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CORRELATION PROGRAMMED DEATH-LIGAND 1 (PD-L1) EXPRESSION WITH CLINICOPATHOLOGICAL PROFILE OF PAPILLARY THYROID CARCINOMA AT PROF. DR. I G.N.G. NGOERAH DENPASAR HOSPITAL

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer and is generally associated with a favorable prognosis. However, subset of cases exhibits aggressive behavior, characterized by metastasis and high recurrence rates. The expression of Programmed Death-Ligand 1 (PD-L1) plays a role in tumor immune evasion mechanisms and associated with various clinicopathological markers that reflect poor prognosis. Although the correlation between PD-L1 expression and aggressive features of PTC has been extensively studied, local research in Indonesian particularly in Bali, remains limited. This study aims to evaluate the association between PD-L1 expression and the clinicopathological profile of PTC, including age, sex, tumor size, pathological T stage (pT), lymph node metastasis, histological variants, in an effort to assess the potential of PD-L1 as a prognostic biomarker and therapeutic target in aggressive forms of PTC.

Methods: This study employed a cross-sectional analytical design with a sample size of 43. PD-L1 expression was assessed using immunohistochemical staining with antibody clone 28-8. The data were analyzed using Chisquare analysis to assess the correlation between PD-L1 expression and the clinicopathological profile of papillary thyroid carcinoma, with statistical significance set at p<0.05.

Result: The results showed an age range from 20-80 years, with a median age of 43 years and a mean age of 45.23±16.12 years. Chi-square analysis revealed statistically significant correlation between PD-L1 expression and pathological T stage (p=0.009), lymph node metastasis (p<0.001), and histological variant (p=0.002). However, there was no significant correlation between PD-L1 expression and age (p=0.265) or gender (p=1.000). **Conclusion:** There is a statistically significant correlation between PD-L1 expression and pathological T stage, lymph node metastasis, and histological variant. There is no significant correlation was found between PD-L1

Keywords: Papillary thyroid carcinoma., PD-L1 expression., Clinicopathological profile.

INTRODUCTION

expression and age or gender.

Thyroid cancer is one of the most common cancers in productive age. Papillary thyroid carcinoma (KTP) is the most common type of thyroid cancer which amounts to 80-85%, more often found in women. Based on a report made by the Global Cancer Observatory in 2020, there were 13,114 new cases of thyroid cancer in Indonesia. Papillary thyroid carcinoma is a group of tumors that tend to have indolent biological behavior and with a good prognosis. The prognosis of KTP is strongly influenced by tumor aggressiveness, where at stage IV the 10-year life expectancy decreases to around 41%.

Various risk factors show clinicopathologic features associated with the aggressiveness of KTP, namely: age at diagnosis, tumor size, extensive extrathyroidal extension,

metastasis to KGB, distant metastasis, lymphovascular invasion (LVI), and histological variants. ¹⁰ Apart from clinicopathologic factors, the immune system also plays an important role in controlling the spread of cancer cells, but cancer cells can develop mechanisms to evade or suppress this immune response. The immune factor involved is PD-L1. ⁶ In thyroid carcinoma, PD-L1 (Programmed Death-Ligand 1) plays an important role in helping tumors evade the body's immune response. Thus, tumor cells can escape immune surveillance and the process of tumor progression continues to progress. ⁶

Until now there have been no studies on PD-L1 expression in papillary thyroid carcinoma associated with clinicopathological profiles, especially in Bali. The objective of this research is to prove the relationship

between Programmed Death-Ligand 1 (PD-L1) expression and clinicopathological profile in papillary thyroid carcinoma.

METHODS Study Subjects

This study employs a cross-sectional design. A total of 43 paraffin block samples will be selected using consecutive sampling. The samples will be obtained from patients with papillary thyroid carcinoma who underwent resection at the Department of Anatomic Pathology, Faculty of Medicine, Udayana University / Prof. Dr. I G.N.G. Ngoerah Denpasar General Hospital from January 1, 2023 to December 31, 2024.

Data on patients with papillary thyroid carcinoma, who underwent histopathological examination, were obtained from the SIMARS database and the registration book at the Laboratorium of Anatomical Pathology, Prof. Dr. I G.N.G. Ngoerah Denpasar Hospital. The inclusion criteria used were paraffin block preparations from resection material of papillary thyroid carcinoma patients who had been histopathologically established, paraffin blocks containing enough tumor tissue and had not received radiotherapy / chemotherapy. Exclusion criteria were incomplete clinicopathological data, doubtful diagnosis, KTP with lymphocytic thyroiditis and damaged or moldy parafin blocks.

Clinicopathologic Variables

Data on clinicopathologic variables categorized included age, gender, histologic variants, pT stage and KGB metastasis. For age variables, <55 years and ≥55 years were categorized. Histological variants were categorized into non-aggressive variants (classic, encapsulated, follicular, spindle, KTP with fibromatosis/fasciitis-like stroma, oncocytic, clear cell and warthin-like) and aggressive variants (diffuse sclerosing, tall cell, collumnar cell, hobnail, solid/trabecular and insular). The pT stage was categorized into early stage (pT1 and pT2) and advanced stage (pT3 and pT4).

Immunohistochemical Staining

PD-L1 expression assessed bv was examination immunohistochemical using Monoclonal Rabbit Anti-PD-L1 primary antibody, Clone 28-8. Immunohistochemical staining was evaluated on the membrane and/or cytoplasm of tumor cells which could be homogeneous or heterogeneous, brown in color with weak to strong intensity. The smear on the tumor cell membrane can be all or part of the membrane. Cytoplasmic smears can be evenly distributed or fine granules. PD-L1 expression on tumor cells will be assessed based on the proportion of tumor cells stained compared to the entire tumor mass. A positive value is assigned if there is a smear on $\geq 5\%$ of the tumor cells. Negative values were assigned if the cells were stained on <5% of the tumor cells. ≥100 tumor cells are

required to evaluate PD-L1 expression. Interpretation of PD-L1 expression by immunohistochemical staining using a Leica DM 750 binocular light microscope was performed by the researcher and 2 anatomical pathology specialists. If there were differences in the interpretation of PD-L1 expression, a consensus agreement was made.

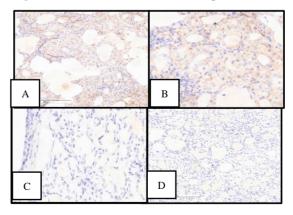
Statistical Analysis

Bivariate analysis of these variables was carried out using the Chi- Square test. For data that did not meet the Chi square requirements, the fisher exact test was performed. The inference process was based on a 95% confidence interval (CI) value and a probability value (p) <0.05. Data were processed using the Statistical Package for the Social Sciences (SPSS) 27.0 for Windows.

RESULTS

The characteristics of the study sample based on age showed that the youngest age was 20 years and the oldest age was 80 years, the median age was 43 years and the mean age was 45.23 ± 16.12 years. The distribution of cases based on clinicopathological characteristics is presented in Table 1. The table shows the distribution of cases based on age, where most of the cases were in the age group of ≤55 years, namely 30 cases (69.8%). Based on gender, most cases were female, totaling 31 cases (72.1%). Based on histology variants, most cases were non-aggressive variants, namely 33 cases (76.7%). Based on pathology stage, most cases were advanced stage, namely 22 cases (51.2%). Based on KGB metastasis, most cases did not show KGB metastasis, namely 35 cases (81.4%). The results obtained in this study showed that 31 cases (72.1%) did not exhibit PD-L1 expression. Figure 1 illustrate cases that stained positive and negative.

Figure 1. illustrate cases that stained positive and negative.



A and B. Positive PD-L1 expression: membranous and cytoplasmic staining (PD-L1 immunohistochemistry A. 100x B. 400x); **C and D.** Negative PD-L1 expression: absent or weakly stained membranous and cytoplasmic (PD-L1 immunohistochemistry C. 100x D. 400x)

Sample Characteristics Frequency Percentage (%) 30 69.8 Age ≤ 55 year > 55 year 13 30,2 Sex Female 31 72,1 Male 12 27.9 33 Histological Variant Not aggressive 76,7 aggressive 10 23,3 48,8 Pathological T Stage Early 21 22 51,2 Late Lymph node metastasis Negative 35 81,4 8 18.6 Positive 31 PD-L1 Expression Negative 72.1

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Table 1. Case distribution based on Clinicopathological Characteristics

To assess the relationship between age and PD-L1 expression, a bivariate chi-square analysis was performed. **Table 2** shows that out of 43 cases of PTC at Prof. dr. I.G.N.G. Ngoerah General Hospital Denpasar, 30 cases were in the age group \leq 55 years and 13 cases were in the age group \geq 55 years. In the 30 cases of the \leq 55 years age group, 8 (26.7%) cases showed positive PD-L1 expression, while 22 (73.3%) cases showed negative PD-L1 expression. In the 13 cases of the > 55 years age group, 9 (69.2%) cases showed negative PD-L1 expression, while 4 (30.2%) cases showed positive PD-L1 expression.

Positive

In the Fisher's exact test analysis to assess the relationship between PD-L1 expression and age, the resulting p-value was 1.000, indicating that there was no statistically significant relationship between PD-L1 expression and age.

Table 3 shows that out of 43 PTC cases at Prof. dr. I.G.N.G. Ngoerah General Hospital Denpasar, 31 (72.1%) cases were female and 12 (27.9%) cases were male. Among the 31 female cases, 7 (22.6%) cases showed positive PD-L1 expression, while 24 (77.4%) cases showed negative PD-L1 expression. In the 12 male cases, 7 (58.3%) cases showed negative PD-L1 expression, while 5 (41.7%) cases showed positive PD-L1 expression.

In the chi-square test analysis to assess the relationship between PD-L1 expression and sex, the resulting p-value was 0.265, indicating that there was no statistically significant relationship between PD-L1 expression and sex.

To assess the relationship between pathological T stage and PD-L1 expression, a bivariate chi-square analysis was performed. **Table 4** shows that out of 43 PTC cases at Prof. dr. I.G.N.G. Ngoerah General Hospital Denpasar, 12 (27.9%) cases showed positive PD-L1 expression and 31 (72.1%) cases showed negative PD-L1 expression. Among the cases with positive PD-L1 expression, 2 (16.7%) cases were early stage and 10 (83.3%) cases were advanced stage. In the cases with negative PD-L1 expression, 19 (61.3%) were early stage and 12 (38.7%) were advanced stage.

In the chi-square test analysis to assess the relationship between PD-L1 expression and pathological T stage (pT), the resulting p-value was 0.009, indicating a statistically significant relationship between PD-L1 expression and pathological T stage (pT). Prevalence risk analysis showed that positive PD-L1 expression had a 7.9 times greater prevalence risk of being in an advanced stage compared to negative PD-L1 expression (95% CI 1.5-42.5).

27.9

Table 5 shows that out of 43 PTC cases at Prof. dr. I.G.N.G. Ngoerah General Hospital Denpasar, 12 (27.9%) cases showed positive PD-L1 expression and 31 (72.1%) cases showed negative PD-L1 expression. Among the cases with positive PD-L1 expression, 7 (58.3%) cases had negative lymph node metastasis and 5 (41.7%) cases had positive lymph node metastasis. In the cases with negative PD-L1 expression, 28 (90.3%) had negative lymph node metastasis and 3 (9.7%) had positive lymph node metastasis.

In the chi-square test analysis to assess the relationship between PD-L1 expression and pathological T stage (pT), the resulting p-value was 0.009, indicating a statistically significant relationship between PD-L1 expression and pathological T stage (pT). Prevalence risk analysis showed that positive PD-L1 expression had a 7.9 times greater prevalence risk of being in an advanced stage compared to negative PD-L1 expression (95% CI 1.5-42.5).

Table 6 shows that out of 43 PTC cases at Prof. dr. I.G.N.G. Ngoerah General Hospital Denpasar, 12 (27.9%) cases showed positive PD-L1 expression and 31 (72.1%) cases showed negative PD-L1 expression. Among the cases with positive PD-L1 expression, 7 (58.3%) cases had negative lymph node metastasis and 5 (41.7%) cases had positive lymph node metastasis. In the cases with negative PD-L1 expression, 28 (90.3%) had negative lymph node metastasis and 3 (9.7%) had positive lymph node metastasis.

In the chi-square test analysis to assess the relationship between PD-L1 expression and histological variant, it was found that there was 1 cell (25%) with an expected count <5, so Fisher's exact test was used. The Fisher's exact test results showed a p-value of 0.002, indicating a statistically significant relationship between PD-L1 expression and histological variant. Prevalence risk analysis showed that the aggressive histological variant had a 13.1 times greater

prevalence risk of showing positive PD-L1 expression compared to the non-aggressive histological variant (95% CI 2.5-68.3).

Table 7 shows the relationship between pathological T stage and lymph node metastasis in PTC patients. The results showed that out of 21 early-stage cases (48.8%), 19 cases (90.5%) did not show lymph node metastasis and 2 cases (9.5%) showed lymph node metastasis. Meanwhile, out of 22 advanced-stage cases (51.2%), 16 cases (72.7%) did not show lymph node metastasis and 6 cases (27.3%) had lymph node metastasis.

In the chi-square test analysis to assess the relationship between pathological T stage and lymph node metastasis, it was found that there were 2 cells (50%) with an expected count <5, so Fisher's exact test was used. The Fisher's exact test results showed a p-value of 0.240, indicating no statistically significant relationship between pathological T stage and lymph node metastasis.

Table 8 shows the relationship between histological variant and lymph node metastasis in PTC patients. The

results showed that out of 33 cases (76.7%) with an aggressive histological variant, 31 cases (93.9%) did not show lymph node metastasis and 2 cases (6.1%) showed lymph node metastasis. Meanwhile, out of 10 cases (23.3%) with a non-aggressive histological variant, 4 cases (40%) did not show lymph node metastasis and 6 cases (60%) had lymph node metastasis.

In the chi-square test analysis to assess the relationship between histological variant and lymph node metastasis, it was found that there was 1 cell (25%) with an expected count <5, so Fisher's exact test was used. The Fisher's exact test results showed a p-value of 0.001, indicating a statistically significant relationship between histological variant and lymph node metastasis. Prevalence risk analysis showed that the aggressive histological variant had a 23.2 times greater prevalence risk of developing lymph node metastasis compared to the non-aggressive histological variant (95% CI 3.5-156.9).

Table 2. Correlation between age and PD-L1 expression in PTC patients at Prof. dr. I.G.N.G. Ngoerah General Hospital

Age	PD-L1 expression		Total	р
	Negative	Positive		
≤ 55 year	22 (73,3%)	8 (26,7%)	30 (69,8%)	1,000
> 55 year	9 (69,2%)	4 (30,8%)	13 (30,2%)	

The significance level is set at p < 0,05

Table 3. Correlation between sex and PD-L1 expression in PTC patients at Prof. dr. I.G.N.G. Ngoerah General Hospital

Sex	PD-L1 expr	i otai	p	
	Negative	Positive		
Female	24 (77,4%)	7 (22,6%)	31 (72,1%)	0,265
Male	7 (58,3%)	5 (41,7%)	12 (27,9%)	

The significance level is set at p < 0,05

Table 4. Correlation between histological variant and PD-L1 expression in PTC patients at Prof. dr. I.G.N.G. Ngoerah General Hospital

Histological Variant	Ekspresi PD-L1		Total	p	PR	IK 95%
	Negative	Positive				
Not aggressive	28 (84,8%)	5 (15,2%)	33 (76,7%)	0,002	13,1	2,5-68,3
aggressive	3 (30%)	7 (70%)	10 (23,3%)			

The significance level is set at p < 0.05

Table 5. Correlation between PD-L1 expression and Pathological T stage (pT) in PTC patients at Prof. dr. I.G.N.G. Ngoerah General Hospital

Hospital						
PD-L1	Stage		Total	p	PR	IK 95%
expression	Early	Late				
	(pT1-pT2)	(pT3-pT4)				
Negative	19 (61,3%)	12 (38,7%)	31 (72,1%)	0,009	7,9	1,5-42,5
Positive	2 (16,7%)	10 (83,3%)	12 (27,9%)			

The significance level is set at p < 0.05

Table 6. Correlation between PD-L1 expression and lymph node metastasis in PTC patients at Prof. dr. I.G.N.G. Ngoerah General Hospital
PD-L1 Lymph node metastasis Total p PR IK 95%
expression Negative Positive

PD-L1	Lympn node metastasis		1 otai	p	PK	IK 95%	
expression	Negative	Positive					
Negative	28 (90,3%)	3 (9,7%)	31(72,1%)	< 0,001	10,5	2,1-52,9	
Positive	7 (58,3%)	5 (41,7%)	12 (27,9%)				

The significance level is set at p < 0,05

Table 7. Correlation between Pathological T stage (pT) and lymph node metastasis in PTC patients at Prof. dr. I.G.N.G. Ngoerah General Hospital

Stage(pT)	Metastasis KGB		Total	p
	Negative	Positive		
Early	19 (90,5%)	2 (9,5%)	21 (48,8%)	0,240
Late	16 (72,7%)	6 (27,3%)	22 (51,2%)	

The significance level is set at p < 0.05

Table 8. Correlation between histological variant and lymph node metastasis in PTC patients at Prof. dr. I.G.N.G. Ngoerah General

		Н	ospital			
Histological	Lymph node	e metastasis	Total	p	PR	IK 95%
variant	Negative	Positive				
Not aggressive	31 (93,9%)	2 (6,1%)	33 (76,7%)	0,001	23,2	3,5-156,9
aggressive	4 (40%)	6 (60%)	10 (23,3%)			

The significance level is set at p < 0.0

DISCUSSION

The age distribution of patients with papillary thyroid carcinoma (PTC) tends to vary, but the majority of patients are in middle to older adulthood. This study found similar results, with the youngest patient being 20 years old and the oldest 80 years old, a median age of 43 years, and a mean age of 45.23 ± 16.12 years. According to a study by Harahap et al., out of 52 patients with thyroid carcinoma evaluated, it was found that approximately 61.5% of patients were 45 years of age or older, with an age range between 18 and 70 years and a median age of 48.5 years.8 Similar findings were also reported by Kocaöz and Turan, who showed that the average age of PTC patients was 50.26 years. Papillary Thyroid Carcinoma (PTC) is more frequently found in women compared to men, with a ratio of 2:1 to 4:1.9 Papillary thyroid carcinoma (PTC) has a clear tendency in terms of sex distribution, with a dominance in female patients women compared to men. The dominance of women in PTC cases is suspected to be related to hormonal factors, particularly the influence of the hormone estrogen, which is believed to play a role in the development of thyroid cancer. Overall, data from various studies confirm that PTC is more commonly found in women than in men. ⁷,

Based on histological variants, the majority of cases were of the non-aggressive variant, totaling 33 cases (76.7%). Besides the classic variant, there are several other variants of PTC. Histological variants are classified into aggressive and non-aggressive variants. The aggressive variants include diffuse sclerosing, tall cell, columnar cell, hobnail, solid/trabecular, and insular. The non-aggressive variants include classic, encapsulated classic, infiltrative clear follicular, spindle cell, cell, PTC fibromatosis/fasciitis-like stroma, oncocytic, and Warthinlike.4

The distribution of papillary thyroid carcinoma (PTC) cases based on pathological T stage reflects the size of the primary tumor and the degree of invasion into surrounding tissues. This study found that based on pathological T stage, the majority of cases were advanced stage, with 22 cases (51.2%). A study by Kocaöz and Turan, showed that the

majority of PTC cases (51.4%) had a tumor size between 1–2 cm (T1 stage), followed by 37.1% of cases with a tumor size between 2.1–4 cm (T2 stage), and 11.4% of cases larger than 4 cm (T3 or T4 stage). In general, this data indicates that PTC is often found in low to intermediate T stages, although some cases may show more aggressive extensive invasion.⁹

Metastasis to lymph nodes (LNs) is an important characteristic in papillary thyroid carcinoma (PTC) that can affect the prognosis of the disease. This study found similar results, with the majority of cases not showing lymph node metastasis, totaling 35 cases (81.4%). A study by Harahap et al., reported that out of 52 thyroid carcinoma cases studied, 36.5% of patients showed lymph node metastasis at the time of surgery. These findings indicate that although the majority of cases do not experience lymphatic metastasis at the initial diagnosis, there is still a significant proportion of patients who experience spread to regional lymph nodes. Overall, these findings suggest that metastasis to lymph nodes is a fairly common clinical manifestation in PTC and is an important indicator for determining prognosis and further treatment planning. ⁸

This study found positive PD-L1 expression in 27.9% of cases. Several other studies also describe PD-L1 expression in papillary thyroid carcinoma (PTC). Chowdhury et al., reported that positive PD-L1 expression was found in 72% of aggressive variant PTC cases, such as the tall-cell variant and the diffuse sclerosing variant. Bai et al., showed positive PD-L1 expression in 59.1% of PTC cases.⁵ Ahn et al., reported that positive PD-L1 expression was found in 6.1% of PTC cases in a large study involving 326 patients. Although this figure is relatively lower compared to other studies, that research indicated that PD-L1 expression was significantly associated with aggressive variants and lymphatic metastasis. ¹

In this study, no statistically significant relationship was found between PD-L1 expression and age (p = 0.265). Age is one of the factors determining the aggressiveness of PTC. A meta-analysis study conducted by Zhao et al., showed that there was no significant difference in PFS between patients aged \leq 55 years and \geq 55 years.18 In the 8th edition of the

American Joint Committee on Cancer (AJCC), the age limit for determining stage was changed to 55 years. This was based on research showing that patients under 55 years of age have a better prognosis even if risk factors such as metastasis or local invasion are present. Although age is known to affect prognosis (older patients usually have a higher risk of recurrence), this relationship is separate from PD-L1 expression. High PD-L1 expression in PTC is associated with more aggressive tumor characteristics such as metastasis to lymph nodes and extrathyroidal extension. This condition increases the risk of disease recurrence independently of the patient's age.

Older patients (>55 years) with PD-L1 positive tumors may have a higher risk of recurrence compared to younger patients. However, in general, PD-L1 expression remains an important prognostic factor regardless of age.¹⁷

Sex is suspected to influence PD-L1 expression. This study found that there was no statistically significant relationship between PD-L1 expression and sex (p=1.000). A mini-review journal by Rodriguez-Lara et al., explaining the role of sex and sex hormones in PD-L1 expression showed significant differences between men and women, largely influenced by sex hormones such as estrogen and androgen. However, the role of these hormones in the immune response is not yet fully understood. Some studies suggest that men tend to have higher levels of PD-L1 expression, which may explain the greater benefit of PD-L1based immunotherapy in men compared to women. Nevertheless, the available data are still contradictory and require further validation.¹⁴ Another cohort study by Liu et al., in East Asia found that premenopausal female patients showed higher PD-L1 expression, presumably due to the influence of hormonal fluctuations that stimulate immunological pathways as well as the direct regulation of PD-L1 expression. 10

This is largely due to the influence of the hormone estrogen, which is known to modulate the immune system and stimulate PD-L1 expression through the activation of the estrogen receptor (ER) pathway. Therefore, female sex and hormonal status need to be considered in risk stratification and therapeutic approaches for PTC patients, especially in the context of immunology-based therapies. Thus, female sex shows an influence on the increased expression of PD-L1 in papillary thyroid carcinoma, through hormonal and immunological mechanisms. ^{3, 13}

This study found a statistically significant relationship between PD-L1 and pathological T stage (pT) with a p-value of 0.009 and a 7.9 times greater prevalence risk of being in an advanced stage compared to negative PD-L1 expression. PD-L1 expression in papillary thyroid carcinoma (PTC) has a positive correlation with the pathological T stage of the tumor, which reflects the size of the primary tumor and the extent of local invasion. Several studies have shown that PD-L1 expression tends to increase in tumors with higher or more advanced T stages. PD-L1 expression is significantly higher in tumors of higher T

stages, especially those showing extrathyroidal extension or invasion into surrounding tissues.⁵ Consistent with these findings, Bai et al., also found that PD-L1 expression was positively correlated with higher pathological T stages, indicating that tumors with larger sizes or extrathyroidal invasion have a more immunosuppressive microenvironment through high PD-L1 expression.³

The pathogenesis explaining the relationship between PD-L1 expression and increased pathological T stage in papillary thyroid carcinoma is closely related to the local immunosuppressive effect mediated by PD-L1, thereby promoting tumor growth and invasion into surrounding tissues. PD-L1 expressed on the surface of tumor cells binds to the PD-1 receptor on T lymphocytes, leading to a decrease in the antitumor activity of these lymphocytes, thus allowing tumor cells to evade immune surveillance and grow more aggressively.⁵

Papillary thyroid carcinoma (PTC) with a more advanced pathological T stage (advanced stage) correlates with an increased risk of metastasis to regional lymph nodes. In the early stages, the risk of lymph node metastasis is relatively low, while in the advanced stages, almost all patients show lymph node metastasis. Clinicopathological factors such as larger tumor size (>4 cm), extrathyroidal extension, lymphovascular invasion, patient age ≥45 years, and aggressive histological variants are associated with an increased risk of lymph node metastasis in PTC. Metastasis to regional lymph nodes occurs in 30-80% of PTC patients and is associated with a worse prognosis, including an increased risk of recurrence and decreased patient survival. In general, a higher pathological stage in PTC indicates a greater risk of metastasis to lymph nodes, which has implications for a worse prognosis and the need for more aggressive clinical management and close monitoring. ¹⁹

This study found no statistically significant relationship between pathological T stage and lymph node metastasis. Similar results were found in a study conducted by Aljohani et al., Theoretically, lymph node metastasis in PTC is influenced by the biological characteristics of the tumor, such as anatomical location, multifocality, and capsular invasion. Tumor location in the upper lobe of the thyroid, for example, has closer access to the lateral lymphatic system, which may explain the increased risk of metastasis in that area. Multifocality indicates the presence of multiple tumor foci, which can increase the likelihood of spread to lymph nodes. Capsular invasion and extrathyroidal extension indicate higher tumor aggressiveness, which can also increase the risk of metastasis. ², ¹¹

An increased N stage, which indicates involvement of cervical lymph nodes, is associated with an increased risk of distant metastasis in PTC. N1a stage (metastasis to central lymph nodes) does not significantly increase the risk of distant metastasis in papillary thyroid microcarcinoma (PTMC), whereas N1b stage (metastasis to lateral lymph nodes) increases the risk of lung and bone metastasis, especially in older patients (>55 years). The risk of distant

metastasis increases with increasing N stage, with lung metastasis being the most common site of metastasis. 19

This study found a statistically significant relationship between PD-L1 and lymph node metastasis (p<0.001) with a 10.5 times greater prevalence risk of having positive lymph node metastasis compared to negative PD-L1 expression. The relationship between PD-L1 expression in papillary thyroid carcinoma (PTC) and metastasis to lymph nodes has been investigated in various studies. One study conducted by Chowdhury et al., showed that PD-L1 expression was significantly higher in PTC cases with lymph node metastasis compared to those without metastasis.⁵ The pathogenesis explaining how PD-L1 expression can lead to metastasis to lymph nodes in papillary thyroid carcinoma is closely related to its role in the mechanism of immune response evasion by tumor cells. Programmed death-Ligand 1 (PD-L1) is a ligand that binds to the PD-1 receptor on the surface of T cells, which, when activated, inhibits T cell function and proliferation, allowing the tumor to escape immune system surveillance.3

The relationship between PD-L1 expression and aggressive histological variants in papillary thyroid carcinoma (PTC) has been investigated in several studies. This study found a statistically significant relationship between PD-L1 and histological variant with a p-value of 0.002 and a 13.1 times greater prevalence risk of showing positive PD-L1 expression compared to non-aggressive histological variants. Aggressive histological variants in PTC, such as tall-cell, columnar-cell, diffuse sclerosing, and solid variants, are known to have a worse prognosis compared to the classic variant. A study by Chowdhury et al., found that PD-L1 expression was significantly increased in aggressive histological variants such as tall-cell and diffuse sclerosing, compared to the classic variant, suggesting that PD-L1 may be an important marker for identifying histological subtypes with aggressive potential. Thus, increased PD-L1 expression in PTC is closely associated with aggressive histological variants and reflects a more invasive disease potential and poor prognosis.⁵ PD-L1 expression, assessed using the Tumor Proportion Score (TPS), was found to be significantly higher in aggressive histological types compared to less aggressive histological types. The histological type with the highest PD-L1 expression was anaplastic thyroid carcinoma (ATC), the tall cell variant of PTC, as well as several other aggressive types containing anaplastic components. These findings open up opportunities for the use of immunotherapy as a new treatment modality in patients with aggressive histological types of thyroid carcinoma.8

Although Papillary Thyroid Carcinoma (PTC) generally has a good prognosis, some PTC variants exhibit different levels of aggressiveness, particularly in terms of the risk of metastasis to lymph nodes (LNs). Recent research indicates a significant association between histological variants of PTC and the tendency to metastasize to LNs, which is an important factor in determining treatment strategies and

long-term prognosis. Papillary Thyroid Carcinoma has several histological variants with distinct clinical and pathological characteristics. The classic variant is the most common subtype, accounting for approximately 55-60% of all PTC cases. The second most frequent is the follicular variant of PTC (FVPTC), with a prevalence of 22-34% of all PTC cases. The tall cell variant and the oncocytic variant are also reported, although in smaller percentages. Previous research has shown that the risk of nodal metastasis is significantly higher in the classic variant compared to the follicular variant (FVPTC). ¹⁸

It is known that the BRAFV600E mutation has been extensively studied as a molecular marker associated with the risk of lymph node metastasis. This mutation has a different prevalence in various PTC variants, with 55-75% in the classic variant, 77-90% in the tall cell variant, and 0-12% in the follicular variant. This difference in the prevalence of the BRAFV600E mutation correlates with the risk of lymph node metastasis for each variant. According to research, the average BRAF expression level differs among different risk groups: 62.31±18.213 in the low-risk group, 74.80±16.80 in the intermediate-risk 81.39±13.5911 in the high-risk group. This indicates that the level of BRAF expression correlates with the risk of metastasis.²⁰ Another molecular factor is the TERT mutation, where classic PTC cases with high TERT expression show an odds ratio for metastasis that is 4.2 times greater. 16

The results of this study can be used as a reference for the relationship between PD-L1 expression and the stage, nodal metastasis, and variants of PTC. More research with broader centers is needed so that if consistent results are found, PD-L1 expression can be established as a prognostic and predictive factor in PTC. The limitations of this study include not yet considering other confounding factors such as genetic mutation status (e.g., BRAF V600E mutation) or previous treatment history that may affect PD-L1 expression. The lack of a universal standardized cut-off value for PD-L1 expression (Tumor Proportion Score/TPS) in thyroid cancer can lead to variations in the interpretation of results across studies, making comparisons between studies difficult.

CONCLUSION

The conclusions that can be drawn from this study are as follows: there is a relationship between PD-L1 and pathological T stage (pT), with positive PD-L1 expression having a 7.9 times greater prevalence risk of being in an advanced stage compared to negative PD-L1 expression (95% CI 1.5-42.5) at Prof. dr. I.G.N.G. Ngoerah General Hospital. There is a relationship between PD-L1 and lymph node metastasis. Positive PD-L1 expression has a 10.5 times greater prevalence risk of being positive for lymph node metastasis compared to negative PD-L1 expression (95% CI 2.1-52.9) at Prof. dr. I.G.N.G. Ngoerah General Hospital. There is a statistically significant relationship between PD-

L1 and histological variant. Aggressive histological variants have a 13.1 times greater prevalence risk of showing positive PD-L1 expression compared to non-aggressive histological variants (95% CI 2.5-68.3) at Prof. dr. I.G.N.G. Ngoerah General Hospital.

Further research is needed that considers other confounding factors such as genetic mutation status (e.g., BRAF V600E mutation) or previous treatment history that may affect PD-L1 expression. Further research is also needed to understand whether there is a significant correlation between sex and PD-L1 expression in patients Papillary Thyroid Carcinoma (PTC). It is recommended to use internationally validated methods and to establish a universal or clear cut-off for PD-L1 expression values. This aims to make the research results easier to compare with other studies globally. It is recommended to conduct prospective studies that allow for more standardized and accurate data collection, as well as the observation of patients over a specific period. This research can be more effective in evaluating the relationship between PD-L1 expression and long-term prognosis, such as recurrence rates and patient survival.

1. CONFLICT OF INTEREST

There are no conflicts of interest in this study.

2. ETHICAL APPROVAL

This study has received approval from the Research Ethics Committee of the Faculty of Medicine, Udayana University/ Prof. dr. I.G.N.G. Ngoerah General Hospital Denpasar with ethical clearance number 0389/UN14.2.2.VII.14/LT/2025 and has been granted permission by Prof. dr. I.G.N.G. Ngoerah General Hospital with letter number DP.04.03/D.XVII.2.2.2/16413.2025.

3. FUNDING

None.

4. AUTHOR CONTRIBUTIONS

All authors have made equal contributions to the writing of this research, from the development of the conceptual framework, data collection, data analysis, to the interpretation of the research results.

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