The Relationship of Programmed Death-Ligand 1 Expression to the Survival of Triple Negative Breast Cancer Patients in West Sumatera

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Abstract

Triple negative breast cancer (TNBC) is a subtype of breast cancer that does not express estrogen receptors, progesterone receptors and HER2. TNBC has a poor prognosis with high recurrence and mortality rates due to very limited treatment modalities. Currently, the therapeutic modality being developed for TNBC is a programmed death-ligand 1(PD-L1) inhibitor, which is a 33-kDa type 1 transmembrane glycoprotein, containing 290 amino acids expressed by tumor cells as an adaptive immune mechanism. West Sumatra ranks 12th for breast cancer in Indonesia and more than 20% are TNBC. To determine the relationship between PD-L1 expression on the survival of triple negative breast cancer patients in West Sumatra. Paraffin block material from triple negative breast tumor tissue was carried out by immunohistochemical examination. The sample collection method is consecutive sampling with a total sample of 56 patients from the 2016-2021 data period. Data analysis in this study were used univariate descriptive analysis, bivariate analysis, and logistic regression analysis, significance test at p <0.05 and data precision with 95% CI. The relationship of PD-L1 expression to the survival of TNBC patients were using the Kaplan-Meier statistical test method. The characteristics of the most samples in this study were the age group >40 years, tumor size T3 and T4, at advanced local stage, histopathological type NST, Ki67 20% (high proliferation), the type of surgery was mastectomy with local residif incidence of 10.7%. and the incidence of distant metastases is 50%. PD-L1 expression was positive at 55.4%(CPS≥10). The results of the Chi-square test found that there was no significant relationship between age, tumor size, stage, histopathology, Ki-67 expression, and local residive events with PD-L1 expression in TNBC patients. Meanwhile, distant metastases with PD-L1 expression in TNBC patients had a significant relationship. The results of the Kaplan-Meier method showed that there was a significant relationship between PD-L1 expression with DFS and OS of TNBC patients. There is a significant relationship between positive PD-L1 expression on disease free survival and overall survival in TNBC patients in West Sumatra.

Key Words: Triple Negative Breast Cancer (TNBC), Programmed Death-Ligand1 (PD-L1), Disease Free Survival (DFS), Overall Survival (OS)

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Introduction

Breast cancer occupies the first position in the world in 2020 based on data from Global Burden Cancer (GLOBOCAN). There will be 2.3 million new cases of breast cancer in 2020 (Peraboi, 2020; Sung et al., 2021). Based on GLOBOCAN data, the incidence of breast cancer in Southeast Asia is 41.2 per 100,000 with a mortality of 15 per 100,000. In Indonesia, breast cancer is the most common cancer in women, covering 31.4% of cases.2 In 2020, there were 65,850 new cases of breast cancer in Indonesia with 22,430 deaths. The number of new cases in 2020 has increased from 2018 which was 58,256 cases (Globocan, 2020; Riskesdas, 2018).

Throughout 2012, there were 112 new cases of breast cancer in Dr. RSUP. M. Djamil Padang (Rahmatya et al., 2015). In 2017 the number of visits was 213 cases of breast cancer at RSUD Dr. Achmad

Mochtar Bukittinggi City which shows the incidence of breast cancer is increasing from year to year in West Sumatra Province 9 (Sari & Maharani, 2019). In 2017 there were 246 cases, in 2018 there were 386 cases, while in 2019 there were 421 cases. This resulted in West Sumatra Province having the prevalence of breast cancer is higher than the national prevalence of 0.9% (2,285 cases), so it is in the third position with the highest prevalence of breast cancer in Indonesia after Yogyakarta and East Kalimantan. and health services, and has a DR. M. Djamil who noted an increase in breast cancer cases. In 2013 there were 570 people with breast cancer, and in 2014 it increased to 620 people (Sasmita, 2016).

Triple negative breast cancer (TNBC) is one of the subtypes of breast cancer based on immunohistochemical classification (de Ruijter et al., 2011). Ten to twenty percent of breast cancer in the world is TNBC type, of which 200,000 new cases of TNBC occur every year (Morris et al., 2007). Research on TNBC in Indonesia is one of them carried out at the General Hospital Dr. Sardjito, Yogyakarta, where data obtained that TNBC constitutes 20-25% of breast cancer cases in the hospital (Purwanto et al., 2020; Widodo et al., 2014).

Triple negative breast cancer is associated with a poor prognosis, whereas TNBC occurs at a younger age and in premenopausal women, it is associated with aggressive disease. In addition, patients with TNBC often present with high-grade histopathological features (tumor grading) and larger tumor size, thus making the patient's prognosis worse. Lymph node involvement is also a prognostic factor in TNBC. The prognosis is worse if there are lymph node metastases in TNBC patients (Morris et al., 2007; Bonsang-Kitzis et al., 2015)).

Programmed Death-Ligand 1 (PD-L1) expressed by tumor cells as an adaptive immune mechanism to evade anti-tumor responses (Ruchi Sharma et al., 2017). PD-L1 is pro-tumorigenic by binding to tumor receptors and activating proliferative and survival signaling pathways (Dong et al., 2018). Qin Tao reported PD-L1 expression in 21.7% of all patients with breast cancer and of these patients 59% were TNBC type (Qin et al., 2015).

Research related to PD-L1 with TNBC has developed in Indonesia. Purwanto et al. (2020) found overexpression of PD-L1 receptor mRNA in TNBC patients and found that PD-L1 expression was associated with poor prognosis in TNBC patients in Indonesia. Distant in TNBC patients (Sudarsa et al., 2021). The association between PD-L1 and TNBC was confirmed by the study of Purwanto et al. in 2020 that the administration of PD-L1 inhibitors showed a promising response in TNBC patients in Indonesia. Lazarus et al. (2019) also conducted a study on PD-L1 inhibitors in TNBC patients in Indonesia and found that targeted therapy of PD-L1 inhibitors has a potential effect on TNBC with tolerable drug side effects (Purwanto et al., 2020).

Research by Zhang (2017); Mao et al. (2015) found that PD-L1 expression was associated with lymph node metastases, higher histological grade, estrogen receptor (ER)-negative in TNBC, so this study supports PD-L1 can be used as a biomarker of breast cancer prognosis. The same result was also obtained by Muenst et al. associated with poor prognosis in breast cancer (Muenst et al., 2014).

Previous research on TNBC in West Sumatra was conducted by Mirwas (2017) and found that the number of TNBC cases was 29.2% (second highest) with a higher mortality rate for TNBC patients than non-TNBC patients. However, research on PD-L1 expression in TNBC has never been carried out in West Sumatra, even though several studies have found a high proportion of PD-L1 expression in TNBC which may have an effect on the high mortality rate in TNBC subtypes in West Sumatra (Purwanto et al., 2020; Sudarsa et al., 2021; Irsyad, 2017).

Based on the description that has been described regarding the current high cases of breast cancer, the poor prognosis of TNBC cases, the high expression of PD-L1 in TNBC, and the absence of research on the effect of PD-L1 on the survival of TNBC patients in West Sumatra, researchers are interested in conducting research on the rate survival in TNBC cases associated with PD-L1 expression.

Methods

This study used a retrospective cohort study design, conducted at the Division of Surgical Oncology and the Laboratory of Anatomical Pathology, FK UNAND/ Dr. RSUP. M. Djamil Padang in January to May 2022, with the period of TNBC patient data starting from 2016 – 2021.

The study population was patients diagnosed with TNBC who were recorded in the medical records of RSUP DR. M. Djamil Padang, Ropanasuri Padang Hospital, and Yarsi Padang Hospital for the last six years, starting from January 2016 to January 2021,

where IHK examinations (ER, PR, HER2 and Ki-67) have been carried out.

The research sample was taken by consecutive sampling technique from breast cancer patients who had complete histopathological and immunohistochemical examination results at RSUP DR. M. Djamil Padang, Ropanasuri Padang Hospital, and Yarsi Padang Hospital in 2016-2021.

The sample in this study was 28 people for each group. So, the total sample is 56 patients.

The inclusion criteria for this study were patients with complete medical record data, diagnosed with stage I, II, and III breast cancer with TNBC who had received surgical therapy with Modified Radical Mastectomy, Radical Mastectomy, BCT, and chemotherapy therapy. Meanwhile, stage IV patients and paraffin block tissue preparations that were damaged and could not be used were excluded from this study.

Immunohistochemical assessment of PD-L1 protein using Rabbit ABclonal Anti-Human PD-L1 Antigen, Genetex with 1/300 dilution. Observed with an Olympus CX21 binocular light microscope starting from weak magnification (40x) to strong magnification (400x). Counting was carried out on all tumor cells starting from the tumor site with the strongest PD-L1 expression to the weaker enlargement area.26

Cells expressing PD-L1 will appear brown in the malignant epithelial and stromal cell membranes. Assessment of PD-L1 expression was made based on analysis of the percentage of tumor cells and immune cells that were positive and staining intensity.

It is said to be positive if the CPS value is 10, and it is said to be negative if the CPS is <10.

This study retrospectively analyzed the relationship between PDL-1 expression and the survival of triple negative breast cancer patients in West Sumatra. The data that has been collected is first edited, coded, and entered in a computer file. The data obtained were analyzed including univariate and bivariate. The mathematical model used in this research is logistic regression analysis. The significance test was determined at $p<0.05$. Data precision is determined by 95% Confident Interval (CI).

To see the relationship between PD-L1 expression on the survival of TNBC patients, a statistical test will be carried out using the Kaplan-Meier method. The processing of the collected data was analyzed using the SPSS 25 for Windows application. Significant value in the study if it has $p <0.05$.

Results and Discussion

The characteristics of the research sample obtained from medical record data on 56 research samples of TNBC patients from January 2016 to December 2021 can be seen from table 1.

Table 1. Characteristics of Distribution and Frequency of TNBC Patients in West Sumatra

Variable	Categorical	f	%
Age	≤40 years	12	21,4
	>40 years	44	78,6
Tumor Size	T1 & T2	15	26,8
	T3 & T4	41	73,2
Stadium	Early (I & II)	19	33,9
	LocalLy Advanced (III)	37	66,1
Histopathology	Nst	43	76,8
	Non NST	13	23,2
Ki-67	<20%	6	10,7
	≥20%	50	89,3
Operation	Mastectomy	54	96,4
	Lumpectomy	2	3,6
Radiotherapy	Exist	22	39,3
	None	34	60,7
Chemotherapy	Exist	56	100
Local recidive	Exist	6	10,7
	None	50	89,3

Metastasis	Exist None	28 28	50,0 50,0
Description of the patient's life	Live Die	30 26	53,6 46,4

From table 1, it can be seen that the most age group of patients is the age of >40 years as many as 44 patients (78.6%). And the young age group of TNBC ≤40 years as many as 12 patients (21.4%). When viewed from the size of the tumor at the time the patient came, the highest frequency was in the size of the T3 and T4 tumors with the number of patients as many as 41 people (73.2%). Most patients came in the advanced stage lokal which was 37 patients (66.1%). A total of 6 patients (10.7%) of TNBC occurred local recidive, and the incidence of distant metastases was 28 patients (50.0%).

Pthere isa histopathological assessment obtained the highest number is the type of carcinoma mammae no special type (NST) as many as 43 patients (76.8%) and carcinoma type Non NST 13 patients (23.2%). In the examination of Ki-67 proliferation, 89.3% or as many as 50 patients had a value of Ki-67 ≥20% or high proliferation, while the rest (10.7%) or as many as 6 patients had a value of Ki-67 <20% or low proliferation.

Almost all patients in this study were surgically performed in the form of Mastectomy as much as 96.4%, and BCT as much as 3.6%. The history of chemotherapy was carried out on all TB patients carried out in this study. A total of 22 patients (39.3%) received radiotherapy, while the remaining 34 patients (60.7%) had no history of radiotherapy.

TNBC occurred local recidively in 6 patients (10.7%) and the incidence of distant metastases was 28 patients (50.0%). The number of living patients was found to be 30 patients (53.6%) and the number who died was 26 people (46.4%)

Pd-L1 expression in TB patients can be seen in table 2.

Table 2. EXPRESSION OF PD-L1 in TNBC Patients

PD-L1 expression	Sum	Percentage (%)
Positive	31	55,4%
Negative	25	44,6%
Total	56	100,0

From table 2, it can be seen that as many as 25 patients (44.6%) with negative PD-L1 expression with CPS<10 values. Meanwhile, pd-L1 positive expression with CPS≥10 values were 31 patients (55.4%). The results of the PD-L1 CPI examination can be seen in the following figure:

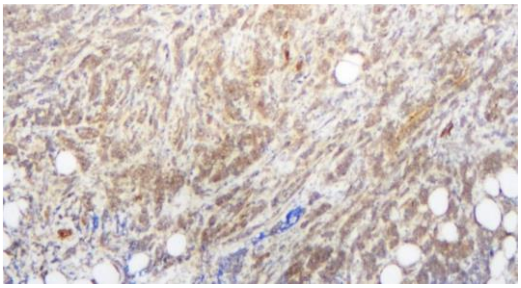

Figure 1. PD-L1 *Positive* CPS expression ≥10 on TNBC (40x magnification)

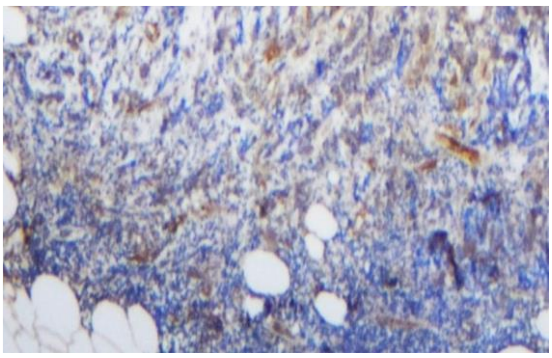

Figure 2. PD-L1 *Negative* CPS expression< 10 on TNBC (40x magnification)

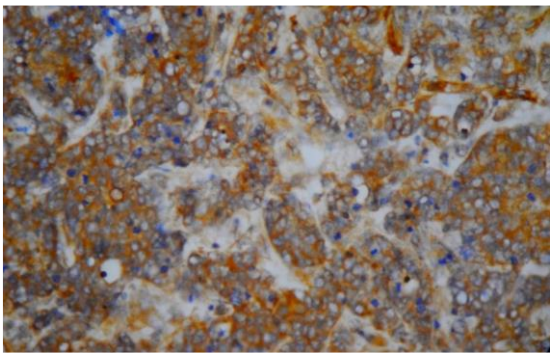

Figure 3. PD-L1 *Positive* CPS 90 expression on TNBC (400x magnification)

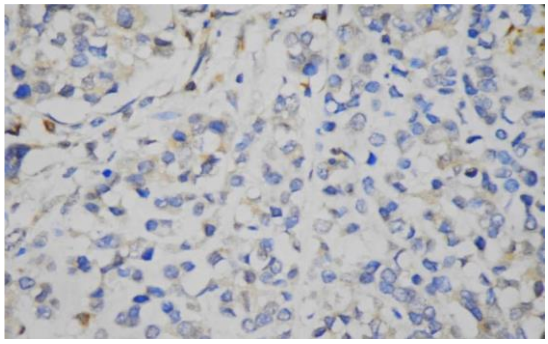

Figure 4. Pd-L1 *Negative* CPS 5 expression on TNBC (400x magnification)

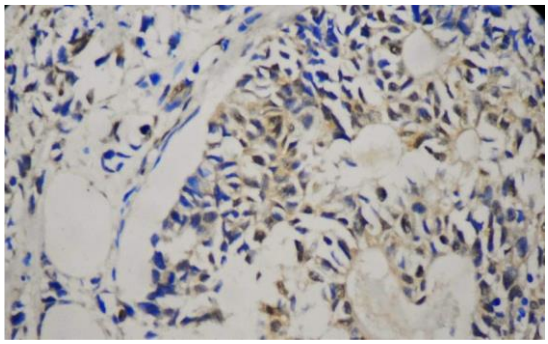

Figure 5. PD-L1 Negative CPS 7 expression on TNBC (400x magnification)

Relationship of PD-L1 Expression with Age in TB Patients

In the age group ≤40 years, as many as 75.0% had a positive PD-L1 expression. In the age group >40 years, as many as 50.0% had pd-L1 positive excretion. The results of the Chi Square Test showed no significant association between age and PD-L1 expression in TNBC patients (p value ≥0.05: 0.224). Meanwhile, the odds ratio (OR) results showed that patients aged ≤40 years were 0.3 times at risk of

having pd-L1 positive expression compared to those aged >40 years.

Table 3. Relationship of PD-L1 Expression to Age of TNBC Patients in West Sumatra

Variable	PD-L1						OR (95% CI)	p-value
	Negative		Positve		Total			
	f	%	f	%	f	%		
≤40 th	3	25,0	9	75,0	12	100	0,333 (0,79-1,399)	0,224
>40 th	22	50,0	22	50,0	44	100		

Relationship of PD-L1 Expression with Tumor Size in TNBC Patients

In the tumor size variable (T), the results of pd-L1 positive expression were obtained the most in T3&T4, which was 61.0%, while for T1&T2, the pd-L1 positive expression was 40.0%. The results of the Chi Square Test showed no significant association between tumor size (T) and PD-L1 expression in TNBC patients (p value ≥0.05: 0.274). Meanwhile, the OR results showed that the size of the T3&T4 tumor was 2.3 times the risk of having pd-L1 positive expression compared to the T1&T2 tumor size.

Table 4. Relationship of PD-L1 Expression with Tumor Size in TNBC Patients

Variable	PD-L1						OR (95% CI)	p-value
	Negative		Positive		Total			
	f	%	f	%	f	%		
T1 & T2	9	60,0	6	40,0	15	100	2,344 (0,700-7,849)	0,274
T3 & T4	16	39,0	25	61,0	41	100		

Relationship of PD-L1 Expression with Stage in TNBC Patients

In the stage variable, the highest positive PD-L1 expression results were obtained at the local advanced stage, namely 59.5%, and for the early stage that had a positive PD-L1 expression, 47.4% was obtained. The results of the Chi Square Test showed no significant association between the stage and pd-L1 expression in TB patients (p value ≥0.05: 0.563). Meanwhile, or results showed that local advanced stages were 1.6 times at risk of having pd-L1 positive expression compared to patients who were early stage.

Table 5. Relationship of PD-L1 Expression with Stage in TB Patients

Variable	PD-L1						OR (95% CI)	p-value
	Negative		Positive		Total			
	f	%	f	%	f	%		
Early	10	52,5	9	47,4	19	100	1,630 (0,535-4,966)	0,563
Carry on	15	40,5	22	59,5	37	100		

Relationship of PD-L1 Expression with Histopathology in TB Patients

In the NST histopathology variable, 60.5% of PD-L1 expressions were positive, while in Non-NST histopathology, 38.5% of PD-L1 expressions were positive. The results of the Chi Square Test showed no significant relationship between histopathology and PD-L1 expression in TNBC patients (p value ≥0.05: 0.280). Meanwhile, OR results showed that NST histopathology was 0.4 times at risk of having positive PD-L1 expression compared to NST No n histopathology.

Table 6. Relationship of PD-L1 Expression with Histopathology in TB Patients

Variable	PD-L1						OR (95% CI)	p-value
	Negative		Positive		Total			
	f	%	f	%	f	%		
NST	17	39,5	26	60,5	43	100	0,409 (0,144-1,460)	0,280
Non NST	8	61,5	5	38,5	13	100		

Relationship of PD-L1 Expression with Ki-67 in TNBC Patients

In the KI67 expression variable ≥20% 56.0% pd-L1 expression was positive, while in KI67 expression <20% as much as 50% pd-L1 expression was positive. The results of the Chi Square Test showed no significant relationship between KI67 expression and PD-L1 expression in TNBC patients (p value ≥0.05: 1,000). While the OR results showed Ki-67 expression ≥20% 1.2 times the risk of having pd-L1 positive expression compared to Ki-67 expression <20%.

Table 7. Relationship of PD-L1 Expression with Ki-67 in TB Patients

Variable	PD-L1						OR (95% CI)	p-value
	Negative		Positive		Total			
	f	%	f	%	f	%		
KI67≥20%	22	44,0	28	56,0	50	100	1,273 (0,234-6,932)	1,000
KI67<20%	3	50,0	3	50,0	6	100		

Relationship of PD-L1 Expression with Local Recidive Events in TB Patients

The results obtained from pd-L1 *positive* expression in patients who had a local recidive were 83.3%, while pd-L1 *positive* expression for patients who did not have a local recidive was 52.0%. The results of the *Chi Square* Test showed no significant association between patients who had a local recidiveness with PD-L1 expression in TNBC patients (*p value* ≥0.05: 0.306). Meanwhile, or results showed that patients who had local recidive were 4.6 times at risk of having pd-L1 *positive* expression compared to patients who did not have local recidive.

Table 8. Relationship of PD-L1 Expression with Local Recidive Incidence in TNBC Patients

Variable	PD-L1						OR (95% CI)	p-value
	Negative		Positive		Total			
	f	%	f	%	f	%		
Ada	1	16,7	5	83,3	6s	100	4,615 (0,502-42,392)	0,306
Tidak ada	24	48,0	26	52,0	50	100		

Relationship of PD-L1 Expression with Distant Metastatic Events in TB Patients

The results obtained from pd-L1 *positive* expression in patients who had distant metastasis were 82.1%, while PD-L1 *positive* expression for patients who did not have distant metastasis was 28.6%. The results of the *Chi Square* Test showed that there was a significant relationship between patients who had distant metastasis with PD-L1 expression in TNBC patients (*p value* <0.05: 0.000). OR results showed patients who had distant metastasis were 11.5 times at risk of having PD-L1 *positive* expression compared to patients who did not have distant metastasis.

Table 9. Relationship of PD-L1 Expression with Incidence of Distant Metastasis in TNBC Patients

Variable	PD-L1						OR (95% CI)	p-value
	Negative		Positive		Total			
	f	%	f	%	f	%		
Available	20	71,4	8	28,6	28	100	11,500 (3,236-40,864)	0,000
Unavailable	5	17,9	23	82,1	28	100		

***Disease Free Survival* (DFS)**

To assess DFS from observations made for 72 months (January 2016-December 2021) on PD-L1 expressions, *a Kaplan Meier* analysis test was carried out, the results of which were in table 10 and the graph below.

Table 10 *Mean Disease-Free Survival* based on PD-L1 Expression in TUBERCULOSIS

	Mean survival 95% CI	Rate	p-value	HR (95% CI)
PD-L1 *positive*	25,2 (19,61-30,76)	23/31	<0,001	8,16 (3,06-21,72)
PD-L1 *negative*	61,8 (52,46–71,11)	5/25		

From tabel 10 can be seen *the mean* value for DFS PD-L1, where the average DFS value for PD-L1 *positive* expression is obtained 25.2 months and for PD-L1 *negative* is 61.8 months. Patients with PD-L1 p*ositive* e-expression were statistically at 8.16 times risk of experiencing a significant Local and metastatic recidive event compared to patients with *negative* PD-L1 expression. From *kaplan Meier's* graph analysis, a meaningful relationship was found between expresi PD-L1 and DFS of TNBC patients (*p-value* <0.05: 0.000).

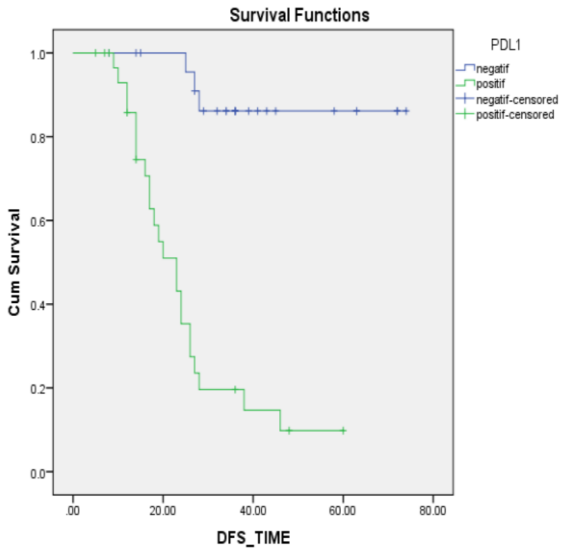

Figure 6. *Kaplan Meier* Graph of PD-L1 Expressions against *Disease Free Survival* in TNBC

***Overall Survival* (OS)**

Analysis *of Overall Survival* (OS) aims to determine the relationship of PD-L1 expression with the survival (OS) of TNBC patients, can be seen in table 11 and the Kaplan Meier chart below:

Table 11. *Mean Overall Survival Kaplan Meier* Expression of PD-L1 on TNBC

	Mean survival 95% CI	Rate	p-value	HR (95% CI)
PD-L1 positive	30,23 (25,23-35,23)	23/31	<0,001	14,1 (4,18-47,59)
PD-L1 negative	65,9 (57,86-73,95)	3/25		

From Table 11, it can be seen that *the MEAN* OS value for pd-L1 *positive* expression was obtained 30.23 months, and m*ean* OS for PD-L1 *negative* for 65.9 months. Patients with positive PD-L1 e-expression statisticallyk are at risk of 14.1 times death compared to patients with *negative* PD-L1 expression. From *kaplan Meier's* chart analysis, a meaningful relationship was found between PD-L1 excprsion and OS of TNBC patients (*p value* <0.05: 0.000)

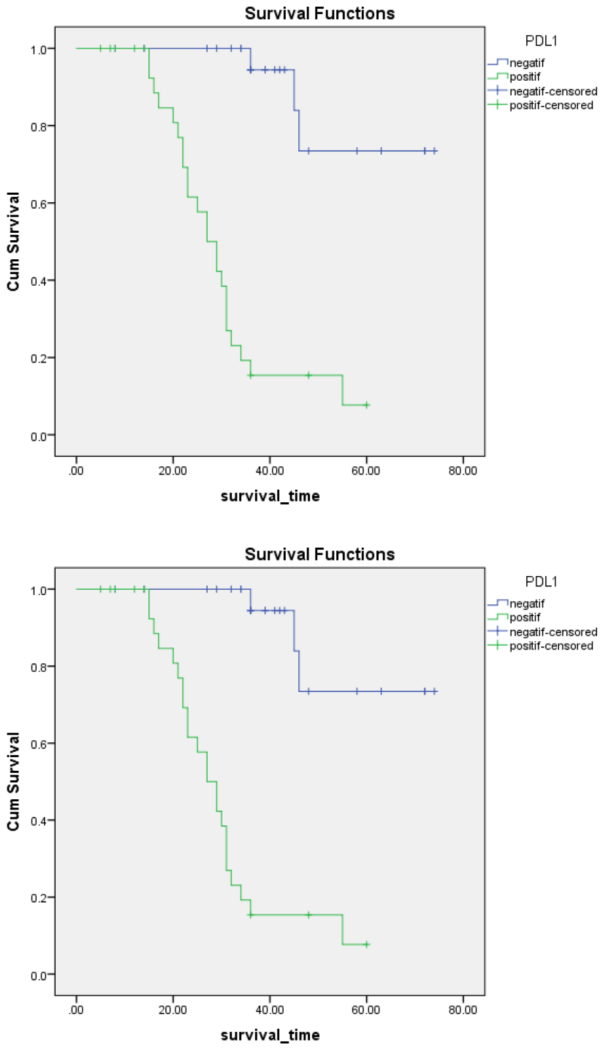

Figure 7. Kaplan Meier Chart of PD-L1 Expression of Overall Survival in TNBC

Discussion

The distribution of age groups in this study is in accordance with the theory that age is the most important risk factor in breast cancer, where the incidence of breast cancer increases with age. In addition, it is also in line with research by Chen, et al. which found that women over the age of 50 years accounted for as many as 78% had new breast cancer cases, and in 2016 it was found that as many

as 99.3% of deaths due to breast cancer occurred at the age of over 40 years. 27th

The results of the clinical stage assessment in the form of tumor size, local recidive events, and metastases in this study are in line with research conducted by Farisyi, et al. (2018) who found that the most breast cancer frequency distribution had an enlarged KGB axillary positive withtumor size T3 and T4. Other studies have also found that most patients with breast cancer have positive lymph node enlargement, the size of the tumor is greater than two cm, with a high degree of tumor (Harahap et al., 2017; 2019).

Research conducted by Harahap, et al. (2019 states that breast cancer patients come for treatment for the first time at an advanced stage. Based on medical records from one of the national referral hospitals, it was also found that about 24 out of 30 breast cancer patients came first to the hospital at an advanced local stage (Deliana et al., 2019).

The most type of istopathology in this study was the NST type, which was 76.8%. This is in accordance with other studies that state that in TUBERCULOSIS the most common type of histopathology found is the type of NST which is characterized by an aggressive histopathological picture (Elsawaf & Sinn, 2011). Grading histopathology is a predictor of survival and a worse prognosis. It is associated with an increased risk of involvement of axillary lymph nodes and metastases (Firdaus et al., 2016; Simbolon, 2021).

Examination of the proliferation of Ki-67 from CPI in this study found that 89.3% or 50 patients had a Ki-67 value >20% (high proliferation), while the remaining 6 patients or (10.7%) had a Ki-67 value < 20% (low proliferation). These results are in line with research by Qin Tao, et al. who also suggested that PD-L1 expression was more common in patients with clinical characteristics of larger tumor size, more positive lymph node involvement, higher tumor grading, higher Ki-67 index, and negative relationship with ER and PR (Qin et al., 2015).

Almost all patients in this study underwent surgery in the form of mastectomy, which was 96.4%. For a history of radiotherapy, 39.3% received radiotherapy, while the remaining 34 patients (60.7%) did not have a history of radiotherapy. One factor in the high number of patients who do not receive radiotherapy is the factor of radiotherapy equipment which is still very limited. A history of chemotherapy was carried out in all TNBC patients in this study. The chemotherapy regimens used were CAF, CMF or AC-T, either as neoadjuvant or as adjuvant therapy.

Surgery or surgery plays a major role in the treatment of breast cancer, because the early or locally advanced stage of breast cancer is still resectable and therefore requires surgery. Survival rates for patients who have undergone surgical therapy (MRM) have more than doubled, with 5-year survival rates reaching 40% in advanced stages, even without adjuvant therapy. According to the results of the meta-analysis, patients with early stages can undergo BCT, which combines BCS and whole breast radiation, and still produce the same long-term survival as mastectomy (Sobri et al., 2017). Operasi dan radioterapi dapat menghasilkan kesintasan hidup kira-kira sebesar 50% dan menurunkan kekambuhan lokoregional sebesar 20-25%. Hasil studi longitudinal retrospektif melaporkan bahwa kesintasan hidup 5 tahun penderita kanker payudara stadium lanjut lokal dengan pengobatan lengkap adalah 69% (Purwanto et al., 2015). Recent studies recommend that the procedure for the management of locally advanced breast cancer is the administration of neoadjuvant chemotherapy/chemoradiation, followed by surgery either lumpectomy or mastectomy and adjuvant chemotherapy (Argadikoesoema et al., 2012).

In this study, it was found that in the assessment of PD-L1 expression, patients who had positive values with CPS values ≥10 more than negative values with CPS values <10, namely 31 patients (55.4%) with positive values and as many as 25 patients (44.6%) had negative values. This is in accordance with research by Zeng et al. (2019) who found PD-L1 was expressed high in TUBERCULOSIS compared to non-TUBERCULOSIS. The positivity rate of PD-L1 is also higher in TNBC than non-TNBC. An increase in PD-L1 could be due to a high mutation load and an increase in resistance by neoantigens. Another study also showed high expression of PD-L1 in various breast cancer subtypes and obtained results of 20% in HER2 positive cells, 33% in the luminal subtype, and 59% in tuberculosis. This study is also in line with the research of Qin Tao et al. (2015) who found that as many as 55.9% of subtypes had a high expression of PD-L1 in TUBERCULOSIS.

This study showed no meaningful relationship between age and PD-L1 expression in TUBERCULOSIS. The results of this study are in accordance with the study by Huang et al. which showed that pd-L1 expression did not have a

meaningful relationship with the age of TB patients (Huang et al., 2021). Other studies have also stated that PD-L1 expression is more prevalent in young breast cancer patients (Baptista et al., 2016).

The results of this study showed no meaningful relationship between tumor size, stage, and Ki-67 with PD-L1 expression in TB patients. Hal is in line with research by Kurata et al. which says that PD-L1 expression is independently influenced by tumor size and Ki-67 expression, and is related to the clinicopathology of TNBC patients (Huang et al., 2021; Kurata et al., 2020). Other studies have also found that PD-L1 positive correlates with Ki-67 expression (Botti et al., 2017). This is also supported by studies of patients with higher positive PD-L1 expression at tumor size ≥2 cm, histological degree III, metastatic lymphatic, and Ki-67 expression ≥20% (Huang et al., 2021).

In histopathology variables, there was no meaningful relationship between histopathology and PD-L1 expression in TNBC patients. The results of this study are different from the study by Kim et al (2017) which showed that PD-L1 expression was meaningfully related to the type of histopathology. In other studies it was also found that pd-L1 positive expression in tumor cells was associated with a high histological grade (p=0.012) (Sitompul et al., 2021).

The results of uji Chi Square showed no meaningful relationship between patients who had local recidiveness and PD-L1 expression in TB patients. This is different from the research conducted by Satier et al. that pd-L1 expression is positively associated with an increase in local recidive numbers (Sabatier et al., 2015). In other studies it was also mentioned that high PD-L1 expression was associated with poor prognosis and high local recurrence rates (Muenst et al., 2014).

This study found that there was a meaningful relationship between patients who had distant metastasesand PD-L1 expression in TNBC patients. The OR results showed that patients who had distant metastaseswere 11 times more at risk of having PD-L1 positive expression compared to patients who did not have distant metastasis.

Sudarsa IW et al. in his research also found that there was a meaningful relationship between PD-L1 and distant metastases in TB patients (Sudarsa et al., 2021). Research by Zhang M et al. (2017) Mao et al (2015) also found PD-L1 expression associated with lymph node metastases, higher histological levels, estrogen receptors (ER)-negative in TNBC, thus supporting PD-L1 can be used as a biomarker of breast cancer prognosis.

From kaplan Meier's chart analysis, it was found that there was a meaningful relationship between PD-L1 and DFS of TB patients (p-value <0.05). Mean DFS in patients who were PD-L1 negative who had DFS was 61 months and in PD-L1 positive who had DFS was 25 months. Hazard ratio of 8.61 means that patients with PD-L1 positive who have DFS have an 8 times greater risk of experiencing recurrence or metastasesis far compared to patients who have PD-L1 negative.

In addition, a meaningful relationship was also obtained between PD-L1 and the OS of TNBC patients (p-value <0.05). Mean OS in patients who are PD-L1 negative is 65 months and in PD-L1 positive is 30 months. Hazard ratio of 14.1 means that patients with PD-L1 positive have a 14 times greater risk of death compared to patients who have PD-L1 negative. So that in this study it was concluded that there was a meaningful relationship between pd-L1 expression to survival (DFS & OS) of TB patients in West Sumatra.

The results of this study are supported by research by Purwanto et al. (2020) Mao et al. (2015) who found that PD-L1 expression was associated with poor prognosis in TNBC patients in Indonesia. Several studies have found a high proportion of PD-L1 expression in TB which is likely to affect the high mortality rate in breast cancer subtypes of TB in West Sumatra (Purwanto et al., 2020; Sudarsa et al., 2021; Irsyad, 2017). Recent studies have shown PD-L1 to increase in various types of tumors and is related to a poor prognosis (Zeng et al., 2019). Other studies have also found a positive association between PD-L1 expression and unfavorable prognostic factors, namely higher tumor rates, tumor necrosis, larger tumor size, and lymph node metastases (Hoda et al.,2020).

The results of this study are in line with several studies that show that PD-L1 positive is associated with a significantly poor level of survival (Zhang, et al., 2017). In studies by Muenst et al, patients with increased expression of PD-L1 were found to have a poor prognosis. Research by Parvathareddy et al. (2014) found PD-L1 expression in 32.8% (329/1003) cases of breast cancer and was significantly associated with poor prognosis indicators such as young patients, high grade tumors, estrogen receptor (ER) negative, progesterone receptor (PR) negative,

TUBERCULOSIS, as well as a high Ki-67 index (Parvathareddy et al., 2021). Research by Ai Erken et al. also found something similar in that TB patients had longer rates of disease-free survival due to an increase in stromal lymphocytic infiltrates (STILs) in PD-L1 positive (AiErken et al., 2017). In the study by Matikas et al. it isargued that the expression of the PD-L1 protein is related to shorter survival ability (Matikas et al., 2019). The meta-analysis study by Li et al. also provides strong evidence that PD-L1 expression in tumors is significantly associated with worse overall survival. Poor survival rates in positive PD-L1 are based on the fact that PD-L1 plays a role in tumor immune escape, where the PD-L1/PD-1 pathway can help tumors avoid an antitumor immune response. These tumor cells even replicate and spread faster. PD-L1 expressed in tumor cells binds itself to PD-1 on the surface of T cells, thereby inhibiting the function of T cells by losing their killing effect on tumor cells. PD-L1 not only induces tumorigenesis and is invasive, but also makes tumor cells less susceptible to specific CD8+ T cells (Li et al., 2019).

Conclusion

Most TNBC patients in West Sumatra in this study were found at the age of 40 years. Patients came on average at an advanced local stage, with histopathological type NST, K1-67 20%, and a history of mastectomy surgery. The incidence of local residif is only 10.7%, while the incidence of metastases is 50% and 30 patients still survive. The positive expression of PD-L1 in TNBC was found to be quite high at 55.4%.

In this study, it can be concluded that there is no statistically significant relationship between PD-L1 expression with age, tumor size, stage, histopathological type, Ki-67 expression, and local residive events. However, a significant relationship was found between PD-L1 expression and the incidence of metastasis. Furthermore, there was also a significant relationship between PD-L1 expression and survival, where positive PD-L1 expression was associated with lower DFS and OS compared to patients with negative PD-L1 expression.

References

1. Peraboi. (2020). *Panduan Pelaksanaan Kanker PERABOI 2020*. Jakarta: Perhimpunan Ahli Bedah Onkologi Indonesia; 2020.
2. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, *71*(3), 209-249.
3. GLOBOCAN (2020). Indonesia. https://gco.iarc.fr/today/data/factsheets/populations/360-indonesia-fact-sheets.pdf diakses pada 2 September 2021. 2020.
4. Riskesdas. Riskesdas 2018. 2018.
5. Rahmatya, A., Khambri, D., & Mulyani, H. (2015). Hubungan usia dengan gambaran klinikopatologi kanker payudara di bagian bedah RSUP Dr. M. Djamil Padang. *Jurnal Kesehatan Andalas*, *4*(2), 478-84.
6. Sari, N. W., & Maharani, D. (2019). Karakteristik kejadian kanker payudara di RSUD Dr. Achmad Mochtar Kota Bukittinggi. *Jurnal Ilmiah J-HESTECH*, *2*(2), 73-82.
7. Profil Kesehatan Indonesia Tahun (2017). Jakarta: Kementerian Kesehatan RI. 2018.
8. Profil Kesehatan Indonesia Tahun (2015). Jakarta: Kementerian Kesehatan RI. 2016.
9. Sasmita, S. (2016). *FAKTOR YANG MEMPENGARUHI KUALITAS HIDUP PASIEN KANKER PAYUDARA DI RSUP DR. M. DJAMIL PADANG TAHUN 2016* (Doctoral dissertation, Universitas Andalas).
10. de Ruijter, T. C., Veeck, J., de Hoon, J. P., van Engeland, M., & Tjan-Heijnen, V. C. (2011). Characteristics of triple-negative breast cancer. *Journal of cancer research and clinical oncology*, *137*(2), 183-192.
11. Morris, G. J., Naidu, S., Topham, A. K., Guiles, F., Xu, Y., McCue, P., ... & Mitchell, E. P. (2007). Differences in breast carcinoma characteristics in newly diagnosed African–American and Caucasian patients: A single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and end results database. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *110*(4), 876-884.
12. Purwanto, I., Dwiprahasto, I., Aryandono, T., & Mubarika, S. (2020). Treatment options for Indonesian triple negative breast cancer patients: a literature review of current state

and potentials for future improvement. *J Med Sci*, *52*(1), 81-101.

13. Purwanto, I., Dwiprahasto, I., Aryandono, T., & Mubarika, S. (2020). Treatment options for Indonesian triple negative breast cancer patients: a literature review of current state and potentials for future improvement. *J Med Sci*, *52*(1), 81-101.
14. Widodo, I., Dwianingsih, E. K., Triningsih, E., Utoro, T., & Soeripto, S. (2014). Clinicopathological features of Indonesian breast cancers with different molecular subtypes. *Asian Pacific Journal of Cancer Prevention*, *15*(15), 6109-6113.
15. Bonsang-Kitzis, H., Chaltier, L., Belin, L., Savignoni, A., Rouzier, R., Sablin, M. P., ... & Reyal, F. (2015). Beyond axillary lymph node metastasis, BMI and menopausal status are prognostic determinants for triple-negative breast cancer treated by neoadjuvant chemotherapy. *PLoS One*, *10*(12), e0144359.
16. Ruchi Sharma, V., Kumar Gupta, G., K Sharma, A., Batra, N., K Sharma, D., Joshi, A., & K Sharma, A. (2017). PI3K/Akt/mTOR intracellular pathway and breast cancer: factors, mechanism and regulation. *Current pharmaceutical design*, *23*(11), 1633-1638.
17. Dong, P., Xiong, Y., Yue, J., Hanley, S. J., & Watari, H. (2018). Tumor-intrinsic PD-L1 signaling in cancer initiation, development and treatment: beyond immune evasion. *Frontiers in oncology*, 386.
18. Qin, T., Zeng, Y. D., Qin, G., Xu, F., Lu, J. B., Fang, W. F., ... & Wang, S. S. (2015). High PD-L1 expression was associated with poor prognosis in 870 Chinese patients with breast cancer. *Oncotarget*, *6*(32), 33972.
19. Purwanto, I., Heriyanto, D. S., Ghozali, A., Widodo, I., Dwiprahasto, I., Aryandono, T., & Haryana, S. M. (2020). Overexpression of programmed death-ligand 1 receptor mRNA as an independent negative prognostic factor for triple negative breast cancer. *World journal of oncology*, *11*(5), 216.
20. Sudarsa, I. W., Gunawan, I. P. A., & Manuaba, I. B. T. W. (2021). The Association of Tumor-Infiltrating Lymphocytes and Programmed Cell Death 1 Expression with the Incidence of Distant Metastasis in Triple-Negative Breast Cancer Subjects in Sanglah General Hospital, Bali, Indonesia. *Case Reports in Oncology*, *14*(1), 347-351.
21. Lazarus, G., Audrey, J., & Iskandar, A. W. B. (2019). Efficacy and safety profiles of programmed cell death-1/programmed cell death ligand-1 inhibitors in the treatment of triple-negative breast cancer: A comprehensive systematic review. *Oncology Reviews*, *13*(2), 425-425.
22. Mao, Y., Li, W., Chen, K., Xie, Y., Liu, Q., Yao, M., ... & Tao, M. (2015). B7-H1 and B7-H3 are independent predictors of poor prognosis in patients with non-small cell lung cancer. *Oncotarget*, *6*(5), 3452.
23. Zhang, M., Sun, H., Zhao, S., Wang, Y., Pu, H., Wang, Y., & Zhang, Q. (2017). Expression of PD-L1 and prognosis in breast cancer: a meta-analysis. *Oncotarget*, *8*(19), 31347.
24. Muenst, S., Schaerli, A. R., Gao, F., Däster, S., Trella, E., Droeser, R. A., ... & Soysal, S. D. (2014). Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. *Breast cancer research and treatment*, *146*(1), 15-24.
25. Irsyad, M. (2017). *HUBUNGAN SURVIVAL PASIEN KANKER PAYUDARA SUBTIPE TRIPLE NEGATIVE DENGAN MODALITAS PENGOBATAN DI KOTA PADANG TAHUN 2010-2015* (Doctoral dissertation, Universitas Andalas).
26. Mittendorf, E. A., Philips, A. V., Meric-Bernstam, F., Qiao, N., Wu, Y., Harrington, S., ... & Alatrash, G. (2014). PD-L1 expression in triple-negative breast cancer. *Cancer immunology research*, *2*(4), 361-370.
27. Chen, H. L., Zhou, M. Q., Tian, W., Meng, K. X., & He, H. F. (2016). Effect of age on breast cancer patient prognoses: a population-based study using the SEER 18 database. *PloS one*, *11*(10), e0165409.
28. Al Farisyi, M., & Khambri, D. (2018). Analisis Survival Pasien Kanker Payudara Usia Muda di RSUP DR. M. Djamil Padang Tahun 2008-2017. *Jurnal Kesehatan Andalas*, *7*, 25-29.
29. Harahap, W. A., Khambri, D., Haryono, S., & Nindrea, R. D. (2017). Outcomes of trastuzumab therapy for 6 and 12 months in Indonesian national health insurance system clients with operable HER2-positive breast

cancer. *Asian Pacific Journal of Cancer Prevention: APJCP*, *18*(4), 1151.

30. Harahap, W., Khambri, D., Nindrea, R., & Yetti, H. (2019, May). Breast Cancer Immunohistochemistry Features Among Young Women in West Sumatera, Indonesia. In *Proceedings of the 1st EAI International Conference on Medical And Health Research, ICoMHER November 13-14th 2018, Padang, West Sumatera, Indonesia*.
31. Deliana, M., Suza, D. E., & Tarigan, R. (2019). Advanced stage cancer patients experience in seeking treatment in Medan, Indonesia. *Open Access Macedonian Journal of Medical Sciences*, *7*(13), 2194.
32. Elsawaf, Z., & Sinn, H. P. (2011). Triple-negative breast cancer: clinical and histological correlations. *Breast Care*, *6*(4), 273-278.
33. Firdaus, V. R. P., Asri, A., Khambri, D., & Harahap, W. A. (2016). Hubungan Grading Histopatologi dan Infiltrasi Limfovaskular dengan Subtipe Molekuler pada Kanker Payudara Invasif di Bagian Bedah RSUP. Dr. M. Djamil Padang. *Jurnal Kesehatan Andalas*, *5*(1).
34. Simbolon, Y. Y. (2021). Hubungan Infiltrasi Limfovaskular dengan Subtipe Molekuler Kanker Payudara Invasif: Telaah Sistematis. *JIMKI: Jurnal Ilmiah Mahasiswa Kedokteran Indonesia*, *9*(1), 15-22.
35. Sobri, F. B., Azhar, Y., Wibisana, I. G. N. G., & Rachman, A. (2017). *Manajemen terkini kanker payudara*. Jakarta: Media Aesculapius.
36. Purwanto, H., Handoyo, D., Haryono, S., & Harahap, W. (2015). Panduan penatalaksanaan kanker payudara. *Jakarta. PERABOI*, 15-21.
37. Argadikoesoema, S., Djoerban, Z., Siregar, N. C., & Poetiray, E. D. (2012). Kesintasan Hidup dan Kekambuhan Lokoregional berdasarkan Prosedur Pengobatan pada Penatalaksanaan Kanker Payudara Stadium Lanjut Lokal. *Radioterapi & Onkologi Indonesia*.
38. Zeng, Y., Wang, C. L., Xian, J., Ye, Q., Qin, X., Tan, Y. W., & Cao, Y. D. (2019). Positive correlation between programmed death ligand-1 and p53 in triple-negative breast cancer. *OncoTargets and therapy*, *12*, 7193.
39. Huang, X., Wang, X., Qian, H., Jin, X., & Jiang, G. (2021). Expression of PD-L1 and BRCA1 in Triple-Negative Breast Cancer Patients and Relationship with Clinicopathological Characteristics. *Evidence-Based Complementary and Alternative Medicine*, *2021*.
40. Baptista, M. Z., Sarian, L. O., Derchain, S. F., Pinto, G. A., & Vassallo, J. (2016). Prognostic significance of PD-L1 and PD-L2 in breast cancer. *Human pathology*, *47*(1), 78-84.
41. Kurata, K., Kubo, M., Kai, M., Mori, H., Kawaji, H., Kaneshiro, K., ... & Nakamura, M. (2020). Microsatellite instability in Japanese female patients with triple-negative breast cancer. *Breast Cancer*, *27*(3), 490-498.
42. Botti, G., Collina, F., Scognamiglio, G., Rao, F., Peluso, V., De Cecio, R., ... & Di Bonito, M. (2017). Programmed death ligand 1 (PD-L1) tumor expression is associated with a better prognosis and diabetic disease in triple negative breast cancer patients. *International journal of molecular sciences*, *18*(2), 459.
43. Kim, A., Lee, S. J., Kim, Y. K., Park, W. Y., Park, D. Y., Kim, J. Y., ... & Choi, K. U. (2017). Programmed death-ligand 1 (PD-L1) expression in tumour cell and tumour infiltrating lymphocytes of HER2-positive breast cancer and its prognostic value. *Scientific reports*, *7*(1), 1-10.
44. Sitompul, P. I. M., Saputra, H., Maker, L. P. I. I., Dewi, I. G. A. S. M., Sriwidyani, N. P., & Muliarta, I. M. (2021). Hubungan antara Stromal Tumor Infiltrating Lymphocytes (TIL) dengan ekspresi Programmed Death-Ligand 1 (PD-L1) pada karsinoma payudara invasif tipe tidak spesifik subtipe Human Epidermal Growth Factor Receptor-2 (HER-2) enriched di RSUP Sanglah, Bali, Ind. *Intisari Sains Medis*, *12*(2), 543-550.
45. Sabatier, R., Finetti, P., Mamessier, E., Adelaide, J., Chaffanet, M., Ali, H. R., ... & Bertucci, F. (2015). Prognostic and predictive value of PDL1 expression in breast cancer. *Oncotarget*, *6*(7), 5449.
46. Hoda, R. S., Brogi, E., Dos Anjos, C. H., Grabenstetter, A., Ventura, K., Patil, S., ... & Wen, H. Y. (2020). Clinical and pathologic features associated with PD-L1 (SP142) expression in stromal tumor-infiltrating immune cells of triple-negative breast carcinoma. *Modern Pathology*, *33*(11), 2221-2232.
47. Parvathareddy, S. K., Siraj, A. K., Ahmed, S. O., Ghazwani, L. O., Aldughaither, S. M., Al-Dayel, F.,

... & Al-Kuraya, K. S. (2021). PD-L1 protein expression in middle eastern breast cancer predicts favorable outcome in triple-negative breast cancer. *Cells*, *10*(2), 229.

48. AiErken, N., Shi, H. J., Zhou, Y., Shao, N., Zhang, J., Shi, Y., ... & Lin, Y. (2017). High PD-L1 expression is closely associated with tumor-infiltrating lymphocytes and leads to good clinical outcomes in Chinese triple negative breast cancer patients. *International journal of biological sciences*, *13*(9), 1172.

49. Matikas, A., Zerdes, I., Lövrot, J., Richard, F., Sotiriou, C., Bergh, J., ... & Foukakis, T. (2019). Prognostic implications of PD-L1 expression in breast cancer: systematic review and meta-analysis of immunohistochemistry and pooled analysis of transcriptomic data. *Clinical Cancer Research*, *25*(18), 5717-5726.

50. Li, S., Chen, L., & Jiang, J. (2019). Role of programmed cell death ligand-1 expression on prognostic and overall survival of breast cancer: a systematic review and meta-analysis. *Medicine*, *98*(16).