

Medium platelet volume and lymphocyte-platelet index as prognosis factors in papillary thyroid cancer

Volumen plaquetario medio e índice de plaquetas-linfocitos como factores de pronóstico en cáncer papilar de tiroides

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Abstract

Background: Papillary thyroid cancer is the most common endocrine neoplasia. There are prognostic factors that establish risk of recurrence and mortality; however, patients considered low risk may have a less favorable evolution and hence the importance of finding new markers. **Objective:** To assess whether the mean platelet volume (MPV) and the platelet-lymphocyte index (PLI) show a relationship with the clinical staging in papillary thyroid cancer. **Method:** Retrospective, observational and analytical study. Preoperative MPV and PLI were recorded, its relationship with TNM and MACIS systems was sought, as well as locally advanced invasion and tumor focality. **Results:** 107 cases treated from November 2017 to February 2020. No statistically significant difference was observed in these two preoperative parameters with advanced and initial stages, risk groups or tumor focality. The statistical analysis used was one-way ANOVA with SPSS 25, a 95% confidence interval and $p < 0.05$. **Conclusions:** Despite the logical reasoning of tumor pathophysiology, our study did not find a relationship between papillary thyroid carcinoma with MPV and PLI, and should be complemented with more extensive studies.

Keywords: Papillary thyroid cancer. Lymphocyte platelet index. Mean platelet volume.

Resumen

Antecedentes: El cáncer papilar de tiroides es la neoplasia endocrina más frecuente. Existen factores pronósticos que establecen el riesgo de recurrencia y mortalidad; sin embargo, los pacientes considerados de bajo riesgo pueden llegar a presentar una evolución menos favorable, y de ahí la importancia de encontrar nuevos marcadores. **Objetivo:** Evaluar si el volumen plaquetario medio (MPV) y el índice plaquetas-linfocitos (PLR) presentan una relación con la etapificación clínica en el cáncer papilar de tiroides. **Método:** Estudio retrospectivo, observacional y analítico. Se registraron el MPV y el PLR preoperatorios, y se buscó su relación con los sistemas TNM y MACIS, así como con la invasión localmente avanzada y la focalidad del tumor. **Resultados:** Se trataron 107 casos de noviembre de 2017 a febrero de 2020. No se observó diferencia estadísticamente significativa en estos dos parámetros preoperatorios o en estadios avanzados e iniciales, grupos de riesgo ni focalidad del tumor. El análisis estadístico utilizado fue ANOVA de una vía, con SPSS 25, con intervalo de confianza del 95% y $p < 0.05$. **Conclusiones:** Pese al razonamiento lógico de la fisiopatología tumoral, en nuestro estudio no se encontró relación entre el carcinoma papilar de tiroides, el MPV y el PLR, y debiera complementarse con estudios más extensos.

Palabras clave: Cáncer papilar de tiroides. Índice plaquetas-linfocitos. Volumen plaquetario medio.

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Introduction

The functional relationship between inflammation and cancer has always existed. The fact that tumors often grow in sites of chronic inflammation led Rudolf Virchow, in 1863, to suggest that there is a link between the immune system and cancer^{1,2}. At first, it may seem contradictory that the immune system and platelet function can promote the development of tumor cells in sites of chronic inflammation and, on the other hand, contribute to its elimination³.

The main cellular mediators of the anti-tumor immune response are the activated CD8+ T cells and CD4+ Th1 lymphocytes. The former are responsible for eliminating tumor cells through the production of apoptosis-inducing molecules or cytotoxic granules (eg, granzymes, perforin, and granulysin), while the latter promote the production of anti-tumor cytokines, such as interferon-gamma⁴. On the other hand, the mechanisms that drive tumorigenesis through inflammation are as diverse as DNA damage due to inflammatory mediators (oxygen free radicals and extracellular matrix metalloproteinases), as well as cytokines such as interleukins 1B and 8, which promote neoplastic risk. Similarly, once a tumor has popped up, growing malignant cells promote neoangiogenesis, the acquisition of new mutations, extracellular matrix disruption, tumor cell migration, and ultimately metastasis. This is how cancer can regulate the production of circulating platelets^{5,6}.

Platelet biology is essential for hemostasis, vascular integrity, angiogenesis, inflammation, innate immunity, wound healing, and cancer biology. Also, platelets are the first cells to be activated during the process of hemostasis^{7,8}. The growth of tumor masses depends on the creation of new blood vessels, a process that is known as tumor angiogenesis^{9,10}. Angiogenesis occurs during tumor growth, requires increased oxygen supply, and is due to the activation of Ras and Raf oncogenes^{11,12}, which stimulate the release of pro-angiogenic factors such as vascular endothelial growth factor, platelet-derived endothelial growth factor, and angiopoietins 1 and 2¹³⁻¹⁵. As a matter of fact, former studies have demonstrated the presence of a specific receptor, called the alpha receptor for the platelet-derived growth factor, which, if expressed by papillary thyroid cancer cells, confers greater aggressiveness associated with lymph node metastases compared to patients who do not express it constitutively¹⁶.

Platelet coatings also protect circulating tumor cells from high-flow shear forces in the vascular wall, and evade the immune system and tumor necrosis factor-alpha-mediated cytotoxicity¹⁷⁻¹⁹. A plethora of preoperative hematological parameters, such as platelet count, platelet size evaluated by the mean platelet volume, the neutrophil-lymphocyte ratio, and the platelet-lymphocyte ratio have been associated with the clinical, pathological, and survival characteristics of many different cancers. However, the role of these indices in papillary thyroid cancer is still to be elucidated²⁰⁻²³.

Papillary thyroid cancer is the most common endocrine neoplasm and often responds well to treatment^{24,25}. Surgical resection and adjuvant therapy for this type of malignant neoplasm have been defined based on well-known prognostic factors that determine the risk of recurrence and long-term mortality, such as advanced age, sex, tumor size, invasion of the thyroid capsule and extrathyroidal tissues, lymphovascular invasion or incomplete tumor removal. Some of these factors are more relevant than others^{26,27}. This is why some patients have less favorable outcomes, with long-term recurrences despite of being initially considered as low-risk patients²⁸. Therefore, the early identification of patients who may have unfavorable outcomes despite being from low clinical risk groups is of paramount importance.

We have been able to see that tumors of the same histological lineage behave different biologically, perhaps due to the presence of genes that better evade the immune response or because they have more effective metastasis mechanisms, which are not clearly understood at the moment²⁹. Nevertheless, these factors ultimately make these tumors more aggressive. However, in the case of papillary thyroid carcinoma, this cannot yet be detected in early treatment periods.

The mean platelet volume (MPV) and platelet distribution width are early indices of platelet activation^{30,31}. Their value, along with the platelet-lymphocyte ratio (PLR), has been relevant when it comes to comparing malignant thyroid disease to benign conditions³². Therefore, if the MPV and PLR were related to these mechanisms that confer greater tumor aggressiveness, they would create the possibility of being able to plan the proper therapeutic approach for patients classified as low risk, thus avoiding incomplete treatments. Therefore, these platelet and lymphocyte characteristics could represent an additional, accessible, and easily applicable tool.

The objective of this study was to evaluate whether the MPV and the PLR change in patients with papillary thyroid cancer according to their initial risk group assessment or staging.

Method

This was a retrospective, observational, analytical, and cross-sectional study of 107 patients with papillary thyroid cancer treated at the Thyroid Clinic of the General Surgery Department at the Hospital General de Mexico Dr. Eduardo Liceaga, Mexico City, Mexico from November 1, 2017 through February 28, 2020.

The study analyzed 3 variables: preoperative mean platelet volume (MPV), preoperative absolute lymphocyte count, and preoperative absolute platelet count. These measurements were systematically reported in a complete blood count and obtained using the MAPPS method by impedance and optical vision using ethylenediaminetetraacetic acid as anticoagulant agent.

The PLR was estimated dividing the absolute platelet count by the absolute lymphocyte count.

To confirm the patients' risk group classification, surgical reports and histopathological study results were retrieved from the hospital electronic database to gather intraoperative findings. All patients were classified according to the TNM (Tumor, Node, Metastasis) staging system of the American Joint Committee on Cancer (stages I, II, III, and IV) and based on severity according to the MACIS (Metastases, Age, Completeness of resection, Invasion, Size) system (very low risk < 6; low risk, 6-6.99; intermediate risk, 7-7.99; and high risk > 8).

Inter-group comparisons were made based on the MACIS and TNM classifications, and the statistical analysis used a 4×1 one-way ANOVA test that was complemented with Tukey's post hoc test if there were any inter-group differences and effect size. The latter was considered low if $f \leq 0.24$, medium if $f = 0.25-0.39$, and large if $f \geq 0.40$. Focality and age interactions with MPV and PLR were analyzed using factorial ANOVA. P values < 0.05 were considered statistically significant. Scatter plots of variables were created showing means and confidence intervals, and effect sizes were considered low if $\eta^2 = 0.01-0.05$, medium if $\eta^2 = 0.06-0.13$, and large if $\eta^2 \geq 0.14$. Statistical calculations were performed using SPSS 25.0 statistical software package for Windows.

Results

Out of the 107 patients included, 90 were women (84.11%) and 17 were men (15.88%). The overall mean age was 48.45 years, being women's mean age, 48.27 years (24 to 85 years) and men's mean age 50.05 years (26 to 76 years).

The overall mean MPV was 8.76 fl (8.57 to 8.96 fl), while the mean PLR was 138.77 (126.8 to 150.74).

Based on the MACIS score, the patients were divided into 4 groups:

- Group #1: 64 patients (10 men, 54 women) with MPV of 8.64 and mean PLR of 145.
- Group #2: 20 patients (3 men, 17 women) with MPV of 8.72 and mean PLR of 137.55.
- Group #3: 13 patients (4 men, 9 women) with MPV of 9.16 and mean PLR of 131.63.
- Group #4: 10 patients (all women) with MPV of 9.13 and mean PLR of 110.35.

A comparison of the 4 groups was performed using 2 variables, MPV and PLR through the 4×1 one-way ANOVA test way used as parametric statistical analysis. No statistically significant differences were reported between the cancer severity groups and MPV based on the MACIS score, with a low effect size ($F_{(3,103)} = 1456$; $p = 0.231$; $f = 0.203$). No statistically significant differences were seen either when these groups and PLR were compared, also with a low effect size ($F_{(3,103)} = 0.963$; $p = 0.413$; $f = 0.164$) (Table 1).

Similarly, based on the TNM staging system, patients were divided into four groups: 80 patients as stage I, 14 patients over the age of 55 as stage II, 5 patients as stage III, and 8 patients as stage IV. The ANOVA test did not show any statistically significant differences between the cancer severity groups and MPV based on TNM staging ($F_{(3,103)} = 0.119$, $p = 0.949$; $f = 0.006$). Similarly, no statistically significant differences were reported between the cancer severity groups and the PLR ($F_{(3,103)} = 1.940$; $p = 0.128$; $f = 0.103$). Both analyses presented a low effect size (Table 2).

As a third aspect, a factorial ANOVA analysis was performed to examine the interaction between focality, age (taking age younger or older than 55 years as the reference based on TNM staging in its eighth edition), and MPV. The results obtained were $F = 0.891$, $p = 0.348$, and $\eta^2 = 0.009$, indicative that the interaction was not statistically significant. Similarly, the effect of these two variables on the PLR was also examined, yielding the following values: $F = 1.816$, $p = 0.181$, and $\eta^2 = 0.017$, which was not statistically significant either. Additionally, the interaction between the MACIS score and age with MPV was assessed too, yielding the following values: $F = 0.82$, $p = 0.48$, and $\eta^2 = 0.024$, along with the interaction between these variables and the PLR, resulting in F values of 1.13, $p = 0.34$, and $\eta^2 = 0.033$. All of these interactions showed no statistically significant associations and had low effect sizes.

Table 1. Comparison between mean platelet volume and platelet-to-lymphocyte ratio by groups based on the MACIS score

Risk Group	MPV (mean ± SD)	PLR (mean ± SD)
Very low risk (< 6)	8.64 (0.84)	145.04 (68.93)
Low risk (6-6.99)	8.72 (1.08)	137.55 (56.08)
Intermediate risk (7-7.99)	9.16 (1.03)	131.63 (55.89)
High risk (> 8)	9.13 (1.56)	110.36 (25.23)
p	0.23	0.41
f	0.20	0.16

MPV: mean platelet volume; PLR: platelet-to-lymphocyte ratio; SD: standard deviation.

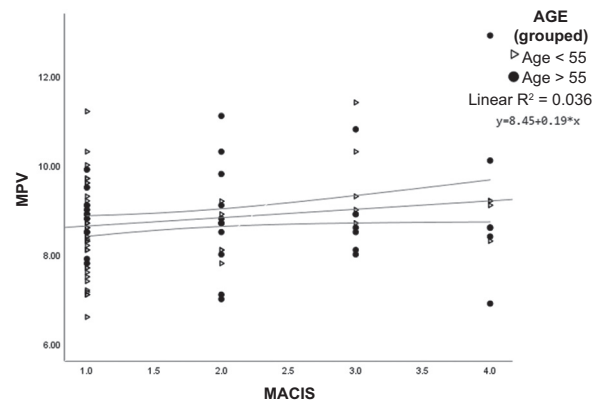
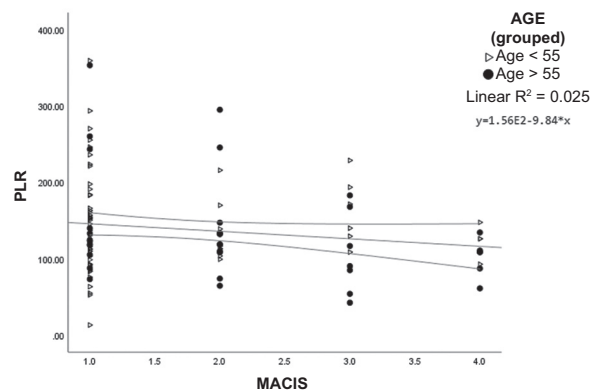
Table 2. Group comparison based on the TNM classification

Stage	n (total = 107)	MPV (fl)	PLR (thousands/ μ L)
Stage I, mean (SD)	n = 80	8.73 (0.876)	143.50 (62.62)
Stage II, mean (SD)	n = 14	8.87 (1.48)	146.52 (70.67)
Stage III, mean (SD)	n = 5	8.90 (1.12)	89.00 (29.43)
Stage IV, mean (SD)	n = 8	8.82 (1.25)	108.97 (43.59)

MPV: mean platelet volume; PLR: platelet-to-lymphocyte ratio; SD: standard deviation.
p = 0.94 for MPV, and p = 0.12 for PLR groups.

Scatter plots were used to analyze the relationship between the MACIS score and MPV and PLR, considering two age groups with a cut-off value of 55 years. The graphs displayed the mean values and confidence intervals. Figure 1 shows that for lower MACIS score categories, MPV values tend to be more closely clustered and homogeneous compared to higher MACIS score categories, showing wider dispersions. Additionally, a positive trend was seen with a regression model $y = 8.45 + 0.19 \cdot x$, with an r^2 value of 0.036 for MPV, indicating that as the MACIS score increases, the MPV value also tends to go up. Regarding the PLR, the trend was negative with a regression model $y = 1.56e2 - 9.84 \cdot x$, and an r^2 value of 0.025. It is obvious that the distribution of PLR values become less scattered as the MACIS score increases, meaning that higher MACIS scores are associated with lower PLR values (Figs. 1 and 2).

Similarly, scatter plots were used to explore the relationship between TNM staging and MPV, as well as between TNM staging and PLR, with consideration of two age groups using 55 years as the cut-off value. The graphs showed the mean values and confidence intervals. Figure 3 shows that the lower the TNM stage, the more closely grouped together

**Figure 1. MACIS-MPV scatter plot.****Figure 2. MACIS-PLR scatter plot.**

the MPV values are compared to higher TNM staging categories, exhibiting more scattered values. A positive trend was also seen with a regression model $y = 8.0.7 + 0.05 \cdot x$, $r^2 = 0.002$ for MPV. Regarding the PLR, the trend is negative with a regression model $y = 1.58e2 - 13.08 \cdot x$, $r^2 = 0.035$, in such a way that the higher the TNM staging, the lower the PLR (Fig. 4).

One notable observation is that in all the graphs, patients under the age of 55 tend to be in lower MACIS score categories, both for MPV and PLR, as well as for TNM.

According to what figures 1 to 4 show regarding the levels of MACIS and TNM in their last categories, linearity seems to be lost. Therefore, it was decided to transform these variables into dummy variables, resulting into 2 different categories: low and high risk. Subsequently, a comparison of the variables MPV and PLR was made with these new levels whose results are shown on table 3.

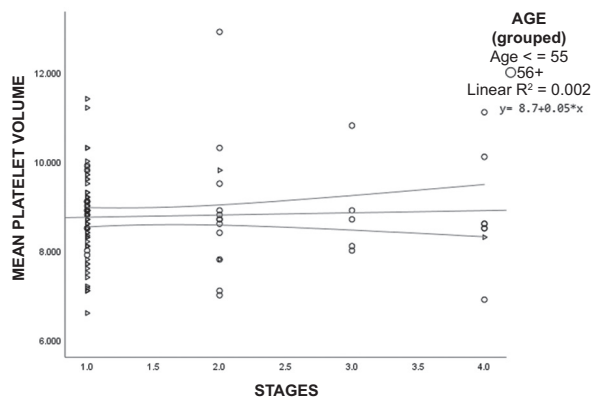


Figure 3. TNM-MPV scatter plot.

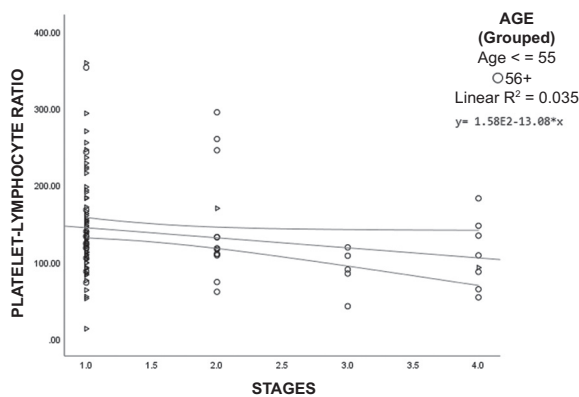


Figure 4. TNM-PLR scatter plot.

As we can see, statistically significant differences were found for the MACIS variable. Those in the high category had higher MPV values compared to those in the lower category. However, the effect size in these results was low. On the other hand, no differences were seen regarding the TNM variable.

Discussion

The current approach for patients with papillary thyroid microcarcinoma classified as low risk involves “active surveillance”^{33,34}. However, as it occurs with almost everything in medicine, this strategy is not perfect, and over time, some patients may still require conventional treatment. Up until now, the reason why some low-risk patients eventually experience disease persistence or recurrence is not yet clearly understood, not even after identifying the genetic factors associated with aggressiveness^{35,36}. Therefore, we should have accessible diagnostic tools to help us make the proper therapeutic decisions^{37,38}.

Table 3. Dummy variables for MACIS and TNM classifications

Category	MPV (fl) (mean ± SD)	PLR (mean ± SD)
MACIS		
Low risk	0.86 (0.89)	143.26 (65.85)
High risk	9.14 (1.25)	122.38 (45.61)
p	0.040	0.157
d	0.49	0.33
TNM		
Stages I & II, mean (SD)	8.72 (0.87)	143.83 (62.3)
Stages III & IV, mean (SD)	8.90 (1.32)	123.00 (61.51)
p	0.419	0.140
d	0.18	0.33

MPV: mean platelet volume; PLR: platelet-to-lymphocyte ratio; SD: standard deviation.

MPV has been investigated in multiple types of cancer, and it has been demonstrated that MPV values are significantly higher in patients with endometrial, ovarian, colorectal, and gastric cancers compared to healthy controls. However, the findings related to thyroid cancer are inconclusive. Baldane et al.³⁹ reported on significantly higher MPV values in thyroid cancer patients compared to benign goiters and healthy subjects, with a significant decrease after tumor resection.³⁹ However, a different study conducted by Dincel and Bayraktar⁴⁰ failed to find such difference. Both studies included very few patients and did not discard the impact of comorbidities and use of drugs. A different study found that blood cell indices, specifically the PLR and MPV, can provide information on multifocal tumors, extrathyroidal spread, and presence of a T3 tumor, thus serving as a means to exclude these characteristics⁴¹. In our study, we sought to investigate the interaction between age and tumor focality, but no such association was found. Similarly, no relationship was ever found between the PLR and MPV in the detection of more advanced stages based on the MACIS and TNM classifications. In both analyses, both the P values and the effect size did not show any differences or interactions, as the effect size was consistently low. We should remember that low effect sizes indicate, in this case, that the levels of MACIS and TNM cannot account for the differences or interactions described in the dependent variables of PLR and MPV.

Another study conducted by Yu et al.⁴² found no significant correlations between the MPV and platelet distribution width with TNM classification, lymph node metastases or distant metastases in patients with papillary and medullary thyroid cancer. However, it was

useful in follicular thyroid cancer stages T3 and T4, with lower MPV values being reported in the presence of lymph node metastases. This effect was not seen in patients in stages T1 and T2, suggesting that platelets may exert different effects based on the different subtypes of thyroid cancer. This leads us to believe that our study focused specifically on papillary thyroid cancer, without including patients with follicular, medullary or anaplastic thyroid cancer. We chose to study this population group because papillary thyroid cancer is the most predominant type worldwide and is the most prevalent one among Mexicans. However, we should determine whether these platelet markers are useful in other subtypes of thyroid cancer, something we did not analyze in our study. Still, its clinical utility should not be overlooked.

Our study is no stranger to limitations given its observational and cross-sectional nature, which affects our ability to draw conclusions of causality. It was also impossible to exclude unmeasured confounders, such as comorbidities that could be altering platelet index counts (diabetes, hypertension, obesity, history of heart diseases or smoking), and the use of certain drugs. Despite these limitations, our study had strengths, including a sample size that was not as small as in other studies and the fact that it was conducted at a single center, thus ensuring more uniform data curation, especially obtaining preoperative platelet index measurements, and avoiding biases that could arise from data obtained from external laboratories or hospitals. The findings of this study might serve as a starting point for further research, considering the heterogeneity of results on this topic and the fact that the mechanisms through which papillary thyroid cancer evades or elicits the immune response and its degree of invasion and recurrence are still to be elucidated.

An incidental finding of the study was that, when the issue of linearity in MACIS and TNM scores was addressed by downgrading from 4 (very low, low, intermediate, and high risk) to just 2 categories (low and high risk), statistically significant differences were found in MPV for MACIS, although the effect size was low. However, in the case of TNM, where 4 categories were downgraded into 2 based on the absence or presence of lymphovascular invasion, no statistically significant differences were seen.

Conclusions

In our study, the PLR and the MPV did not show any possible relationships to distinguish between

early and advanced stages of papillary thyroid cancer. Additionally, no association was found between locally advanced invasion or multifocality, which is indicative that these platelet markers cannot predict a more aggressive behavior of cancer initially classified as early stage despite the reasoning behind tumor pathophysiology. We should understand that this study represents only the first step in the ongoing search for new markers that can help us make better decisions to treat patients with papillary thyroid cancer. By identifying such markers preoperatively, we could gain a deeper understanding of the tumor's biological behavior.

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Conflicts of interest

none reported.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this study.

Patients' data protection. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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