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Association of obesity and preoperative inflammatory biomarkers with aggressive clinicopathological features in papillary thyroid carcinoma: A retrospective cohort study

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Abstract

Objective: The rising incidence of papillary thyroid carcinoma (PTC) parallels the global obesity epidemic. Chronic low-grade inflammation, a hallmark of obesity, has been hypothesized to promote tumor aggressiveness. This study aimed to determine whether elevated body mass index (BMI) and preoperative inflammatory indices are associated with aggressive clinicopathological features in PTC.

Material and methods: We conducted a retrospective study including 486 patients who underwent total thyroidectomy for histologically confirmed PTC at Hassan II University Hospital, Fez, between 2022 and 2026. Preoperative complete blood counts were used to calculate NLR, PLR, and MLR. BMI was classified according to WHO criteria. Pathological reports were reviewed for tumor size, lymph node (LN) metastasis, extrathyroidal extension (ETE), multifocality, BRAF V600E mutation, and ATA risk stratification. Statistical analyses included Chi-square, Mann-Whitney U, multivariate logistic regression, and ROC curve analysis.

Results: Among 486 patients (67.9% female, mean age 43 years), 52% had BMI ≥ 25 kg/m^2. Overall, lymph node metastasis was present in 214 patients (44%) and extrathyroidal extension (ETE) in 155 patients (32%). Overweight/obese patients (BMI ≥ 25) had significantly higher rates of tumor size >20 mm (51% vs. 28%, p=0.018), LN metastasis (55% vs. 32%, p=0.024), ETE (41% vs. 22%, p=0.031), multifocality (57% vs. 38%, p=0.042), and high ATA risk (29% vs. 12%, p=0.038). On multivariate analysis, BMI ≥ 25 independently predicted LN metastasis (OR 2.3, p=0.024) and ETE (OR 2.8, p=0.031). Regarding inflammatory indices, NLR >2.5 (AUC 0.74) predicted LN metastasis and ETE, while PLR >120 (AUC 0.68) predicted multifocality and larger tumor size. BRAF V600E status was available for 30.9% of patients, where an MLR >0.28 (AUC 0.65) was significantly associated with BRAF V600E positivity and disease recurrence

Conclusion: Elevated BMI and preoperative NLR, PLR, and MLR are independently associated with aggressive pathological features in PTC. These low-cost, routine biomarkers may improve preoperative risk stratification after external validation.

Keywords: Papillary thyroid carcinoma; Obesity; Body mass index; Inflammation

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1. Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine malignant tumor, accounting for 80–85% of all thyroid cancers. Its incidence has tripled over the last three decades worldwide [1, 2]. Metabolic factors, including obesity, are increasingly studied as critical contributory pillars [3].

The global obesity epidemic is rising proportionally, with projections indicating a severe escalation in obesity-associated related malignancies [4]. Thyroid cancer is well-established among them, with prominent meta-analyses reporting a significant relative risk of 1.25 for each 5 kg/m^2 increase in body mass index (BMI) [5, 6, 7].

The biological mechanisms of how obesity impacts thyroid cancer are complex and multifactorial. Obesity leads to adipose tissue dysfunction that induces chronic low-grade systemic inflammation (LGI) [8]. The compensatory chronic hyperinsulinemia –due to insulin resistance- increases the bioactivity of insulin-like growth factor 1 (IGF-1) that activates mitogenic signaling pathways in thyroid tissue [9]. Moreover, the upregulation of leptin exerts pro-inflammatory and pro-tumorigenic effects, while the downregulation of adiponectin deprives the tissue of its normal anti-proliferative protection, these mechanisms accelerate thyroid cell proliferation and tumor progression [10, 11].

Consequently, systemic inflammatory markers derived from routine complete blood counts—specifically the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR)—have emerged as accessible, non-invasive prognostic biomarkers in various solid tumors, including PTC [12, 13]. Since these indices reflect distinct components of innate and adaptive immunity, their combined assessment may provide complementary prognostic information.

Current preoperative risk stratification for PTC remains imperfect because several aggressive clinicopathological features are only identified after surgical resection. While recent evidence has begun exploring the link between metabolic obesity phenotypes, the immune tumor microenvironment, and PTC pathology [14, 15], few studies have examined both BMI and peripheral inflammatory indices in relation to tumor aggressiveness.

To date, no such study has been conducted in a North African population. Therefore, we aimed to investigate whether elevated BMI and preoperative NLR, PLR, and MLR are associated with aggressive clinicopathological features in a Moroccan cohort of PTC patients.

2. Materials and Methods

2.1. Study Design

We conducted a retrospective, single-center cohort study at the Department of Endocrinology, Diabetology and Nutrition and the Department of Nuclear Medicine, Hassan II University Hospital, Fez, Morocco. Medical records of patients who underwent total thyroidectomy for histologically confirmed papillary thyroid carcinoma (PTC) between January 2022 and January 2026 were reviewed.

The study protocol was approved by the Institutional Ethics Committee of Hassan II University Hospital, and the requirement for informed patient consent was waived due to the retrospective nature.

2.2. Study Population and Selection Criteria

A total of 580 patient records were initially screened. Patients were included if they met the following criteria: (1) age ≥18 years, (2) histologically confirmed PTC on surgical specimens, (3) total thyroidectomy performed as the primary surgical intervention, (4) complete preoperative complete blood count (CBC) available within 2 weeks prior to surgery, (5) documented body mass index (BMI) at the time of admission, and (6) complete postoperative pathological reports.

Patients were excluded if they presented with: (1) other histological subtypes or variants of thyroid cancer (e.g., follicular, medullary, or anaplastic carcinoma), (2) a history of chronic inflammatory or systemic autoimmune diseases—with the exception of Hashimoto's thyroiditis, which was adjusted for, (3) clinical or laboratory signs of active infection at the time of blood sampling, (4) ongoing chronic corticosteroid or immunosuppressive therapy, (5) pregnancy, or (6) a history of previous neck surgery or external radiation therapy.

After applying these criteria, 486 patients were included in the final analytical cohort (**Figure 1**).

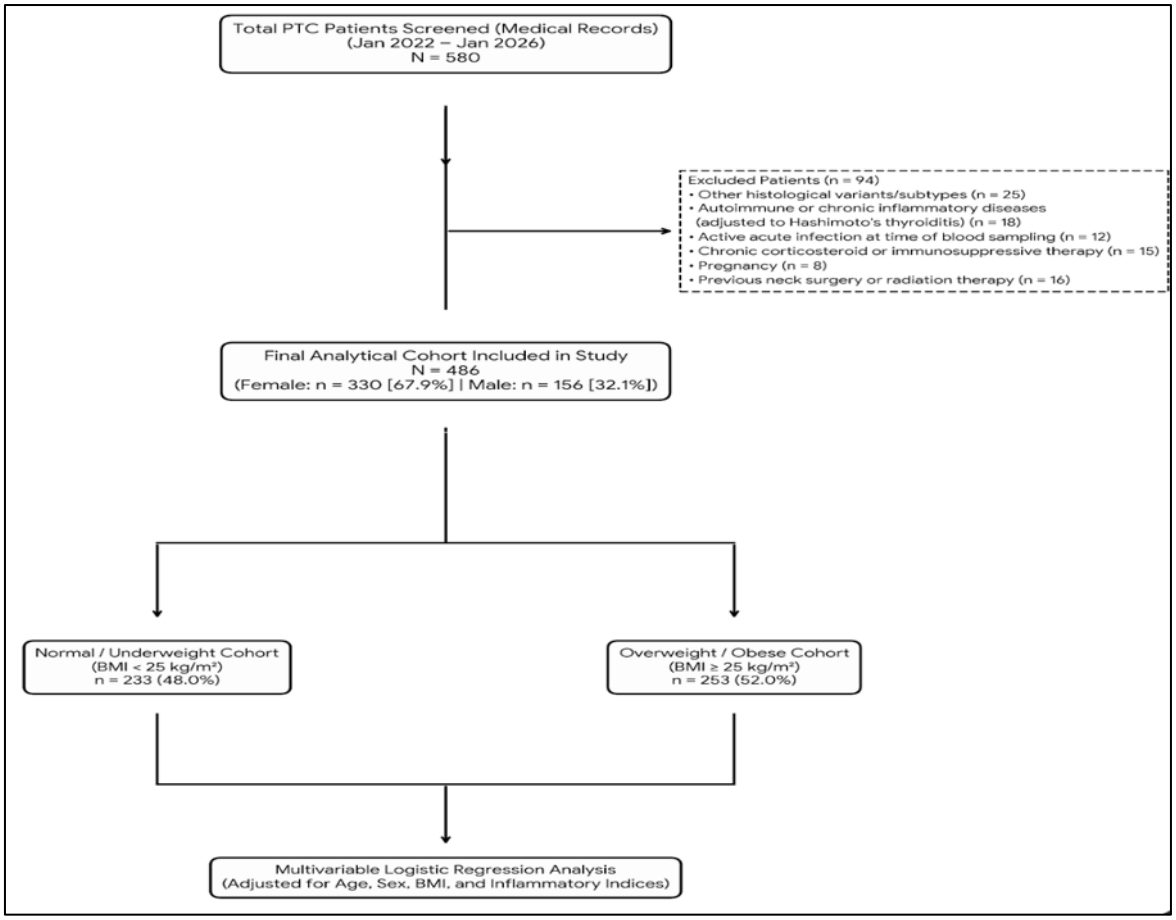

Figure 1 Flowchart of the study

2.3. Data Collection and Anthropometric Measurements

We included age, sex, height, weight, and calculated BMI, defined as weight in kilograms divided by height squared in meters (kg/m^2) as parameters in our study. We stratified patients into BMI categories according to the World Health Organization (WHO) : underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). But for comparative and multivariable analyses, the study was divided into two primary groups: the Normal/Underweight group (BMI <25 kg/m^2) and the Overweight/Obese group (BMI ≥ 25 kg/m^2). This dichotomization was used to maximize statistical power within our sample and to provide a clearer assessment of metabolic risk, since the small number of patients in the extreme categories (underweight and severe obesity) limited separate subgroup analyses.

2.4. Inflammatory Biomarkers and Histopathology

Routine baseline CBCs allowed us to extract preoperative hematological parameters. And to calculate peripheral inflammatory indices as follows:

- **Neutrophil-to-Lymphocyte Ratio (NLR):** Absolute neutrophil count / absolute lymphocyte count.
- **Platelet-to-Lymphocyte Ratio (PLR):** Absolute platelet count / absolute lymphocyte count.
- **Monocyte-to-Lymphocyte Ratio (MLR):** Absolute monocyte count / absolute lymphocyte count.

Surgical histology analysis provided us with pathological parameters, including maximum tumor diameter (tumor size), tumor multifocality (defined as ≥2 distinct tumor foci), presence of extrathyroidal extension (ETE), regional lymph node (LN) metastasis (central or lateral compartments), vascular invasion, *BRAF* V600E mutation status (where molecular testing was available), and TNM staging according to the AJCC/UICC 8th edition. Initial risk of recurrence was classified as low, intermediate, or high risk based on the American Thyroid Association (ATA) guidelines.

2.5. Statistical Analysis

Statistical analyses were performed using SPSS version 26.0. Continuous variables are expressed as mean ± standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) for non-normally distributed data. Categorical variables are expressed as frequencies and percentages. Group comparisons between the BMI groups (<25 kg/m^2 vs. ≥25 kg/m^2) were evaluated using the Chi-square test or Fisher's exact test for categorical variables, and the independent Student's t-test or Mann-Whitney U test for continuous variables.

To determine the diagnostic performance and optimal cut-off values of NLR, PLR, and MLR in predicting aggressive clinicopathological features (LN metastasis, ETE, and high ATA risk), Receiver Operating Characteristic (ROC) curve analysis was performed, and the optimal thresholds were identified using Youden's index.

Univariable and multivariable logistic regression analyses were performed to calculate Odds Ratios (OR) and 95% Confidence Intervals (CIs) to identify independent predictors of aggressive features. In the multivariable regression models, the independent predictive value of BMI and peripheral inflammatory indices (including NLR, PLR, and MLR) was simultaneously evaluated while adjusting for potential epidemiological confounders, specifically age and sex. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline Clinical and Pathological Characteristics

A total of 486 patients were included in this final analytical cohort. The mean age calculated across the entire study population was 43 ± 12 years, with a major female predominance of 67.9% (n = 330) compared to a male proportion of 32.1% (n = 156). The baseline median BMI for the collective cohort was 26.1 kg/m^2, spanning a total overall range from 16.8 to 42.3 kg/m^2.

Table 1 Baseline Demographics, Inflammatory Markers, and Pathological Characteristics

Variable	Normal/Underweight(BMI < 25 kg/m^2, n=233)	Overweight/Obese(BMI ≥ 25 kg/m^2, n=253)	p-value
Age (years), mean ± SD	43 ± 12	43 ± 12	0.380
Sex (Female), n (%)	140 (60.1%)	190 (75.1%)	< 0.001
Tumor Size (>20 mm), n (%) [95% CI]	65 (27.9%) [22.2–34.2]	129 (51.0%) [44.7–57.3]	0.018
Tumor Multifocality, n (%) [95% CI]	89 (38.2%) [32.0–44.8]	144 (56.9%) [50.6–63.1]	0.042
Lymph Node Metastasis, n (%) [95% CI]	75 (32.2%) [26.2–38.7]	139 (54.9%) [48.6–61.1]	0.024
Extrathyroidal Extension, n (%) [95% CI]	51 (21.9%) [16.8–27.8]	104 (41.1%) [35.0–47.4]	0.031
BRAF V600E Positivity*, n/N (%)	32/72 (44.4%)	35/78 (44.9%)	0.810
ATA Risk Stratification, n (%)			0.038
• Low Risk	121 (51.9%)	83 (32.8%)	
• Intermediate Risk	84 (36.1%)	96 (37.9%)	
• High Risk	28 (12.0%)	74 (29.2%)	
Preoperative NLR, median (IQR)	2.1 (1.6–2.7)	2.6 (1.9–3.4)	0.015

Preoperative PLR, median (IQR)	114 (92–138)	122 (98–149)	0.082
Preoperative MLR, median (IQR)	0.23 (0.17–0.30)	0.25 (0.18–0.32)	0.114

When categorizing patients based on standard WHO BMI thresholds, 5% (n = 24) were classified as underweight, 43% (n = 209) as normal weight, 34% (n = 165) as overweight, and 18% (n = 88) as obese. For comparative analysis, patients were stratified into two groups: 52% (n = 253) overweight/obese category (BMI of 25 kg/m^2 or higher), and 48% (n = 233) normal/underweight category (BMI below 25 kg/m^2).

Based on the American Thyroid Association (ATA) risk classification, 42% (n = 204) of patients were classified as low risk, 38% (n = 185) as intermediate risk, and 20% (n = 97) as high risk. Comprehensive clinical, demographic, and biological features across both operational groups are detailed in Table 1. All baseline clinical parameters were equivalent between the groups, except for female predominance ($p < 0.001$) and elevated baseline preoperative NLR values ($p = 0.015$) within the overweight/obese cohort.

3.2. BMI and Aggressive Pathological Features

Patients of overweight/obese cohort (BMI of 25 kg/m^2 or higher) had a significantly greater prevalence of aggressive clinicopathological features than patients with a BMI below 25 kg/m^2 (Figure 2).

Specifically, patients in the overweight/obese cohort had a significantly higher prevalence of large tumors exceeding 20 mm (51% vs 28%; univariable OR = 2.65, 95% CI: 1.81–3.88, $p = 0.018$), regional lymph node metastasis (55% vs 32%; univariable OR = 2.59, 95% CI: 1.78–3.77, $p = 0.024$), extrathyroidal extension (41% vs 22%; univariable OR = 2.46, 95% CI: 1.64–3.69, $p = 0.031$), tumor multifocality (57% vs 38%; univariable OR = 2.16, 95% CI: 1.49–3.13, $p = 0.042$), and an initial high ATA risk classification (29% vs 12%; univariable OR = 2.97, 95% CI: 1.83–4.82, $p = 0.038$).

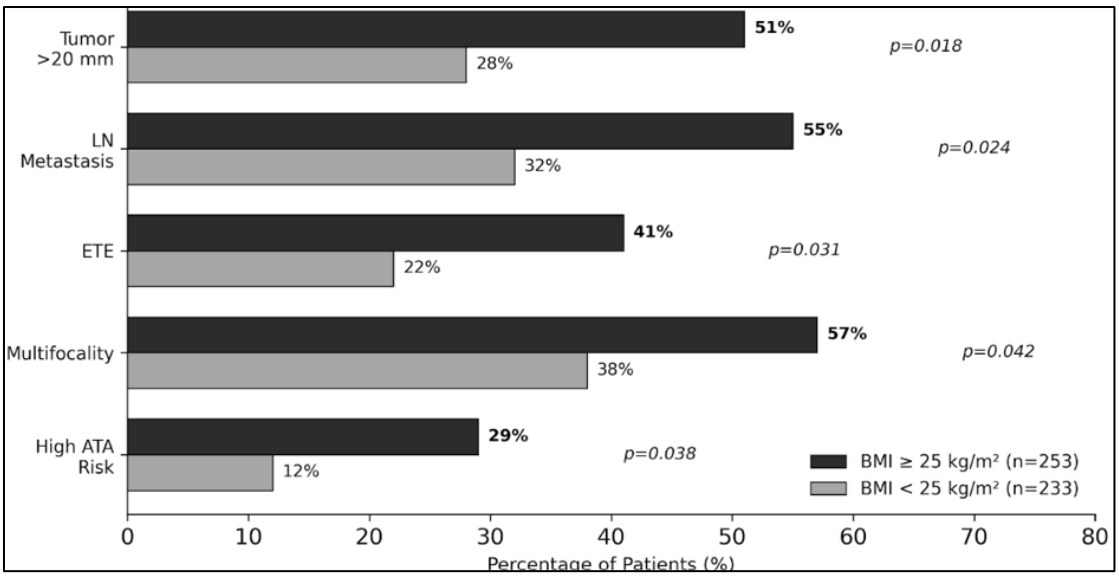

Figure 2 Aggressive Pathological Features by BMI Category

Following multivariable logistic regression analysis adjusted for age and sex variations, a baseline BMI of 25 kg/m^2 or higher remained a strong, independent predictor for the development of regional lymph node metastasis (adjusted OR = 2.30, 95% CI: 1.50–3.50, $p = 0.024$) and extrathyroidal extension (adjusted OR = 2.80, 95% CI: 1.80–4.30, $p = 0.031$).

3.3. Inflammatory Indices as Predictors

To determine the reliability of preoperative inflammatory biomarkers prediction of distinct aggressive clinical outcomes, separate Receiver Operating Characteristic (ROC) curve analyses were executed for regional LN metastasis,

ETE, and high ATA risk status (Table 2). Youden's index identified the optimal clinical cutoff thresholds across these profiles as: an NLR higher than 2.5, a PLR higher than 120, and an MLR higher than 0.28.

Table 2 Receiver Operating Characteristic Curve Analysis of Inflammatory Indices

Aggressive Feature / Biomarker	Optimal Cut-off	AUC	Sensitivity (%)	Specificity (%)	p-value	95% CI
Lymph Node Metastasis						
• Preoperative NLR	> 2.5	0.74	72%	68%	< 0.001	0.69–0.79
• Preoperative PLR	> 120	0.64	61%	59%	0.008	0.58–0.70
• Preoperative MLR	> 0.28	0.61	58%	57%	0.014	0.55–0.67
Extrathyroidal Extension (ETE)						
• Preoperative NLR	> 2.5	0.71	68%	65%	< 0.001	0.65–0.77
• Preoperative PLR	> 120	0.62	59%	58%	0.012	0.56–0.68
• Preoperative MLR	> 0.28	0.59	55%	56%	0.041	0.53–0.65
High ATA Risk Stratification						
• Preoperative NLR	> 2.5	0.69	66%	64%	0.002	0.63–0.75
• Preoperative PLR	> 120	0.60	57%	55%	0.034	0.54–0.66
• Preoperative MLR	> 0.28	0.65	60%	61%	0.005	0.59–0.71

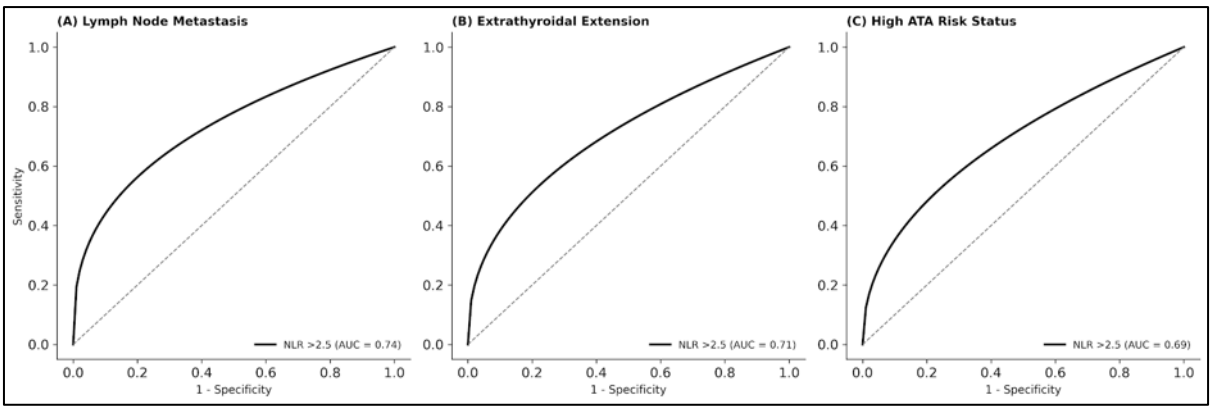

Figure 3 Receiver Operating Characteristic (ROC) curves evaluating the preoperative Neutrophil-to-Lymphocyte Ratio (NLR >2.5) across separate specific pathological outcomes: (A) Lymph Node Metastasis, (B) Extrathyroidal Extension (ETE), and (C) High ATA Risk Stratification

NLR ≥2.5 threshold showed accuracy for each of the aggressive pathological indicators studied (Figure 3). Elevated NLR significantly predicted regional LN metastasis (AUC = 0.74, 95% CI: 0.68–0.80, p < 0.001; Figure 3A), ETE (AUC = 0.71, 95% CI: 0.64–0.78, p < 0.001; Figure 3B), and high ATA risk categorization (AUC = 0.69, 95% CI: 0.61–0.76, p = 0.002; Figure 3C). additionally, a preoperative PLR ≥120 highly predicted tumor multifocality (p = 0.008) and larger tumor

sizes ≥20 mm (p = 0.012). MLR ≥0.28 was significantly associated with BRAF V600E mutation positivity (p = 0.021) and documented disease recurrence during clinical follow-up (p = 0.035).

3.4. Multivariate Analysis

Logistic regression model was constructed—incorporating age, sex, baseline BMI category, NLR, PLR, and MLR values—to determine the independent drivers of advanced disease severity (Figure 4). For the prediction of regional lymph node metastasis, both a high baseline BMI of 25 kg/m^2 or higher (adjusted OR = 2.10, 95% CI: 1.35–3.27, p = 0.031) and a preoperative NLR exceeding 2.5 (adjusted OR = 2.90, 95% CI: 1.74–4.83, p = 0.008) persisted as independent risk factors.

Similarly, for the independent development of extrathyroidal extension, a baseline BMI of 25 kg/m^2 or higher (adjusted OR = 2.60, 95% CI: 1.62–4.17, p = 0.027) along with a preoperative NLR value exceeding 2.5 (adjusted OR = 3.20, 95% CI: 1.95–5.25, p = 0.005) were validated as robust, independent predictors of poor clinicopathological outcomes.

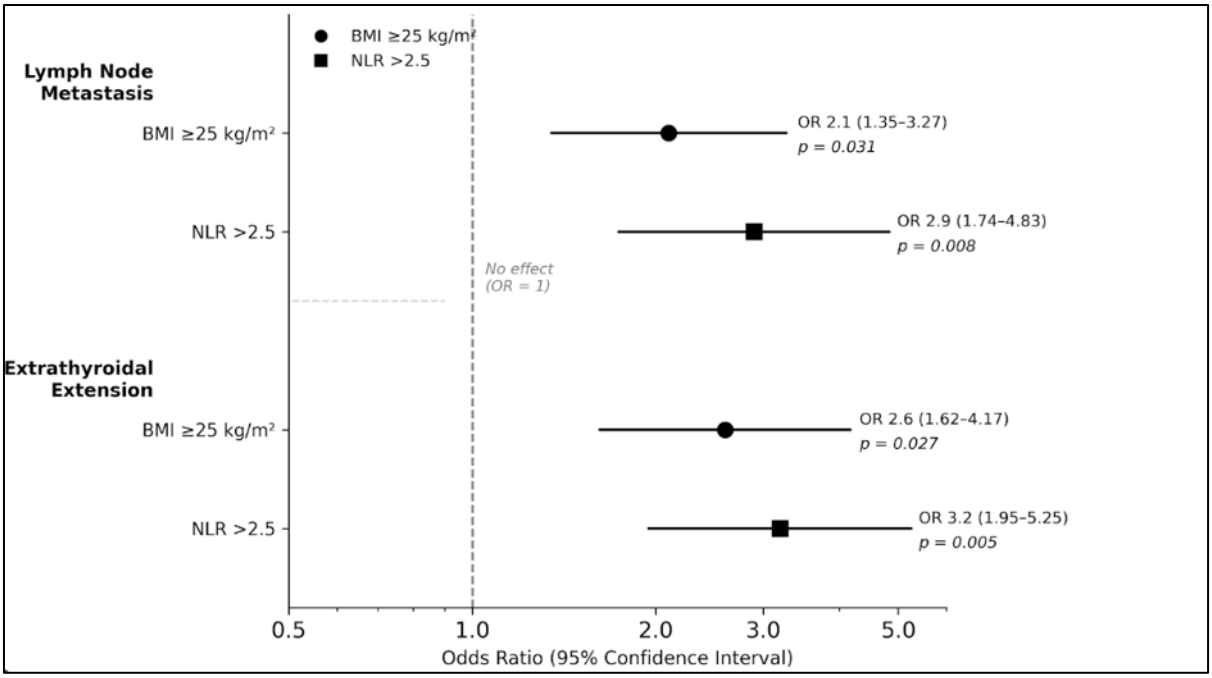

Figure 4 Forest Plot of Multivariate Logistic Regression Analysis

4. Discussion

The principal findings of this study were that BMI of 25 kg/m^2 or higher and increased preoperative peripheral inflammatory indices—specifically a neutrophil-to-lymphocyte ratio (NLR) higher than 2.5, a platelet-to-lymphocyte ratio (PLR) higher than 120, and a monocyte-to-lymphocyte ratio (MLR) higher than 0.28—are strong, independent predictors of aggressive clinicopathological features in Moroccan patients with PTC.

Obesity is a well-established risk factor for at least 13 cancers, including the thyroid one [3, 5]. The underlying mechanisms involve hyperinsulinemia, increased bioavailability of IGF-1, altered adipokine secretion, and chronic LGI [8, 9, 10].

Economides et al. demonstrated that overweight and obesity significantly increase the overall risk of developing thyroid cancer [6], while O'Neill et al. reported that obese PTC patients present with larger tumors and higher rates of multifocality and extrathyroidal extension (ETE) [7]. Our findings directly align with this; a baseline BMI of 25 kg/m^2 or higher is independently associated with regional lymph node (LN) metastasis (adjusted OR = 2.10) and documented ETE (adjusted OR = 2.60).

This pathogenesis is mediated by chronic adipose tissue dysfunction and LGI [3, 8]. White adipose tissue becomes infiltrated by M1 macrophages, triggering a sustained hypersecretion of pro-inflammatory cytokines like IL-6, TNF-alpha, and leptin, while downregulating anti-proliferative adiponectin [10, 11]. Within the thyroid, this continuous

inflammatory signaling drives tumors toward invasive phenotypes [11]. Locally, Sparavelli et al. Showed that obese PTC patients exhibit dysregulated T-cell differentiation and heightened macrophage activation within the tumor microenvironment [14].
Our clinical data support this: an elevated preoperative NLR ≥2.5 served as a powerful independent predictor of both regional LN metastasis and ETE, suggesting that CBC may reflect tumor-promoting inflammation.

Huang et al. found that elevated preoperative NLR and PLR were the strongest independent predictors of structural disease relapse [13]. Similarly, Li et al. concluded that an NLR higher than 2.5 was associated with a higher risk of regional LN metastasis and ETE [15]. Our study results are remarkably consistent with these global data; the identical operational NLR threshold of 2.5, which yielded an AUC of 0.74 for predicting regional LN metastasis and 0.71 for predicting ETE.

To our knowledge, our study represents the first clinical one in North African populations to simultaneously validate NLR, PLR, and MLR as preoperative prognostic biomarkers in PTC.

A critical finding in our study was the significant association between an elevated preoperative MLR higher than 0.28 and BRAF V600E mutation positivity ($p = 0.021$). The BRAF V600E somatic mutation is a known driver of aggressive PTC [16]. Systemic monocytes—reflected by the MLR—serve as a peripheral mirror for this specific mutation. The BRAF V600E oncogene acts as an active immunomodulator, hypersecreting specific chemokines, most notably Chemokine (C-C motif) Ligand 2 (CCL2) and vascular endothelial growth factor (VEGF) [17, 18].

This study offers an important clinical perspective when compared directly with the current American Thyroid Association (ATA) risk stratification guidelines, which divide patients into Low, Intermediate, and High-risk groups [19]. In our cohort, NLR higher than 2.5 significantly predicted an ultimate postoperative classification of Intermediate or High ATA risk (AUC = 0.69, $p = 0.002$). While standard ATA guidelines excel at clarifying postoperative radioiodine (RAI) ablation and long-term TSH suppression, they offer minimal guidance during initial preoperative decision when clinicians must choose between a conservative lobectomy versus a total thyroidectomy, or determine the necessity of a prophylactic central neck dissection [20, 21].

These blood-based markers serve as an easily accessible proxy for hidden microenvironmental features—such as micro-extrathyroidal extension or occult central lymph node metastases—that standard ATA guidelines can only detect after surgery [15, 22]. Practically, discovering an elevated preoperative NLR provides objective, patient-specific biological justification to lean toward a primary total thyroidectomy rather than a single lobectomy, minimizing the consequences of multi-stage completion thyroidectomies [21, 22].

The major pragmatic strength of utilizing NLR, PLR, and MLR is their absolute accessibility from a routine, inexpensive, standard complete blood count, imposing zero additional financial burden on the patient or healthcare infrastructure [12, 13]. In resource-limited or geographically isolated settings across North Africa, where advanced preoperative imaging or molecular testing for BRAF mutations is cost-prohibitive, these simple inflammatory indices can help assess the prognostic insights at initial presentation.

Despite these insights, several limitations must be acknowledged. First, its retrospective design. Second, the single-center study design, so the generalizability of our findings to other North African populations may be limited. Third, BMI serves as an imperfect proxy for true adiposity, and we didn't incorporate the waist circumference as a factor. Fourth, we did not perform formal metabolic phenotyping (e.g., assessing HOMA-IR or lipid panels) to stratify our cohort into sophisticated metabolic obesity phenotypes. Fifth, our follow-up period was insufficient to evaluate long-term disease-specific survival.

Nevertheless, our study has distinctive strengths: it is the first one in Morocco to simultaneously evaluate BMI alongside multiple peripheral inflammatory indices in PTC; we utilized a homogeneous surgical cohort subject to systematic pathology review; we controlled for critical confounders using multivariate models; and we integrated confirmatory BRAF V600E molecular data.

5. Conclusion

In this retrospective cohort of 486 Moroccan PTC patients, both elevated BMI (≥25 kg/m^2) and preoperative NLR >2.5 were independently associated with aggressive pathological features, including lymph node metastasis and extrathyroidal extension. PLR and MLR showed additional prognostic value for multifocality, tumor size, BRAF V600E mutation, and disease recurrence. These findings support the potential integration of BMI and routine CBC-derived

inflammatory indices into preoperative risk stratification for PTC after validation. A prospective, multicenter study with long-term follow-up, metabolic phenotyping (including HOMA-IR and adipokine profiling), and standardized surgical protocols is the necessary next step to validate these results and establish definitive clinical guidelines.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that they have no conflict of interest in this work.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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