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Research Article

Clinicopathological Characteristics of Invasive Breast Carcinoma on PDL-1 Immunohistochemical Expression in H. Adam Malik Hospital Medan

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Abstract
Background: Immune biologic markers that can predict clinical response to anti-PD-1/PD-L1 therapy are needed to identify and validate tumor immunotherapy studies. High PD-L1 expression is associated with increased clinical response in patients with various types of cancer treated with inhibitors of the PD-1/PD-L1 pathway. **Objective:** The researcher wanted to see the clinicopathological characteristics of invasive breast carcinoma according to the immunohistochemical expression of PD-L1. **Methods:** This study is a descriptive study with a cross-sectional, retrospective approach by looking at secondary data from the medical records of the Department of Surgery, Haji Adam Malik Hospital from January 1, 2019, to December 31, 2021. **Results:** Immunohistochemical expression of PD- L1 was positive in 76.6% of invasive breast carcinomas and negative in 23.3% of invasive breast carcinomas. Immunohistochemical expression of PD-L1 was positive in non-specific IBCs that predominated in every molecular subgroup of breast carcinoma. **Conclusion:** Tumours can show positive or negative PD-L1 expression through several biological processes with different functional significance, namely the genetic mechanism of constitutive or oncogene-induced PD-L1 expression, PD-L1 expression induced in T cells, and absence of PD-L1 expression. Due to the absence of T cells and genetic events that block the expression of PD-L1 despite T cell infiltration.

Keyword: clinicopathology, invasive breast cancer, immunohistochemistry, PDL-1

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1. Introduction

Breast cancer is the most common cancer in women (24.2%) and the second most common cancer globally (11.6%) [1]. Around 2,089 million new cases of breast cancer were found in 2018. Breast cancer is the primary malignancy for women in various countries, especially in Asia (22.4%), with 911,014 new and 137,514 cases from Southeast Asia [2]. The incidence of breast cancer is increasing rapidly in developing countries, with most cases found at an advanced stage. In Indonesia, breast cancer is one of Indonesia's most common types of cancer [1, 2].

The incidence of breast cancer in Indonesian women, according to Globocan in 2012, was 40 per 100,000 population [2]. Programmed cell death protein 1 (PD-1) is a co- inhibitory receptor that acts as a negative regulator of the immune system and belongs to the CD28 family [3, 4]. This type I membrane protein is expressed on the surface of T and B cells, natural killer (NK), dendritic, and macrophages. Programmed death-ligand 1 (PD-L1) is one of the PD-1 ligands expressed on tumor cells [5]. The interaction of PD-1 with PD-L1 aims to control excessive inflammation as protection for normal tissues by inducing immune tolerance. However, the interaction of these two proteins on tumors will affect the anti-tumor immune response by causing exhaustion and dysfunction of T cells so that tumor cells fight the immune system, proliferate and metastasize [2, 5].

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Previous studies have shown that PD-L1 expression contributes to a poor prognosis in gastric, lung, liver, pancreatic, and kidney cancers [6, 7]. Several of these studies showed that positive PD-L1 expression was associated with poor survival [8, 10]. They have also reported differing results regarding the association of PD-L1 expression with various clinicopathological features, such as lymph node involvement, tumor size, grade, and hormone receptor negativity [11, 14].

Clinical trials have shown that the effectiveness of this therapy depends on the characteristics of cancer and various other factors. In the era of personalized medicine, biologic immune markers that can predict clinical response to anti-PD-1/PD-L1 therapy are indispensable for identifying and validating immunotherapy studies in tumors. Recent findings have shown that high PD-L1 expression is associated with increased clinical response in patients with various types of cancer treated with PD-1/PD-L1 pathway inhibitors. Therefore, patients who have the potential to show excessive PD-L1 expression should be selected is a question that faces any research that seeks to develop a treatment for breast carcinoma [15, 18].

2. Methods

This study is a descriptive study with a cross-sectional approach, retrospectively by looking at secondary data from the medical records of the Department of Surgery, Division of Oncology, Haji Adam Malik Hospital. This study was conducted at Haji Adam Malik General Hospital Medan from January 1, 2019, to December 31, 2021. The target population in this study were subjects with a diagnosis of invasive breast carcinoma and PD-L1 immunohistochemical examination. The affordable population in this study were subjects diagnosed with invasive breast carcinoma and PD-L1 immunohistochemistry examination from H. Adam Malik Hospital, Medan. The research sample is the population that meets the inclusion criteria and does not meet the exclusion criteria. The sample was selected using a consecutive sampling technique, and the minimum number of samples in this study was 29 patients.

The inclusion criteria for this study were adequate clinical data in medical records (tumor size and lymph node involvement) from January 2019 – to December 2021, data on subjects diagnosed with invasive breast carcinoma, and having examined the PD-L1 immunohistochemical profile, and complete IHC data. The exclusion criteria for this study were clinical data/files that were damaged or missing. The data collection process is carried out through the patient's medical record.

The study began by collecting data regarding patients diagnosed with invasive breast carcinoma at HAM Hospital and patients examined with the PD-L1 immunohistochemical profile. Adequate clinical data from medical records and anatomical pathology archives and assess histopathological characteristics of invasive breast carcinoma according to PD-L1 immunohistochemical expression. The data obtained from the narrative description and tabulation of medical record data will be entered into the Invasive Breast Carcinoma and PD-L1 Expression Grading table. Then the data is processed using a computer with the steps of editing or checking, namely checking the completeness of the medical record data. Coding or marking, namely classifying data and utilizing marking or code to facilitate tabulation and data analysis. Tabulation namely answers given a data category and then entered into a table. The data obtained then analyzed the frequency and cross-tabulation.

3. Results

This study involved 30 cases of invasive breast carcinoma patients who met the inclusion criteria and did not meet the exclusion criteria. Based on clinical data obtained from medical records/pathology archives, the sample in this study had a mean age of 49.7 (± 11.17) years, with the youngest age being 33 years and the oldest being 78 years. Most clinical T tumors were T4 in as many as 19 cases, T3 in 6 cases, and T2 in 5 cases. Pathologically, there were 8 cases of lymph node involvement (26.7%) and 22 cases of negative (73.3%). In addition, there were only 5 cases of distant metastases among all subjects (16.7%), and in the other 25 cases, there were no distant metastases (83.3%).

The results of microscopic examination of HE preparations showed that most of the samples had non-specific breast carcinoma histological types, as many as 24 cases (80%), while 6 cases (20%) had invasive ductal carcinoma histological types. Judging from the grade, as many as 17 cases (56.7%) showed grade 2, followed by grade 1 in as many as 11 cases (36.7%), and grade 3 in as many as 2 cases (6.7%). Based on the immunohistochemical profile, the most subtypes were luminal B HER-2- in 16 cases (53.3%), followed by HER-2 enriched in 5 cases (16.7%), Luminal A in 4 cases (13.3%), TNBC in 3 cases (10%) and finally Luminal B HER-2+ as many as 2 cases (6.7%). 7%) showed grade 2, followed by grade 1 in 11 cases (36.7%) and grade 3 in 2 cases (6.7%). Based on the immunohistochemical profile, the most subtypes were luminal B HER-2- in 16 cases (53.3%), followed by HER-2 enriched in 5 cases (16.7%), Luminal A in 4 cases (13.3%), TNBC in 3 cases (10%) and finally Luminal B HER-2+ as many as 2 cases (6.7%). 7%) showed

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Table 1. Sample distribution based on clinicopathological parameters of invasive breast carcinoma

Age	N	%
Age (Mean±SD)	49.7 ± 11.1792	
Gender	N	%
Woman	30	100
Man	0	0
Types of Breast Cancer	N	%
Invasive Ductal Carcinoma	6	20
Invasive Lobular Carcinoma	0	0
Invasive Medullary Carcinoma Feature	0	0
Invasive Non-Specific Type	24	80
Tumor Size	N	%
T1	0	0
T2	5	16.7
T3	6	20
T4	19	63.3
Grade	N	%
1	11	36.7
2	17	56.7
3	2	6.7
KGB metastases (N)	N	%
Positive	8	26.7
Negative	22	73.3
Distant Metastasis		
Positive	5	16.7
Negative	25	83.3
Immunohistochemistry		
Overexpression of HER-2	5	16.7
Triple-Negative Breast Cancer	3	10
Luminal A	4	13.3
Luminal B HER-2+	2	6.7
Luminal B HER-2-	16	53.3

Regarding the distribution of PD-L1 immunohistochemical expression in invasive breast carcinoma, from 30 samples of breast carcinoma, PD-L1 immunohistochemical expression was found to be positive in 23 cases (76.7%) and negative in 7 cases (23.3%).

Table 2. Distribution of samples based on PD-L1. immunohistochemical expression

Immunohistochemical expression of PD-L1	Total (n)	Percentage (%)
Negative	7	23.3
Positive	23	76.7

Regarding the immunohistochemical expression of PD-L1 based on clinicopathological parameters of invasive breast carcinoma, breast carcinoma with positive PD-L1 expression had a higher clinical T, with T4 in 14 cases (46.7%), followed by T3 in 5 cases (16.7%), and T2 in 4 cases (13,3%). Then in breast carcinoma,

the highest clinical negative T expression of PD-L1 was T4 in 5 cases (16.7%), followed by T2 and T3 in 1 case (3.3%).

In breast carcinoma with PD-L1 expression, 18 cases (60%) were positive for non- specific histologic types and 5 cases (16,7%) for IDC histology. PD-L1 was negative in non- specific histological types in 6 cases (20.0%) and IDC histological types in 1 case (3.3%). The most positive PD-L1 expression based on histological grade was grade 2, with as many as 13 cases (43.3%), followed by grade 1, with as many as 8 cases (26.7%), and grade 3, with as many as 2 cases (6.7%). Breast carcinomas with positive PD-L1 expression in lymph node metastases were 3 cases (10%) and 18 cases (60.0%). PD-L1 was negative in 2 cases of lymph node metastases (6.7%), in those who did not metastasize 4 cases (13,3%). In breast carcinoma expressing PD-L1, there were 5 cases of distant metastases (13.3%), whereas in 19 other cases, no distant metastases were found (63.3%). On the other hand, 7 cases of breast carcinoma did not express PD-L1, of which 1 had distant metastases (3.3%), and 6 had no distant metastases (20%).

Breast carcinomas with positive PD-L1 expression in the immunohistochemistry profile were Luminal B HER-2- in 12 cases (40%) followed by HER-2 enriched in 4 cases (13.3%), Luminal A in 3 cases (10%), and TNBC and Luminal B HER-2+ each with 2 cases (6.7%). The most negative PD-L1 expression in the immunohistochemical profile was TNBC in 7 cases (23.3%), followed by Luminal B HER-2- in 4 cases (13.3%), then HER-2 enriched in 1 case (3, 3%), Luminal A was 1 case (3.3%), and Luminal B HER-2+ had no cases.

Table 3. Immunohistochemical expression of PD-L1 based on clinicopathological characteristics of invasive breast carcinoma

Clinicopathology	Immunohistochemical Expression			
	Positive N=23		Negative N=7	
	N	%	n	%
Tumor size T1	0	0	0	0
T2	4	13.3	1	3.3
T3	5	16.7	1	3.3
T4	14	46.7	5	16.7
KGB involvement Yes (+)	5	16.7	3	10.0
There is not any(-)	18	60.0	4	13.3
Distant Metastasis Yes (+)	4	13.3	1	3.3
There is not any (-)	19	63.3	6	20
Histological type Invasive Ductal Carcinoma	5	16.7	1	3.3
Invasive Non-Specific Type	18	60.0	6	20
Invasive Medullary Carcinoma	0	0	0	0
Feature Invasive Lobular Carcinoma	0	0	0	0
*Grade*histology *Grade*1	8	26.7	3	10
*Grade*2	13	43.3	4	13.3
*Grade*3	2	6.7	0	0
Immunohistochemical profile Luminal A	3	10	1	3.3
Luminal B HER-2+	2	6.7	0	0
Luminal B HER-2-	12	40	4	13.3
HER2-enriched	4	13.3	1	3.3
TNBC	2	6.7	1	23.3

Regarding the immunohistochemical expression of PD-L1 based on the expression of ER, PR, HER2, and Ki-67, breast carcinomas with positive PD-L1 expression were ER-positive in 17 cases (56.7%) and ER-negative in 6 cases (20%). PD-L1 expression was negative in positive ER in 5 cases (16.7%) and ER-negative in 2 cases (6.7%). Then the positive PD-L1 expression in positive PR in as many as 17 cases

(56.7%) and negative PR in as many as 6 cases (20%). PD-L1 expression was negative in 3 cases of positive PR (10%) and negative PR in 4 cases (13,3%). Breast carcinoma with positive PD-L1 expression on HER-2 positive in 6 cases (20%) and HER- 2 negative in 17 cases (56.7%). PD-L1 expression was negative in HER-2 positive in 1 case (3.3%) and HER-2 negative in 6 cases (20%). Breast carcinomas with positive PD-L1 expression in Ki-67 were positive in 19 cases (63.3%) and Ki-67 negative in 4 cases (13.3%). PD-L1 expression was negative in 5 cases, with positive Ki-67 (16.7%) and negative Ki-67 in 2 cases (6.7%).

Table 4. Immunohistochemical expression of PD-L1 based on the expression of ER, PR, HER2, and Ki-67

Expression	Immunohistochemical expression of PD-L1			
	Positive n = 23		Negative n = 7	
	N	%	n	%
ER				
Negative	6	20	2	6.7
Positive	17	56.7	5	16.7
PR				
Negative	6	20	4	13.3
Positive	17	56.7	3	10
HER2				
Negative	17	56.7	6	20
Positive	6	20	1	3.3
Ki-67				
Negative	4	13.3	2	6.7
Positive	19	63.3	5	16.7

4. Discussion

A better understanding of the mechanisms of oncogenesis of breast malignancies has led to significant therapeutic advances with hormonal therapy against the ER gene and targeted therapy against oncogenic proteins, such as HER2. Several other targeted therapies are also under development [19]. However, cancer cells' highly mutagenic and adaptable nature causes resistant clones, and the tumor response to therapy is only temporary. At the same time, the role of the tumor microenvironment, including the immune system, in tumor growth, progression, and resistance has become increasingly apparent in recent years. It has led to new potential therapeutic targets [20].

The development of immune checkpoint inhibitors is one of the most recent breakthroughs in oncology. Monoclonal antibodies directed against PD-1 or its ligand, PD-L1, inhibit the interaction of the two proteins and enhance T cell function and facilitate anti-tumor activity [21, 22]. This therapy causes a long-term response in several types of malignancies, such as NSCLC, melanoma, urothelial carcinoma, lymphoma, and neck and neck malignancies. This response was more significant along with higher PD-L1 expression. Determination of PD-L1 status in tumor cells by immunohistochemical examination is recommended to select potential patients with anti-PD-1/PD-L1 therapy [23]. In this study, 76.7% of cases of invasive breast carcinoma showed positive PD-L1 expression. This number is higher than that previous study that showed 21.7%, and other study reported 46.1%, and also more than another study that mentioned as many as 51.6%, and also other research reported as many as 56.6% of cases [24, 28]. This expression of PD-L1 has been widely associated with poor prognosis [25]. However, it is still controversial for breast malignancies, where previous reported an association of increased PD-L1 expression with poorer overall survival (OS), whereas other research reported a better OS, some study did not find any association of PD-L1 with OS [25, 28]. Even the meta- analysis results showed varying results, although most showed an association of PD-L1 expression with a poorer prognosis.

Evidence suggests that activation of the PD-1/PD-L1 pathway suppresses the adaptive anti-tumor response through mechanisms involving energy, fatigue, cytotoxic T cell apoptosis, and decreased cytokine production. Thus, this interaction causes the evasion of tumor cells from the immune system, which leads to

tumor progression. This is evidenced by the significant relationship between positive PD-L1 expression with larger tumor size and higher histological grade.

Tumor size in breast carcinoma with positive PD-L1 is more significant, as reported previous reseach, with a mean of 5.19 cm (≥T3) [7]. This shows the low number of early diagnostic examinations and the lack of public awareness of breast carcinoma. In addition, this finding is much different from the research of Muenst et al. (2014) and Qin et al. (2015). They found that breast carcinomas with positive PD-L1 were mainly under 5 cm (T2), reflecting the country's broader and more stringent screening system .[8, 9]

Although lymph node involvement is an indicator of tumor progression, most studies, including this study, report that most breast carcinomas with positive PD-L1 expression are associated with lymph node involvement [11, 12]. This difference may be due to the collection of KGB status data, which are not all derived from the results of pathological examinations and the distribution of different KGB status categories. Certain histologic types tend to show a specific immunohistochemical profile; IC NST (non-specific) remains the dominant histological type in every molecular subgroup of breast carcinoma.

Tumors expressing PD-L1 tend to have an aggressive immunohistochemical profile. This can be seen from the proportion of TNBC cases that showed more positive PD-L1 expression, followed by HER2 enriched, luminal B, and the least, luminal A. The mismatch of PD-L1 expression in cancer cells is due to heterogeneity in the development of cancer cells [21, 24].

However, PD-L1 expression was less in metastatic tumors than in primary tumors; half the population of women with PD-L1 positive in the primary tumor had negative metastatic PD-L1, in contrast to one-third of the population with PD-L1 negative in primary tumors has positive PD-L1 expression in metastatic tumors, this could be due to differences in the immune microenvironment. The study analysis also found low PD- L1 expression in metastatic breast cancer patients who had received chemotherapy therapy than those who had not received chemotherapy [25, 28].

Tumors can show positive or negative PD-L1 expression through several biological processes with different functional significance, namely the genetic mechanism of constitutive or oncogene-induced PD-L1 expression, PD-L1 expression induced in T cells, and absence of PD L1 expression. Due to the absence of T cells and genetic events that block the expression of PD- L1 despite T cell infiltration. This mechanism, in turn, leads to 4 categories of tumors based on the expression of PD-L1 and TILs, namely: type I (PD-L1+/TILs+; adaptive immune resistance), type II (PD-L1-/TILs-; immunological ignorance), type III (PD-L1+/TILs-; intrinsic induction) and type IV (PD-L1-/TILs+; tolerance). This theory can explain the finding that cases with positive PD-L1 expression had low TILs (32.4%) in this study [18, 19]

All the similarities and differences between this study and other studies do not escape the problem of the absence of a validated assay method, the differences in the types of PD-L1 antibodies, and the cut-off point of interpretation of PD-L1 expression. Patients with positive PD- L1 may not respond to therapy, and vice versa, resulting in imperfect PD-L1 biologic markers. Only three types of antibodies, PD-L1, two studies have been FDA-approved for several malignancies, particularly NSCLC, each with its media and interpretation cut-off point. The high cost of these three antibodies and the absence of a comprehensive consensus make it difficult to unify the examination and assessment of PD-L1 expression into a dichotomous result.

It remains unclear whether the cut-off point using the proportion and intensity of positively expressed cells has any value in predicting the immunotherapy response in other malignancies, such as breast. Therefore, the researchers applied a scoring method that combines the proportion and intensity of cells expressed [19-20]. Although not identical, performances of the three PD-L1 antibodies. The high concordance rate also causes the three antibodies to have the same relationship with the clinicopathological parameters studied. These findings provide the possibility of examining the expression of PD-L1 in other organs and the opportunity for other, more cost-effective PD-L1 antibodies. However, given the concerns surrounding the analytical and clinical validity of the PD-L1 assay [21, 23].

The results obtained from this study are expected to help provide an overview of breast cancer patients who have the potential to receive anti-PD-1/PD-L1 immunotherapy. Examination of PD-L1 status can also be considered to predict the prognosis of breast carcinoma. Further research is urgently needed to assess therapeutic response and survival rates, especially in research institutions, and further, understand the role of PD-L1 on the complexity of breast carcinoma.

5. Conclusion

From the descriptions that have been described previously, it can be concluded that the immunohistochemical expression of PD-L1 was found to be positive in 76.6% of invasive breast carcinomas and negative in 23.3% of invasive breast carcinomas, and the immunohistochemical expression of PD-L1 was positive in non-specific IBC. which predominates in each molecular subgroup of breast carcinoma.

6. Data Availability Statement
The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical considerations but are available from the corresponding author upon reasonable request.

7. Ethical Statement
This study was approved by the Research Ethics Committee of Universitas Sumatera Utara.

8. Author Contributions
All authors contributed to the design and implementation of the research, data analysis, and finalizing the manuscript.

9. Funding
No funding.

10. Conflict of Interest
Authors declares no conflict of interest.

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