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Original Article

Prevalence of Programmed Death-Ligand 1 Positivity Using SP142 in Patients With Advanced Stage Triple-Negative Breast Cancer in Malaysia: A Cross-Sectional Study

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ABSTRACT

Purpose: Triple-negative breast cancer (TNBC) is a subtype of breast cancer known for its poor prognosis and the absence of viable targets for standard receptor-based therapies. Several studies have suggested that targeting programmed death-ligand 1 (PD-L1) in tumors that express this biomarker, either on tumor cells and/or in the tumor inflammatory infiltrate, may be beneficial in some patients. This study aimed to assess the overall prevalence of PD-L1 positivity using the SP142 antibody clone in patients with advanced TNBC in Malaysia.

Methods: This was a multicenter, cross-sectional prevalence study on PD-L1 positivity among patients with advanced-stage TNBC in Malaysia. Patients were identified using medical records and were enrolled in the study if they met the inclusion criteria. PD-L1 evaluation was performed using archived formalin-fixed paraffin-embedded tissue specimens. Demographic and clinical data were also obtained and summarized using descriptive statistics. The association of these parameters with PD-L1 positivity was assessed using chi-square and logistic regression analysis.

Results: Three medical centers provided 138 complete cases for analysis. Of these 138 cases, 52 (37.7%; 95% confidence interval, 29.6%–46.3%) showed positive PD-L1 expression, defined as immune cell PD-L1 expression ≥ 1%. In a univariate analysis, stage III of the disease and tumor samples from resected specimens were significantly associated with a positive PD-L1 status. However, further assessment using a multivariate model revealed that only resected tumor samples remained significantly associated with PD-L1 positivity after controlling for disease staging.

Conclusion: The prevalence of PD-L1 positivity among patients with stage III or IV TNBC was 37.7%. A significant association was noted between PD-L1 positivity and the tumor tissue obtained from resected specimens. Although the mechanism and clinical significance of this

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Conflict of Interest

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Data Availability

In accordance with the ICMJE data sharing policy, the authors have agreed to make the data available upon reasonable request.

Author Contributions

Conceptualization: Rajadurai P; Data curation: Yap NY, Chiew SF, Md Zin RR, Md Pauzi SH, Jaafar ASB, Yahaya A; Funding acquisition: Rajadurai P; Investigation: Yap NY, Chiew SF, Md Zin RR, Md Pauzi SH, Jaafar ASB, Yahaya A; Methodology: Rajadurai P; Resources: Rajadurai P; Supervision: Rajadurai P, Looi LM; Writing - original draft: Yap NY; Writing - review & editing: Rajadurai P, Yap NY, Chiew SF, Md Zin RR, Md Pauzi SH, Jaafar ASB, Yahaya A, Looi LM.

association remain unclear, this finding indicates a possible disparity in the PD-L1 status of samples obtained using surgical resection or biopsy.

Keywords: Biopsy; PD-L1; Prevalence; Triple Negative Breast Neoplasms

INTRODUCTION

Triple-negative breast cancer (TNBC) refers to a breast cancer phenotype that does not express the three common breast cancer receptor types: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) [1]. TNBC accounts for approximately 10%–20% of all breast cancers worldwide [2] and is considered an aggressive cancer type owing to its poor disease-free and overall survival (OS) rates [3,4]. Furthermore, patients with TNBC do not respond to an array of targeted therapies available for HER2-, ER-, or PR-positive breast cancer [4].

The current treatment modality for TNBC heavily depends on surgery and standard chemotherapy regimens, including anthracyclines and taxanes, in metastatic, adjuvant, or neoadjuvant settings [4]. Recently, immunotherapy has been suggested as a promising treatment strategy for TNBC to prolong survival and delay recurrence [5-7]. The most successful immunotherapeutic agents include immune checkpoint inhibitors (ICIs), which block the activity of programmed death-ligand 1 (PD-L1) on immune cells [5,7]. Inhibition of PD-L1 may be a useful treatment strategy for patients with TNBC because they show higher levels of PD-L1 expression on immune cells, providing direct targets for ICIs [5,7].

The phase III IMpassion130 trial has elevated the importance of immunotherapy in TNBC management [5,6,8,9]. The study reported a statistically significant prolonged progression-free survival (PFS) and clinically meaningful OS in patients with PD-L1 positive advanced TNBC, suggesting that this patient subgroup is more likely to benefit from immunotherapeutic approaches [6,9,10]. Furthermore, the intervention used in the trial has been recommended as the first-line treatment for patients with advanced TNBC whose tumors express PD-L1 on immune cells [7]. This finding emphasized the importance of PD-L1 as a predictive biomarker for identifying patients who would most likely benefit from immunotherapy.

To the best of our knowledge, no data on the prevalence of PD-L1 positivity among patients with advanced TNBC in Malaysia are currently available. Similarly, whether PD-L1 positivity rates in the local patient population are influenced by other factors, such as patient demographics, clinical characteristics, and tumor origin (primary or metastatic) is also unknown. The scarcity of local data restricts both the academic and clinical understanding of the disease burden in this patient population, thereby impeding impact assessments within the Malaysian healthcare system. In this study, we aimed to assess the overall prevalence of PD-L1-positivity in patients with advanced TNBC in Malaysia, the prevalence of PD-L1 positivity based on tumors' histological types and subtypes; we also aimed to examine the association between PD-L1 positivity and patients' demographic and clinical characteristics.

METHODS

Study design and patient population

This was a multicenter observational cross-sectional prevalence study on PD-L1 positivity among patients with advanced-stage TNBC in Malaysia. Patients were retrospectively identified using medical records obtained from three medical centers: Subang Jaya Medical Centre (SJMC), University Malaya Medical Centre (UMMC), and Hospital Canselor Tuanku Muhriz (HCTM). Malaysian adult female patients (aged ≥ 18 years) with stage III (locally advanced) or stage IV (metastatic) histologically documented TNBC (in the absence of HER2, ER, or PR expression in accordance with the Cancer Staging Manual, 8th edition by the American Joint Committee on Cancer [AJCC] [11]) were selected for the study. Disease staging was evaluated based on pathological staging; if pathological staging was not feasible, clinical staging was used to determine study inclusion. Along with PD-L1 evaluation, we also collected information regarding demographic and clinical data using pathology records, medical charts, and histology request forms captured during routine clinical care. Samples were collected between August 2021 and June 2022. This study received ethical approval from the respective Institutional Review Boards (IRBs) of the study sites (SJMC IRB No. 202105.2, UMMC IRB No. 202145-10027, HCTM IRB No. JEP-2021-274). The requirement for patient consent was waived because of the observational and retrospective nature of the study.

PD-L1 evaluation

PD-L1 evaluation was performed using archived formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples obtained from core tissue biopsies and resected specimens. Tumor samples were collected retrospectively starting from the commencement of the study.

The VENTANA PD-L1 (SP142) assay (Roche, Basel, Switzerland) was used for immune cell PD-L1 staining. The FFPE TNBC sections were stained according to the standard SP142 assay [12]. Stained tissues were interpreted using the SP142 assay scoring algorithm for TNBC [13].

Study endpoints

The primary endpoint was the prevalence of PD-L1 positivity, defined as the presence of discernible PD-L1 staining of any intensity in tumor-infiltrating immune cells covering ≥ 1% of the tumor area. The secondary endpoints included the prevalence of PD-L1 positivity stratified by: i) tumor histological subtypes, ii) disease stages, and iii) tumor tissue types (core biopsy or resected specimen) used for PD-L1 evaluation, as well as the association between PD-L1 positivity and patients' demographic and clinical characteristics.

Statistical analysis

Statistical analyses were performed using R statistical software (version 1.1.463, R Core Team 2018; R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were used to summarize the demographic and clinical characteristics of the study cohort. The comparison of PD-L1 positivity in relation to histological subtypes, sources, and tumor tissue types (core biopsy vs. resected specimen) was performed using the chi-square analysis (for categorical variables). A logistic regression model was used to examine the relationship between PD-L1 positivity and patients' demographic and clinical characteristics. A univariate regression analysis was performed using the following variables: age group, ethnicity, parity, tumor grade, disease stage, and origin (primary or metastatic site) and types (core or resected sample) of tumor tissues used for PD-L1 testing. All the variables that had a p-value < 0.1 in the univariate regression model were further considered for the multivariate

regression analysis. In the multivariate analysis, a two-sided significance level of 0.05 was used to reject the null hypothesis. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines were used for reporting [14].

RESULTS

A total of 139 patients with TNBC met the inclusion criteria for analysis. One sample was subsequently excluded because of staining failure (scant tumor cells; PD-L1 results not interpretable). Therefore, 138 samples were included in the analysis.

Demographic and clinical characteristics

The demographic and clinical characteristics of Malaysian patients with TNBC are shown in **Table 1**. The mean age was 57.8 years. Most patients were of Chinese ethnicity (55.8%). A total of 99 patients (71.7%) had grade 3 tumors. Half of the patients had stage IV TNBC (51.4%).

Prevalence of PD-L1 positivity

The overall prevalence of PD-L1 positivity among Malaysian patients with TNBC was 37.7% (52 patients; 95% confidence interval [CI], 29.6%–46.3%). The prevalence of PD-L1 positivity among Malaysian patients with TNBC according to tumor histological types and subtypes is shown in **Table 2**, whereas **Table 3** shows a comparison of PD-L1 positivity in relation to cancer stage, origin, and type of tumor tissues used for PD-L1 evaluation. PD-L1 positivity was significantly more prevalent in resected tumor samples; 52.4.% of resected tumor samples exhibited IC PD-L1 expression ≥ 1% compared to only 25.3% of core biopsy samples ($p = 0.001$) (**Table 3**). Resected tumor samples were more frequently collected in an earlier stage of the disease; 41/67 (61.2%) stage III cases were resection samples and were compared to 22/71 (31.0%) stage IV cases. Subgroup analyses revealed associations between PD-L1 expression status, sample types, and tumor stages (**Table 3**). Significant associations between PD-L1 status and both sample types and tumor stages were retained in primary specimens but not in metastatic specimens.

Association between PD-L1 positivity and patients' demographic and clinical characteristics

Table 4 shows the association between demographic factors (age group, ethnicity, and parity), clinical findings (tumor grade, disease stage, source of tumor tissue, and type of tumor tissue), and PD-L1 positivity status. Apart from stage III of the disease and the use of resected tumor samples for PD-L1 assessment, other factors were not significantly associated with PD-L1 positivity in the univariate logistic model. Further assessment using a multivariate model showed that when these two factors were considered simultaneously, only the relationship between the use of resected tumor samples and PD-L1 status remained statistically significant ($p = 0.010$) (**Table 4**).

DISCUSSION

In this study, we estimated the prevalence of PD-L1 positivity in patients with advanced TNBC in Malaysia. Based on a sample size of 138 patients obtained from 3 participating pathology laboratories in the central region of Malaysia, the prevalence of PD-L1 positivity was 37.7% (95% CI, 29.6%–46.3%). Several previous studies have also reported PD-L1 prevalence

Table 1. Demographic and clinical characteristics of Malaysian patients with triple-negative breast cancer

Variables	Sample size (n = 138)
Demographic characteristics	
Age (yr)	58 (29–88)
Age group (yr)	
< 45	25 (18.1)
45–54	30 (21.7)
55–64	43 (31.2)
≥ 65	40 (29.0)
Ethnicity	
Malay	44 (31.9)
Chinese	77 (55.8)
Indian	14 (10.1)
Others	3 (2.2)
Parity	
Multiparous	37 (26.8)
Nulliparous	7 (5.1)
Unknown	94 (68.1)
Clinical characteristics	
Duration from tissue collection to PD-L1 assessment	
< 1 years	31 (22.5)
1–3 years	61 (44.2)
> 3 years	46 (33.3)
Tumor grade	
2	35 (25.4)
3	99 (71.7)
Unknown	4 (2.9)
Disease stage	
Stage III	67 (48.6)
Stage IV	71 (51.4)
Staging method	
Clinical	48 (34.8)
Pathological	90 (65.2)
Histological type and subtype of breast cancer	
Invasive lobular carcinoma	4 (2.9)
Metaplastic carcinoma — Squamous differentiation	23 (16.7)
Metaplastic carcinoma — Spindle cell differentiation	4 (2.9)
Metaplastic carcinoma — Matrix-producing type	3 (2.2)
Metaplastic carcinoma — Mixed	8 (5.8)
Glycogen-rich clear cell carcinoma	3 (2.2)
Adenoid cystic carcinoma	1 (0.7)
Medullary carcinoma	2 (1.4)
Mixed carcinoma (ductal with other type)	2 (1.4)
Others	88 (63.8)

Values are presented as median (range) or number (%).
PD-L1 = programmed death-ligand 1.

Table 2. Prevalence of programmed death-ligand 1 positivity among Malaysian patients with triple-negative breast cancer according to tumor histological types and subtypes

Variables	PD-L1 positive samples (n = 52)	*p*-value
Invasive lobular carcinoma	2 (3.8)	0.644
Metaplastic carcinoma — Squamous differentiation	13 (25.0)	
Metaplastic carcinoma — Spindle cell differentiation	0 (0.0)	
Metaplastic carcinoma — Matrix-producing type	0 (0.0)	
Metaplastic carcinoma — Mixed	3 (5.8)	
Glycogen-rich clear cell carcinoma	1 (1.9)	
Adenoid cystic carcinoma	0 (0.0)	
Medullary carcinoma	0 (0.0)	
Mixed carcinoma (ductal with other type)	0 (0.0)	
Others	33 (63.5)	

Values are presented as number (%).
PD-L1 = programmed death-ligand 1.

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Table 3. Prevalence of programmed death-ligand 1 positivity among Malaysian patients with triple-negative breast cancer according to the by source and type of tumor tissue used for programmed death-ligand 1 evaluation

Variables	Sample size	PD-L1 positive samples	*p*-value
	No.	No. (%)	
Stage (n = 138)			0.006
Stage III	67	33 (49.3)	
Stage IV	71	19 (26.8)	
Origin of tumor tissue (n = 138)			0.689
Primary tumor site	109	42 (38.5)	
Metastatic site	29	10 (34.5)	
Type of tumor tissue (n = 138)			0.001
Core biopsy sample	75	19 (25.3)	
Resected tumor sample	63	33 (52.4)	
Subgroup analysis			
Primary tumor site only (n = 109)			
Stage			0.004
Stage III	67	33 (49.3)	
Stage IV	42	9 (21.4)	
Type of tumor tissue			< 0.001
Core biopsy sample	57	12 (21.1)	
Resected tumor sample	52	30 (57.7)	
Metastatic site only (n = 29)			0.523
Core biopsy sample	18	7 (38.9)	
Resected tumor sample	11	3 (27.3)	
Core biopsy sample only (n = 75)			0.818
Stage III	26	7 (26.9)	
Stage IV	49	12 (24.5)	
Resected tumor sample only (n = 63)			0.017
Stage III	41	26 (63.4)	
Stage IV	22	7 (31.8)	
Stage III tumors only (n = 67)			0.004
Core biopsy sample	26	7 (26.9)	
Resected tumor sample	41	26 (63.4)	
Stage IV tumors only (n = 71)			0.519
Core biopsy sample	49	12 (24.5)	
Resected tumor sample	22	7 (31.8)	

PD-L1 = programmed death-ligand 1.

among patients with TNBC [10,15,16]. The IMpassion 130 trial recorded a PD-L1 positive prevalence of 40.9% [7]. Similarly, Li et al. [16] reported a positive PD-L1 IC prevalence of 46%, whereas Al-Jussani et al. [17] reported a PD-L1 positivity rate of 36.7%. Contrastingly, Mittendorf et al. [10] reported a low prevalence of approximately 20%. Thus, the prevalence of PD-L1 positivity among Malaysian patients with TNBC reported in our study falls within the range of previously reported findings.

A comparison of the reported PD-L1 prevalence among different studies may not be straightforward. Different studies may employ different staining reagents, testing platforms, or varying PD-L1 expression cutoff points to define PD-L1 positivity. These factors can significantly impact the estimated prevalence [10,15,16]. For instance, studies on PD-L1 expression in TNBC showed that SP142 stained fewer total cells and more IC than other PD-L1 monoclonal antibodies (22C3, SP263, and 28-8) [18,19]. The reasons for discrepancies between these assays are unclear. However, a study assessing SP142 PD-L1+ tumors revealed increased immunogenic traits, an enriched presence of tumor-infiltrating lymphocytes (TILs), and heightened immune gene signatures [20].

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Table 4. Logistic regression analysis of demographic and clinical characteristics associated with programmed death-ligand 1 positivity status in Malaysian patients with triple-negative breast cancer

Variables	Univariate analysis				Multivariate analysis			
	Odds ratio	95% CI		*p*-value	Odds ratio	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Age group (yr)								
< 45	-	-	-	-				
45 to 54	0.643	0.210	1.966	0.439				
55 to 64	0.981	0.358	2.685	0.970				
≥ 65	1.000	0.361	2.773	1.000				
Ethnicity								
Chinese	-	-	-	-				
Indian	1.312	0.413	4.169	0.645				
Malay	1.000	0.463	2.160	1.000				
Others	3.500	0.304	40.355	0.315				
Parity								
No	-	-	-	-				
Yes	0.792	0.155	4.040	0.779				
Unknown	0.335	0.070	1.592	0.169				
Tumor grade								
2	-	-	-	-				
3	1.054	0.475	2.338	0.897				
Unknown	0.564	0.053	6.003	0.635				
Disease stage								
Stage III	-	-	-	-	-	-	-	-
Stage IV	0.376	0.185	0.766	0.007*	0.487	0.230	1.031	0.060
Origin of tumor tissue used for PD-L1 testing								
Metastatic site	-	-	-	-				
Primary tumor site	1.191	0.505	2.807	0.689				
Type of tumor tissue								
Core biopsy sample	-	-	-	-	-	-	-	-
Resected tumor sample	3.242	1.582	6.646	0.001*	2.682	1.271	5.661	0.010†

Variables showing significant association with PD-L1 positivity using a univariate logistic model were further assessed using a multivariate model.
CI = confidence interval; PD-L1 = programmed death-ligand 1.
*Variables with *p*-value < 0.1 were used for multivariate regression model.
†Variable with *p*-value < 0.05.

Another important finding of our study was that resected tumor samples (compared with core biopsy samples) were independently associated with PD-L1 overexpression after adjusting for the disease stage. This association suggests that PD-L1 expression may differ between biopsy and resection samples. Other studies have also demonstrated that the detection rate of PD-L1 in small biopsies was lower than that in surgical resection specimens, indicating that PD-L1 expression can be affected by tumor heterogeneity and specimen size [21-24]. This discrepancy has been reported in biopsies and corresponding surgical resections of breast and lung cancer specimens [22-24], The spatial heterogeneity of PD-L1 expression may be attributed to the TIL score, which reflects the volume of tumor-localized immune cells [23]. A positive correlation between TIL and PD-L1 expression has also been reported [20]. Baek et al. [23] have shown that the TIL score of resected specimens was significantly higher than that of biopsied specimens, indicating that the TIL score may be underestimated in small biopsied samples. These findings suggest that caution should be exercised when assessing PD-L1 status using biopsy specimens. Han et al. [25] have observed differences in PD-L1 expression between primary and metastatic samples. However, unlike Han et al. [25], we did not compare between matched pairs of primary and metastatic samples, or matched resection and biopsy specimens, as our cases were sourced from distinct patients.

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Additionally, although not statistically significant after adjusting for specimen type, our results indicated that stage III tumors were more likely to stain positively for PD-L1 compared with stage IV tumors. This may suggest a potentially higher probability of PD-L1 overexpression among patients who present with an earlier stage of the disease (stage III compared to stage IV), as resected tumor tissues are likely to be obtained from cases where surgical intervention for the primary tumor is indicated. In the current study, 63.4% of stage III cases and 31.8% of stage IV cases were resection samples. However, despite this finding, the reason patients with stage III disease have a higher probability of PD-L1 overexpression than patients with stage IV disease is not immediately clear. Chu et al. [26] have demonstrated that high SP142 IC PD-L1 expression was significantly correlated with smaller tumor size, the absence of lymphovascular invasion, and fewer lymph node metastases. Additionally, previous studies have suggested other associations between PD-L1 positivity and certain clinical characteristics, such as tumor T stage, histological grade, time of tissue collection, cold ischemia time, and location of metastasis [15,16,25,27]. PD-L1 expression has also been shown to be affected by neoadjuvant chemotherapy which can change the tumor immune microenvironment [28]. However, as our study did not include stage I and II cases, a definitive association could not be established between staging and PD-L1 positivity in this cohort. Additionally, our study did not investigate the connection between PD-L1 positivity and the timing of tissue collection or the location of metastasis.

Limitations, including the sample size, might have influenced our findings, and considering the possibility of a noncausal relationship is crucial. Although this observational study offers valuable insights into potential associations, it does not establish a definitive causal link. This study may have limited generalizability, as its data were derived from a limited number of centers in Klang Valley, Malaysia. In addition, matched biopsy and resection samples from the same patients were not available for comparison. Characteristics of the study cohort may differ from those of other sites, parts of the country, or other countries. Hence, the data generated in this study may not be widely applicable to other settings.

In conclusion, the estimated prevalence of PD-L1 positivity among Malaysian patients with stage III or IV TNBC is 37.7%. This estimate appears to be similar to that of a previous study [16]. A significant association was noted between PD-L1 positivity and resected tumor tissue samples in stage III cancer compared to those in stage IV cancer. Although the mechanism and clinical significance of this association is not elucidated, our findings suggest that there may be a disparity in the PD-L1 status for samples obtained using surgical resection or biopsy.

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