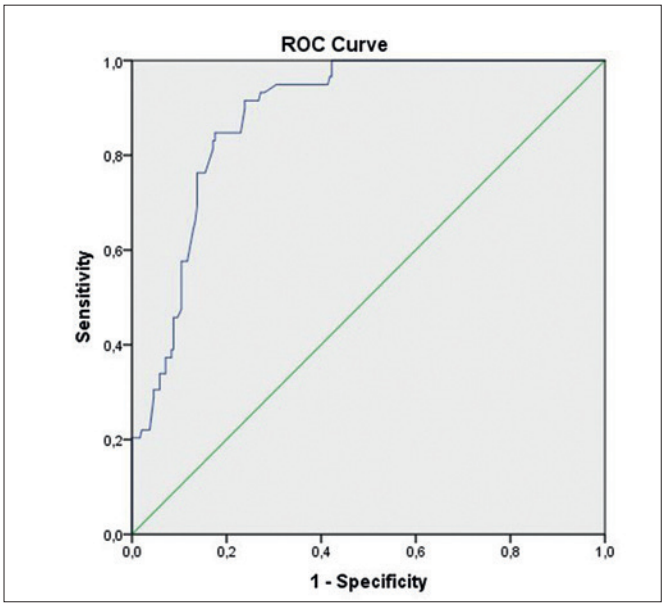

Figure 3. ROC curves of PLR (cut-off value 121.665, AUC 0.623 ± 0.39, sensitivity 69.5% and specificity of 48.1%).

and in patients with differentiated carcinoma on thyroiditis, without finding statistically significant differences [11,12], but there are no examples of how these values can predict a greater risk of malignancy in Tir3a and Tir3b nodules. The aim of our study was to find an instrument that can identify, at the time of cytology diagnosis, patients with indeterminate cytology thyroid nodules with a greater risk of malignancy.

Accurate preoperative diagnosis of thyroid nodules represents a clinical problem for endocrinologists and endocrine surgeons. The key role is played by the pathologist who must cytologically characterise thyroid nodules undergoing FNC to allow the patient to receive tailored treatment. FNAC is the only exam that can provide a definitive preoperative diagnosis with a sensitivity and specificity of 68-98% and 56-100%, respectively [13,14]. The Italian cytological classification includes the following diagnostic categories: Tir1, nondiagnostic; Tir1c, cystic; Tir2, negative for neo-

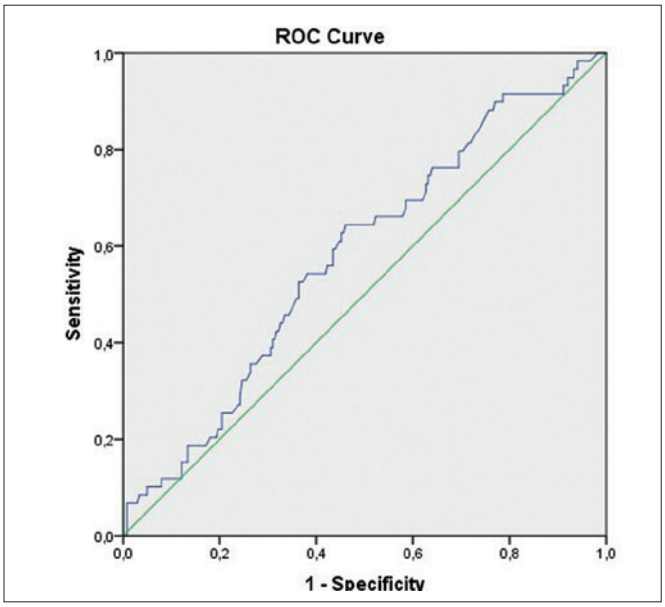

Figure 4. ROC curves of NLR (AUC 0.58 ± 0.4, no valid cut-off value found).

plasia; Tir3a, indeterminate low risk lesion; Tir3b, indeterminate high risk lesion; Tir4, suspicious for malignant neoplasm; and Tir5, positive for malignancy [5]. The indeterminate lesions remain a large and controversial field regarding clinical and surgical treatment of thyroid nodules. The literature suggests that these lesions represent up to 20% of cytological diagnoses and represent a grey area in which both benign and malignant nodules are included [15,16]. These data suggest that the high percentage of thyroid nodules with indeterminate cytology is associated with many thyroid surgeries, a cause of further morbidity and higher costs for increase in costs. Literature data suggests that approximately 70% of thyroid surgeries are unnecessary. Tir3a nodules, indeed, have a risk of malignancy of less than 10%, while Tir3b nodules have a risk of malignancy of 15-30%. Identification of haematological indices that can predict the benignity or malignancy of indeterminate nodules could significantly reduce the percentage of overtreatment. Inflammatory cells in blood can promote cancer initiation, progression and worsen prognosis. The mediators of inflammatory response are neutrophils, lymphocytes, monocytes and platelets. Monocytes and lymphocytes are anti-tumoural mediators. Low levels of lymphocytes and monocytes are associated with poor prognosis and have been observed in advanced cancer stages [7]. Monocytes induce apoptosis of cancerous cells to reduce angiogenesis, thus decreasing invasion and progression of cancer [17,18]. In the literature, low LMR values are associated with poor prognosis and a high risk of recurrence of ATC and DTC [19,20]. In our study, mean LMR value showed a significant difference between the two groups (p-value < 0.001) and univariate analysis had a p-value of < 0.001. We calculated a cut-off value of 4.09 (AUC 0.886 ± 0.1) with a sensitivity of 84.7% and a specificity of 82.4%. An LMR value > 4.09 is indicative of benignity of the indeterminate nodule. Moreover, the univariate OR when LMR value is lower than 4.09 was > 26 with a p-value of < 0.001. This means that the probability of disease in patients with LMR lower than 4.09 is 26 times higher than a patient with LMR value greater than 4.09. Moreover, univariate OR LMR was 0.130 with a p-value of < 0.001. We can interpret this outcome that the higher the LMR, the higher the probability that there is no cancer. According to the recent literature, there are few correlations between PLR and risk of recurrence and prognosis of patients with thyroid cancer [21-23]. In our population study, we observed a significant differences in mean PLR value between the two groups (p-value 0.009), but OR showed no significant significance. We calculated a PLR cut-off value of 121.665 (AUC 0.623 ± 0.39) with a sensitivity of 69.5% and a specificity of 48.1%, but it cannot be considered as a valid cut-off value.

The role of low NLR values as an independent prognostic factor in the prognosis of numerous solid neoplasm and thyroid cancer has been widely ascertained in the literature [7,21,22]. Neutrophils produce VEGF, inhibit TNF-α and promote secretion of IL-2, IL-6 and IL-8; a high neutrophils count facilitates tumour progression and invasion, while a low lymphocyte count reduces antineoplastic activity [6]. In our study, found no significant difference in NLR or a valid cut-off value, due to the low AUC found (AUC 0.58 ± 0.4).

Conclusions

This study showed that only LMR has a concrete probability to identify a thyroid cancer in indeterminate nodule patients. Even if mean PLR had a significant difference between the two groups, univariate analysis with PLR showed no significant results. Further studies are necessary to clarify and validate the specific role of LMR and PLR. Our hope is that these scores can be used to predict malignity of the indeterminate thyroid nodule to be submitted to surgery to avoid delays in treatment and/or avoid overtreatment by implementing tailored therapy.

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