Usefulness of Pre-Thyroidectomy Neutrophil-Lymphocyte, Platelet-Lymphocyte, and Monocyte-Lymphocyte Ratios in Discriminating Lymph Node and Distant Metastases in Differentiated Thyroid Cancer

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Research Article

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Abstract

Purpose

This study aims to show the relationship between neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and monocyte-lymphocyte ratio (MLR), with clinicopathological characteristics in patients with differentiated thyroid cancer (DTC).

Methods

This is a retrospective study involving 390 DTC patients who had complete blood cell count available at the time of the surgery. NLR, PLR, and MLR were calculated, risk of cancer-related death, structural recurrence, and response to therapy were assessed by the 8th edition of the tumor-node-metastasis (TNM), American Thyroid Association (ATA) Risk Stratification System, and ATA Response to Therapy Reclassification, respectively.

Results

PLR was higher in distant metastasis (133.15±43.95 vs 119.24±45.69, p = 0.0345), lower in disease-free versus persistent disease or death (117.72±44.70 vs 131.07±47.85, p = 0.0089). In MLR, patients ≥55 had a higher score than < 55 years old (0.26±0.10 vs 0.24±0.12, p = 0.0379). Higher MLR (OR 8.775; 95% CI = 1.532–50.273; p = 0.0147), intermediate (OR 4.892; 95% CI = 2.492–9.605; p ≤ 0.0001) and high ATA risks (OR 5.998; 95% CI = 3.126–11.505; p ≤ 0.0001) were risk factors associated with active disease. NLR was not significant. ROC curve cut-off values for NLR, PLR, and MLR were able to discriminate distant from lymph node metastasis (NLR > 1.93 sensitivity 73.3%, specificity 58.7%; PLR > 124.34 sensitivity 86.7%, specificity 69.2%; MLR > 0.21 sensitivity 80%, specificity 45.2%).

Conclusion

Cut-off values of NLR, PLR, and MLR discriminated the presence of distant metastasis from lymph node metastasis with good sensitivity and accuracy. PLR was an associated factor with disease-free status and higher in DTC patients with distant metastasis, persistency, and disease-related death. MLR was a risk factor of active disease.

Introduction

Cancer-associated inflammation plays an essential role in clinical evolution of most cancers, mainly by promoting tumor cell proliferation, angiogenesis, invasion, and metastasis [1-3]. Increasing evidence has shown that several biomarkers related to inflammation, like C-reactive protein, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR) or lymphocyte-monocyte

ratio (LMR), are indicators of poor prognosis among a variety of cancers [4] and chronic diseases [5-7]; however, the importance of such inflammatory response is not entirely clear in thyroid cancer. The NLR is by far the most widely investigated inflammation ratio among patients with thyroid cancer, and many authors have demonstrated that a high NLR has a close relationship with more aggressive tumors, lymph nodes metastasis, and poor prognosis [8-13]. Likewise NLR, a high PLR is also linked to poor prognosis, especially among patients with papillary and medullary thyroid cancer [14-16]. More recently, some authors [17-20] have demonstrated that a low LMR could predict recurrence and overall survival in patients with papillary thyroid cancer and poor survival in patients with anaplastic thyroid carcinoma. To the best of our knowledge, none study has evaluated the NLR, PLR, and MLR obtained from patients with differentiated thyroid carcinoma (DTC) in addition to their relationship with different histological types and long-term clinical and laboratory evolution.

The present study aims to show the potential relationship between NLR, PLR, MLR, clinicopathological characteristics, and outcome in patients with DTC.

Materials And Methods

Subjects

This is a retrospective study involving 1,143 patients diagnosed with DTC followed at the Thyroid Disease Unit at the Clinics Hospital of the University of Campinas between January 2000 and January 2019. The ethical committee approval for the study was obtained according to the Declaration of Helsinki, Human Research Ethics Committee in Lausanne, N^{o} 204/14. CAAE: 58234916.3.0000.5404.

Of the 1,143 initially selected patients, 390 patients had adequate clinicopathological information and follow-up. Seven hundred and fifty-three patients were excluded from the study due to the following reasons: patients that underwent total thyroidectomy in other hospitals, unavailable baseline hemogram obtained before surgery, and inadequate follow-up (a minimum of 12 months was required). Patients with a previous history of any acute infectious or inflammatory disease, history of cardiovascular events (myocardial ischemia, unstable angina, and stroke), malignant neoplasia (except thyroid cancer), heart failure (New York Heart Association - NYHA III or IV), severe hepatic or kidney disease (Chronic Kidney Disease stage 4, 5 and hemodialysis), hepatitis B, C and HIV infection, diabetes type 1 and 2 were also excluded. Fig. 1 shows the study flow chart.

Clinical assessment

Clinical characteristics and laboratory data were recorded by chart review. Clinical data collected were: sex, age, age at diagnosis, ethnicity, smoking habits, time of follow-up, use of ablative and/or adjuvant radioiodine therapy (RAI), RAI whole-body scanning, cervical ultrasound, computer tomography scan when available, and response to cancer treatment.

Tumor characteristics analyzed were: histology (papillary or follicular), papillary thyroid cancer variants (classic, follicular and tall cell), tumor size (largest dimension of the lesion measured), multifocality, invasion (extrathyroidal extension, capsule or vascular), metastatic nodes and distant metastasis.

Laboratory data collected were: serum thyroid-stimulating hormone (TSH) (reference value 0.41 – 4.5 mUI/L), free thyroxine (FT4) (reference value 0.9 – 1.8 m/dL), thyroglobulin antibodies (TgAb) (reference value < 115 mUI/L), and thyroglobulin (Tg) (reference value 0.2 – 70 ng/ml) were measured by electrochemiluminescence immunoassay. Complete blood counts and automated differential counts were, in general, collected three days before surgery. The NLR, PLR, and MLR were calculated from complete blood count, including the evaluation of total leukocytes, neutrophils, lymphocytes, monocytes, and platelets. NLR was calculated by dividing the number of neutrophils and lymphocytes. Similarly, PLR and MLR were calculated by dividing platelets and monocytes by the lymphocyte count.

Risk stratification

The 8th edition of the tumor-node-metastasis (TNM) classification elaborated by the American Joint Committee on Cancer (AJCC), was used to classify thyroid tumors and predict the risk of cancer-related death. The risk of structural recurrence was assessed by the American Thyroid Association (ATA) Risk Stratification System, in which patients can be classified as low, intermediate, and high risk. Response to treatment was assessed by the ATA Response to Therapy Reclassification, and patients were classified as an excellent response, biochemical incomplete response, structural incomplete response, or indeterminate response. Patients were also classified regarding disease outcomes as free of the disease, persistent disease, or death disease-related.

Statistical analysis

Statistical analyses were carried out in the Statistical Analysis System (SAS) - System for Windows, version 9.4. SAS Institute Inc., 2002-2008, Cary, NC, USA. Exploratory data analysis was performed using summary measures (mean, standard deviation, minimum, median, maximum, frequency, and percentage). The relationship between neutrophil-to-lymphocyte, platelet-to-lymphocyte, and monocyte-to-lymphocyte ratios with the variables of interest was assessed by the Mann-Whitney or Kruskal-Wallis tests. To identify factors associated with disease-free time, univariate and multiple Cox regression analysis was used. The variable selection process employed was stepwise. To assess the ratio's accuracy, the ROC curve was used. The larger the area under the ROC curve produced, the greater the discriminatory power of the model. As a general rule, models with acceptable discrimination are considered when the area is ≥ 0.7. The significance level was set at $p < 0.05$.

Results

Baseline characteristics

Table 1 shows detailed characteristics of the 390 patients with DTC included in this study. As expected, most of our patients were female (83.08%), Caucasians (73.08%), non-smokers (70.51%), with a mean age of 46.65 ± 15.41 years, diagnosed with PTC (91.54%), and were classified as either classic PTC (40.45%), follicular (42.98%), or tall cell (16.57%) variant. Regarding risk stratification, 50% of all patients were classified as low, 25.90% as intermediate, 24.10% as high risk. Despite the high rate of patients classified as intermediate and high risk, most of them presented an excellent response to treatment (78.72%), while structural incomplete response, indeterminate response, and biochemical incomplete response were 8.21%, 7.95%, and 5.13%, respectively. Our classification in free of the disease (78.72%), persistent disease (19.49%), and death disease-related (1.79%) was similar to the response to treatment ATA classification. The mean NLR, PLR and MLR was 2.05 ± 1.12, 120.56 ± 45.65 and 0.25 ± 0.11, respectively.

NLR, PLR, MLR and tumor characteristics, stage and evolution

Table 2 shows the comparison between NLR, PLR, and MLR with patient's age, histology, PTC variants, tumor size, type of invasion, focal and distant metastasis, and risk stratification. NLR was not statistically significant in any variable analyzed. In contrast, PLR was higher among those patients with distant metastasis with a mean of 133.15 ± 43.95 versus 119.24 ± 45.69 in patients without it, p=0.0345. PLR was also significantly lower in patients classified as disease-free with a mean of 117.72 ± 44.70 versus 131.07 ± 47.85 those with persistent disease or death related to the tumor, p=0.0089. In MLR evaluation, patients ³ 55 years presented a significantly higher score with a mean of 0.26 ± 0.10 versus 0.24 ± 0.12, p=0.0379, in patients < 55 years old. Univariate and multiple logistic regression analysis regarding disease-free DTC patients.

At univariate logistic regression analysis, a higher PLR (OR 1.004; 95% CI=1.001 – 1.008; p=0.0247), tumor size ³ 1 cm (OR 2.942; 95% CI=1.416 – 6.113; p=0.0038), patients older than 55 years (OR 1.701; 95% CI=1.096 – 2.640; p=0.0179), III and IVb 8^{th} TNM stage versus I and II (OR 3.268; 95% CI=1.982 – 5.389; p=<0.0001), tall cell versus follicular variant (OR 2.016; 95% CI=1.106 – 3.676; p=0.0221), intermediate ATA risk (OR 4.916; 95% CI=2.509 – 9.631; p=<0.0001) and high ATA risk (OR 6.652; 95% CI=3.583 – 12.352; p=<0.0001) versus low ATA risk were factors associated with a lower disease-free status as shown in table 3.

At multiple logistic regression analysis of the variables, a higher MLR (OR 8.775; 95% CI=1.532 – 50.273; p=0.0147), intermediate ATA risk (OR 4.892; 95% CI=2.492 – 9.605; p=<0.0001) and high ATA risk (OR 5.998; 95% CI=3.126 – 11.505; p=<0.0001) were factors associated with a lower disease-free status as shown in table 3.

Receiver Operating Characteristic (ROC) Curve Analysis

ROC curve allows finding discriminatory cut-off values for each analysis, with values above cut-off were found in patients with distant metastasis compared to patients with lymph node metastasis. The best cutoff to differentiate lymph node from distant metastasis was: to NLR > 1.93 with a sensitivity 73.3%,

specificity 58.7%, accuracy 63.5%, positive predictive value 20.4%, negative predictive value 93.8%; to PLR > 124.34 with a sensitivity 86.7%, specificity 69.2%, accuracy 78.7%, positive predictive value 28.9% and a negative predictive value 97.3% and to MLR > 0.21 with a sensitivity 80%, specificity 45.2%, accuracy 57.9%, positive predictive value 17.4% and a negative predictive value 94% (Fig. 2). Analysis values did not allow discriminating patients presenting distant metastasis versus disease-free patients (area under the curve NLR 0.574; PLR 0.575 and MLR 0.550); lymph node metastasis versus disease-free (area under the curve NLR 0.540; PLR 0.544 and MLR 0.540); metastasis (lymph node and distant) versus without metastasis (area under the curve NLR 0.524; PLR 0.514 and MLR 0.502) and metastasis (lymph node and distant) versus disease free (area under the curve NLR 0.552; PLR 0.581 and MLR 0.550) (data not shown).

Discussion

The present study evaluated the role of NLR, PLR, and MLR as a predictive tool for disease status in patients with DTC. In this sense, it was possible through cut-off values of NLR, PLR, and MLR, to discriminate the presence of distant metastasis from lymph node metastasis with good sensitivity and accuracy. In addition, we demonstrated that MLR associated with a low ATA risk in DTC patients were considered predictive factors of a disease-free status. Furthermore, PLR was a factor related to a disease-free status, and it was comparatively higher in DTC patients with distant metastasis, persistency, and disease-related death than in patients apparently free of disease. Nonetheless, we did not find any association between NLR and outcome in the same population.

NLR, PLR, and MLR are related to inflammation status; however, the exact pathways between the association these ratios and tumor behavior remain unclear [4,21]. In this sense, it is well known that cancer can secrete inflammatory factors such as IL-1, IL-2, IL-6, IL-8, IL-12, IL-17, granulocyte colony-stimulating factor, and tumor necrosis factor-alfa, which may contribute to leukocytosis. As a result, neutrophilia, thrombocytosis, increased monocytes, and a relative lymphocytopenia may be seen in tissue damage and inflammation. Neutrophils and platelets are linked with cancer survival expanding angiogenesis, tumor progression, and metastasis. Decreased lymphocytes and increased monocytes demonstrate an inadequate immunologic reaction that is also related to tumor progression and metastasis [1,2,4,22].

The NLR is by far the most studied ratio in thyroid cancer as well as in several other malignancies, including gastrointestinal tumors, breast, lung, prostate, and ovarian cancer [4]. Most studies that analyzed NLR in patients with DTC have shown that a high NLR was associated with poor prognosis and survival, and it was primarily related to TNM classification, patients' age, tumor size, multifocality, lymph nodes metastasis, extra thyroid invasion, and risk of recurrence [8-13]. However, two meta-analyses differ in their results regarding the utility of NLR [23,24]. Feng et al. [23] defend that NLR may serve as a biomarker to predict tumor growth, metastasis, and prognosis, whereas Liu et al. [24] stated that NLR seems not a reliable indicator of prognosis in DTC. In line with the former, our study did not confirm the usefulness of NLR since there was no association with prognosis or tumor features in these DTC

patients. On the other hand, it was possible to determine through the ROC curve, a cut-off of NLR, where values greater than 1.93 discriminated patients with distant metastasis from patients with lymph node metastasis, presenting good sensitivity (73.3%) and accuracy (63.5%).

Although PLR was less assessed than NLR in previous studies, some authors have found a link between that ratio and poor prognosis among patients with DTC [13,16,21]. We showed that patients with distant metastasis presented a higher PLR, as well as a lower PLR was found in patients classified as disease-free. Besides that, PLR cut-off values higher than 124 helped differentiate patients with distant metastasis from patients with lymph node metastasis, with a high sensibility (86.7%) and accuracy (78.7%). The majority of the studies analyzed patients with differentiated thyroid cancer; however, two Chinese studies suggested that a high PLR, but not NLR, was associated with poor prognosis among patients with medullary thyroid cancer [14,15]. Jiang et al. [14] showed a link between a high PLR and lymph node metastasis and recurrence. A year later, the same group [15] described that an increased PLR was also predictive of lymph nodes metastasis, capsule invasion, advanced tumor stages, and recurrence.

Regarding MLR or LMR, few studies evaluated LMR among patients with thyroid cancer [17-20]. Ahn et al. [19] performed a retrospective study with 35 subjects diagnosed with anaplastic thyroid cancer and found an association between low LMR and poor survival. In contrast, Yamazaki et al. [25] evaluated a greater number of patients with anaplastic thyroid cancer and did not find a similar association. Other three authors [17,18,20] assessed the LMR among patients with papillary thyroid cancer and found that a low preoperative LMR could predict recurrence and overall survival. A similar relationship was seen in our study, highlighting that we assessed the inverse ratio, which showed a higher MLR among older patients (³ 55 years), and it was also related as a predictor factor of disease-free status. Additionally, we found that values of MLR lower than 0.21 were present in patients with distant metastasis versus patients with lymph node metastasis, with a sensibility of 80% and an accuracy of 58%.

When it comes to comparing those ratios in benign thyroid diseases such as Graves' disease (GD), Hashimoto's thyroiditis (HT), toxic adenoma (TA), and subacute thyroiditis (SAT), few studies have demonstrated this relationship [26-30]. Hu et al. [28] proposed combining thyroid hormones (free thyroxine and triiodothyronine) and eosinophil-monocyte ratio to distinguish GD and SAT. Taskaldiran et al. [30] retrospectively analyzed NLR and PLR in patients with GD, SAT, and TA and suggested that a high PLR and NLR may be useful to differentiate SAT from GD and TA. Another interesting retrospective study performed by Kim et al. [29] have found that an elevated NLR was an independent prognostic factor for relapse in patients with GD. Regarding Hashimoto's thyroiditis, Aktas et al. [26] and Bilge et al. [27] found a significantly higher NLR between patients with Hashimoto's thyroiditis and healthy controls.

As to the pitfalls of this study, first of all, it was a retrospective study from a single institution and presented limitations due to its nature. The total number of subjects included in this study is small compared to other studies; however, our analysis was able to present robust results. In contrast to the

pitfalls, our study is the first to analyze three different ratios covering low, intermediate, and high risk of metastases among patients with differentiated thyroid cancer.

In conclusion, we found that cut-off values of NLR, PLR, and MLR were able to discriminate distant metastasis from lymph node metastasis with good sensitivity and accuracy. A higher PLR and lower MLR were both factors associated with active disease status. PLR was an associated factor with disease-free status and higher in DTC patients with distant metastasis, persistency, and disease-related death. Our study demonstrated that PLR, NLR and MLR could be considered a useful, readily available, and low-cost tool during clinical follow-up of patients with differentiated thyroid cancer. However, a large-scale study is indispensable to confirm our results.

Declarations

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

The ethical committee approval for the study was obtained according to the Declaration of Helsinki, Human Research Ethics Committee in Lausanne, Nº 204/14. CAAE: 58234916.3.0000.5404.

Consent to participate

The requirement for written consent was waived because of the retrospective design.

Consent for publication

All writers consented for publication.

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Tables

Table 1

Baseline and histopathological characteristics and outcomes of patients with differentiated thyroid carcinoma.

Patients characteristics		**N = 390**
Gender	Female Male	324 (83.08%) 66 (16.92%)
Age (years)		46.65 ± 15.41
Age	< 55 years ≥ 55 years	262 (67.18%) 128 (32.82%)
Follow up (months)		82.83 ± 54.17
Platelet (x10.e3/ul)		250 ± 63
White blood cell (x10.e3/ul) Neutrophil (x10.e3/ul) Lymphocyte (x10.e3/ul) Monocyte (x10.e3/ul)		7.20 ± 1.91 4.16 ± 1.48 2.26 ± 0.76 0.52 ± 0.20
Neutrophil-lymphocyte ratio		2.05 ± 1.12
Platelet-lymphocyte ratio		120.56 ± 45.65
Monocyte-lymphocyte ratio		0.25 ± 0.11
DTC characteristics		N = 390
Thyroid cancer	Papillary Follicular	357 (91.54%) 33 (8.46%)
Papillary thyroid Cancer variants	Classic PTC Follicular Tall cell	144 (40.45%) 153 (42.98%) 59 (16.57%)
Diameter of the largest tumor focus (cm)		2.31 ± 1.96
Microcarcinoma		101 (25.96%)
Multifocality		202 (52.06%)
Invasion	Extrathyroidal extension Capsule Vascular No invasion	92 (23.71%) 87 (22.42%) 83 (21.39%) 126 (32.48%)
Metastatic lymph nodes		126 (32.31%)
Distant metastasis	Lung Bone Lung and bone	29 (7.44%) 4 (1.03%) 4 (1.03%)

Patients characteristics		N = 390
T1 T2 T3 T4		181 (46.53%) 69 (17.74%) 86 (22.11%) 53 (13.62%)
N0 N1		263 (67.61%) 116 (32.39%)
M0 M1		351 (90.23%) 38 (9.77%)
TNM 8th	I II III IV	296 (76.09%) 58 (14.91%) 16 (4.11%) 19 (4.88%)
ATA risk	Low Intermediate High	195 (50%) 101 (25.90%) 94 (24.10%)
Radioiodine therapy		366 (94.33%)
Radioiodine activities		195.16 ± 198.34
Anti-thyroglobulin antibody detectable		17 (4.36%)
Response to treatment	Excellent Biochemical incomplete Structural incomplete Indeterminate	307 (78.72%) 20 (5.13%) 32 (8.21%) 31 (7.95%)
Tumor outcome	Free of disease Persistent disease Death disease-related	307 (78.72%) 76 (19.49%) 7 (1.79%)

Values are reported as mean and standard deviation (SD) or counts and percentages. Abbreviations: TNM8th, Tumor-Nodes-Metastasis 8th; ATA Risk, American Thyroid Association Risk; WBS, Whole Body Scan.

Table 2

Comparison between Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR) and Monocyte-Lymphocyte Ratio (MLR), and tumor characteristics, stage, and evolution of differentiated thyroid carcinoma patients.

		Neutrophil Lymphocyte Ratio (NLR)		**Platelet Lymphocyte Ratio (PLR)**		**Monocyte Lymphocyte Ratio (MLR)**	
	Patients	Mean	P-value	Mean	P-value	Mean	P-value
Thyroid Cancer	357 33	2.05 ± 1.15 2.04 ± 0.73	0.4491	120.11 ± 44.66 125.45 ± 55.89	0.7714	0.25 ± 0.12 0.25 ± 0.09	0.2949
Papillary Follicular							
Variants Classic PTC Follicular Tall Cell	144 153 59	2.04 ± 1.18 2.06 ± 1.22 2.01 ± 0.87	0.8484	118.76 ± 39.65 120.98 ± 48.76 120.74 ± 46	0.9810	0.23 ± 0.09 0.26 ± 0.13 0.26 ± 0.14	0.6133
Capsule Invasion Yes No	87 301	1.91 ± 0.74 2.08 ± 1.20	0.6555	119.16 ± 45.91 120.81 ± 45.76	0.7353	0.25 ± 0.12 0.25 ± 0.11	0.8818
Angiolymphatic Invasion Yes No	83 305	2.06 ± 1.15 2.04 ± 1.11	0.7962	120.39 ± 41.86 120.45 ± 46.81	0.6194	0.25 ± 0.12 0.25 ± 0.11	0.5674
Extrathyroidal Invasion Yes No	92 296	2.06 ± 1.19 2.04 ± 1.10	0.8269	118.81 ± 41.33 120.95 ± 47.08	0.9478	0.25 ± 0.13 0.25 ± 0.11	0.9550
Lymph Node Metastasis Yes No	126 264	2.04 ± 1.08 2.05 ± 1.14	0.9334	115.58 ± 38.14 122.94 ± 48.72	0.3197	0.24 ± 0.11 0.25 ± 0.12	0.7524
Distant Metastasis Yes No	37 353	2.15 ± 0.91 2.03 ± 1.14	0.1786	133.15 ± 43.95 119.24 ± 45.69	0.0345	0.24 ± 0.08 0.25 ± 0.12	0.4285

		Neutrophil Lymphocyte Ratio (NLR)		Platelet Lymphocyte Ratio (PLR)		Monocyte Lymphocyte Ratio (MLR)	
Tumor Size < 1 cm ≥ 1 cm	288 101	2.03 ± 1.04 2.05 ± 1.15	0.9992	118.38 ± 41.74 121.25 ± 47.05	0.7888	0.25 ± 0.10 0.25 ± 0.12	0.4843
Age < 55 years ≥ 55 years	262 128	2.04 ± 1.17 2.06 ± 1.00	0.3177	121.17 ± 44.69 119.31 ± 47.72	0.3688	0.24 ± 0.12 0.26 ± 0.10	0.0379
TNM 8th I + II III + IV	354 35	2.04 ± 1.15 2.06 ± 0.8	0.4112	119.20 ± 45 132.64 ± 50.53	0.1004	0.25 ± 0.12 0.26 ± 0.10	0.0986
ATA Risk Low Intermediate High	195 101 94	2.09 ± 1.22 1.98 ± 0.96 2.09 ± 1.22	0.8286	121.85 ± 48.66 115.44 ± 40.44 121.85 ± 48.66	0.4852	0.25 ± 0.12 0.24 ± 0.13 0.25 ± 0.12	0.4317
Radioiodine Therapy Yes No	361 32	2.06 ± 1.13 1.80 ± 0.84	0.3018	120.46 ± 45.50 118.47 ± 49.47	0.8120	0.25 ± 0.12 0.24 ± 0.08	0.8856
Response to treatment Excellent Biochemical incomplete Structural incomplete Indeterminate	307 20 32 31	2.01 ± 1.11 2.27 ± 1.30 2.05 ± 0.77 2.25 ± 1.36	0.3453	117.72 ± 44.70 128.54 ± 44.41 130.46 ± 49.54 133.34 ± 49.64	0.0717	0.24 ± 0.11 0.27 ± 0.12 0.25 ± 0.10 0.27 ± 0.16	0.4423
Tumor outcome Disease free Persistency and disease related to death	307 83	2.01 ± 1.11 2.18 ± 1.14	0.0812	117.72 ± 44.70 131.07 ± 47.85	0.0089	0.24 ± 0.11 0.26 ± 0.13	0.1219

Values are reported as mean and standard deviation (SD). Abbreviations: PTC, Papillary Thyroid Cancer; TNM8th, Tumor-Nodes-Metastasis 8th; ATA Risk, American Thyroid Association Risk. Statistically significant P values < 0.05.

Table 3

Factors associated with disease-free time in patients with Differentiated Thyroid Cancer.

Variables	P-value	HR	95% CI
Univariate analysis			
NLR	0.4074	1.072	0.909–1.265
PLR	0.0247	1.004	1.001–1.008
MLR	0.0904	4.272	0.796–22.944
Tumor Size ≥ 1 cm versus < 1 cm	0.0038	2.942	1.416–6.113
Age ≥ 55 years versus < 55 years	0.0179	1.701	1.096–2.640
TNM 8th III and IV versus I and II	< 0.0001	3.268	1.982–5.389
Papillary Variant Tall Cells versus Follicular Classic versus Follicular	0.0221 0.9494	2.016 1.018	1.106–3.676 0.590–1.756
High versus Low ATA Risk Intermediate versus Low ATA Risk	< 0.0001 < 0.0001	6.652 4.916	3.583–12.352 2.509–9.631
Multivariate analysis			
MLR	0.0147	8.775	1.532–50.273
High versus Low ATA Risk Intermediate versus Low ATA Risk	< 0.0001 < 0.0001	5.998 4.892	3.126–11.505 2.492–9.605

Statistically significant values P<0.05. Abbreviations: NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; TNM8th, Tumor-Nodes-Metastasis 8th; ATA Risk, American Thyroid Association Risk.

Figures

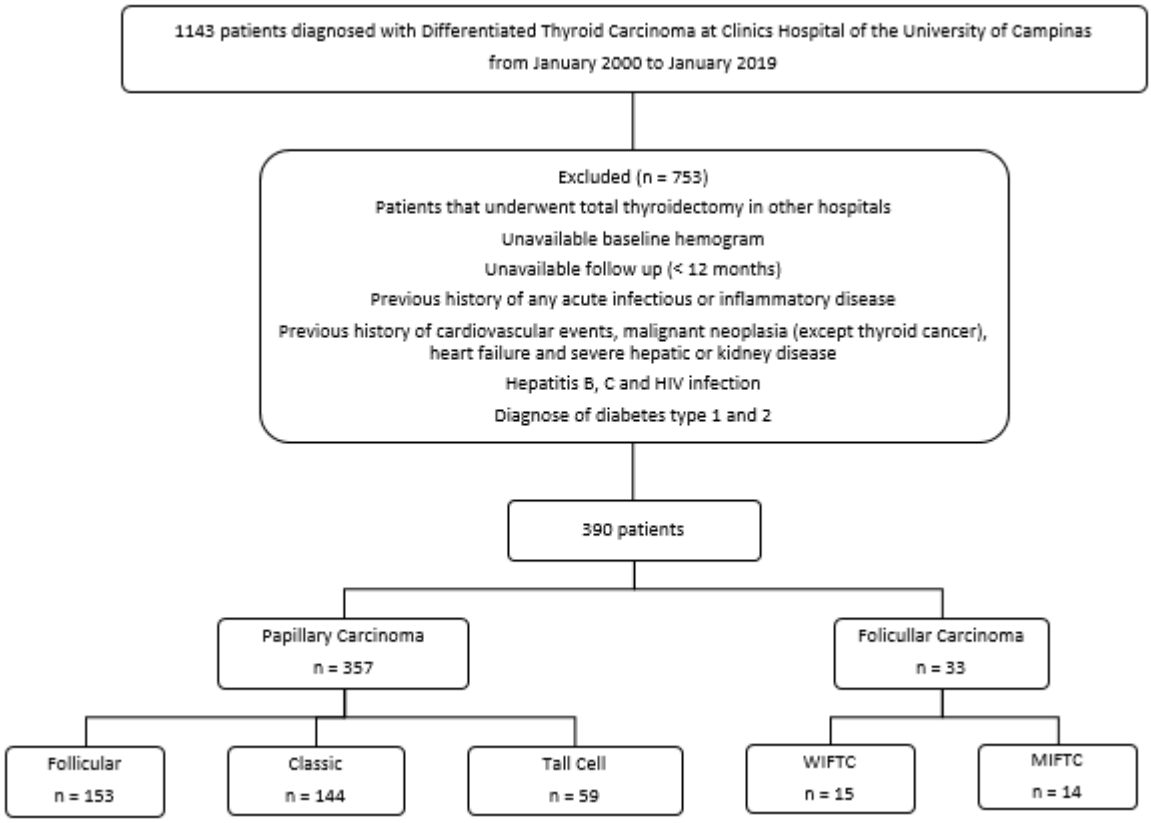
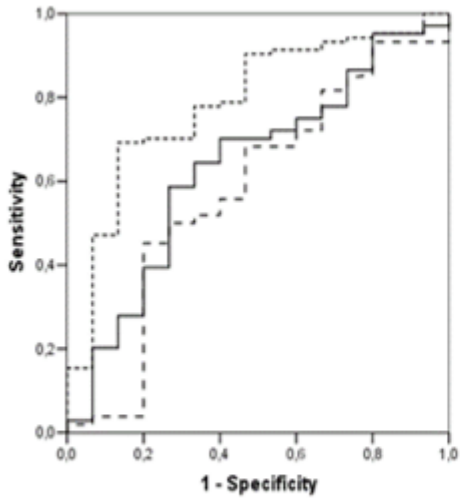


Figure 1

The study flow chart. Abbreviations: WIFTC, Widely Invasive Follicular Thyroid Carcinoma; MIFTC, Minimally Invasive Follicular Thyroid Carcinoma.



	NLR	PLR	MLR
Sensitivity	0.733	0.867	0.800
Specificity	0.587	0.692	0.452
Positive Predictive Value	0.204	0.289	0.174
Negative Predictive Value	0.938	0.973	0.940
Positive Likelihood Ratio	1.774	2.817	1.460
Negative Likelihood Ratio	0.455	0.193	0.443

Figure 2

. ROC curves showing cut-off for ratio values (NLR, PLR, and MLR) discriminating between the presence of distant metastasis and lymph node metastasis. NLR: cut-off value > 1.93 was present in patients with distant metastasis when compared to patients with lymph node metastasis. Sensitivity 73.3%, specificity 58.7%, accuracy 63.5%. PLR: cut-off value > 124.34 was present in patients with distant metastasis when compared to patients with lymph node metastasis. Sensitivity 86.7%, specificity 69.2%, accuracy 78.7%. MLR: cut-off value > 0.21 was present in patients with distant metastasis when compared to patients with lymph node metastasis. Sensitivity 80.0%, specificity 45.2%, accuracy 57.9%.