RESEARCH ARTICLE

AGGRESSIVENESS OF INDONESIAN TRIPLE-NEGATIVE BREAST CANCER: ROLES OF PROGRAMMED DEATH LIGAND-1 AND TUMOR MICROENVIRONMENT

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ABSTRACT

Background: Triple-negative breast cancer (TNBC) is one of the most aggressive breast cancer subtypes in Indonesia. The expression of Programmed death ligand 1 (PD-L1) and Tumor Microenvironment (TME) characteristics play essential roles in both immune system avoidance and medical treatment results. The Indonesian medical field lacks a comprehensive analysis of local TNBC research data because new studies continue to emerge.

Methods: The research followed PRISMA guidelines and PECO framework for analysis. A total of 22 records were identified; 10 studies met eligibility, and 6 studies were included in the final synthesis.

Results: The studies showed a wide range of PD-L1 expression in tumor cells, from 21% to 93.5%, depending on antibody clone (SP142, SP263, 22C3) and scoring threshold. The studies showed that most tumors had high-grade characteristics between 42% and 88% while displaying high proliferative rates with Ki-67 ≥20% in more than 80% of cases. The three most common metastasis locations in patients were the lungs, bones and then the brain. The survival rates of patients improved when their CD8/CD163 and CD4/FOXP3 ratios increased. The survival outcomes of patients worsened when their PD-L1 expression levels or mRNA expression increased.

Conclusion: Indonesian TNBC shows aggressive pathological characteristics with variable PD-L1 expression and diverse tumor microenvironments. PD-L1 alone does not provide consistent prognostic value and is best interpreted together with immune-cell ratios and Tumor Infiltrating Lymphocytes (TIL) density. Establishing standardized biomarker evaluation and adopting immune-based molecular classification could improve the precision of immunotherapy strategies in Indonesia.

Keywords: Triple-negative breast cancer; PD-L1; tumor microenvironment; immune ratios; metastasis; Indonesia.

INTRODUCTION

Triple-negative breast cancer (TNBC) represents 15–24% of breast cancer cases and remains one of the deadliest breast cancer subtypes. Early relapse and high recurrence potential complicate survival rates as TNBC does not express estrogen receptors (ER) or progesterone receptors (PR) or human epidermal growth factor receptor-2 (HER2), allowing for fewer targeted therapies.[1,2]

Recent findings from molecular characterization studies demonstrate that triple-negative breast cancer is not a singular entity but rather multiple subtypes with varying biological behavior and treatment response. The disease consists of four main subtypes, which include basal-like immune-activated (BLIA) and basal-like immune-suppressed (BLIS), mesenchymal (MES), and luminal androgen receptor (LAR) subtypes that show different levels of immune cell presence and genetic damage.[3] Whereas BLIA generally consists of dense tumor-infiltrating lymphocytes (TILs) and high programmed death ligand (PD-L1) expression, it thus represents a potentially responsive tumor type to immune checkpoint inhibitors. On the other hand, BLIS and LAR subtypes often exhibit immune exclusion and are resistant to immunotherapy.[4]

The development of TNBC and its treatment response depends on understanding both TME components and biological adaptations. The TME contains essential elements which include hypoxia-induced factor 1 alpha (HIF-1α), tumor-associated macrophages (TAMs), and regulatory T-Cells (Tregs) and myeloid-derived suppressor cells (MDSC) and redox-regulated exosomes. The TME (Tumor

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Microenvironment) components work together to enable immune evasion and promote angiogenesis, EMT and cancer cell spread.[5] PD-L1 expression and the levels of are the most critical actionable TME components for prognosis and prediction in immunotherapy.[6,7]

Breast cancer stands as the leading cancer diagnosis for women in Indonesia while it causes the majority of cancer deaths among female patients. Indonesian cohorts consistently report a younger age at diagnosis (45-49 years) compared with Western populations.[8] The majority of breast cancer cases in Indonesia occur in young women who develop aggressive tumors with high Ki-67 levels and lymphovascular invasion at the time of diagnosis.[9,10] Research on PD-L1 expression and immune cell infiltration in hospitals has produced inconsistent results because of methodological differences and restricted study designs.[11-14]

The current absence of unified national data regarding TNBC biomarker profiles including PD-L1 expression and TILs composition and molecular subtypes creates difficulties for both patient group identification and precision treatment delivery. The absence of institutional reporting standards makes it difficult to apply existing research findings into medical practice.[6,15]

This article is a systematic review synthesizing TNBC findings from Indonesian studies published between 2019 and 2024. The review combines existing research to analyze histopathological characteristics and PD-L1 expression and metastatic patterns and tumor environment features of TNBC in Indonesian patients. The research identifies present trends and knowledge deficiencies to guide upcoming studies which will help create biomarker-based diagnostic tools and treatment approaches for Indonesian TNBC patients.

METHODS

Search Strategy

The research followed PRISMA guidelines for systematic review procedures. The research team conducted a complete database search to find studies which analyzed TNBC patients from Indonesia through histopathological examination and PD-L1 protein expression assessment. The research team searched PubMed and Google Scholar databases for studies published between 2010 and 2025. The search used Boolean operators to link the following keywords: “triple-negative breast cancer”, “TNBC”, “PD-L1”, “histopathology”, “tumor microenvironment”, “TIL”, “CD4”, “CD8”, “FOXP3”, “CD163”, and “Indonesia”.

Eligibility Criteria

The research study included data from studies which fulfilled these conditions:[1] the research conducted in Indonesia as original research,[2] included patients who received TNBC diagnosis through immunohistochemistry tests,[3] reported data about PD-L1 expression and histopathological characteristics,[4] reported at least one TME parameters, such as TILs, CD4, CD8, FOXP3, or CD163,[5] written in English or Bahasa Indonesia,[6] used observational designs, including cross-sectional, cohort, or retrospective studies. Case reports, editorials, review articles, and studies without relevant biomarker data were excluded.

Tumor Microenvironment Indicators

Tumor microenvironment variables extracted from each study included:[1] TILs density (intratumoral and stromal),[2] immune markers (CD4, CD8, FOXP3, CD163),[3] immune ratios (CD4/FOXP3 and CD8/CD163), and[4] stromal PD-L1 expression. These indicators were selected because they are the primary immune components reported in Indonesian TNBC research and are directly related to prognosis and immunotherapy response.

Data Extraction

Relevant data were extracted using a standardized form including study location, study design, TNBC case numbers, patient demographics, histopathological features, PD-L1 detection methods, PD-L1 expression levels, metastatic patterns, and tumor microenvironment profiling results. The two reviewers conducted independent data screening and extraction before resolving any discrepancies through team discussion. Both reviewers had academic backgrounds in histopathology and molecular oncology, ensuring methodological consistency and appropriate interpretation of biomarker data. Disagreements were resolved through team discussion.

Quality Assessment

The methodological quality of the included studies was evaluated using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist to assess methodological quality of included studies, maintain complete and transparent reporting with consistent methods. The PECO (Population, Exposure, Comparator, Outcome) framework was applied to each study to evaluate their populations, biomarker exposure data, comparison groups, and reported outcomes. The framework allowed researchers to evaluate study populations and biomarker exposure data, including PD-L1 expression and immune microenvironment profiles, comparison variables, and clinical results. The combination of PRISMA and PECO established a robust framework for integrating diverse study findings while reducing bias across included studies.

Data Synthesis

A descriptive narrative synthesis was performed because of heterogeneity in PD-L1 methodologies, antibody clones, scoring systems, TME indicators, and reporting formats across studies. Planned meta-analysis was not

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feasible. Findings are therefore presented in narrative and tabular formats.

RESULTS

A total of 22 studies were initially retrieved from database searches. After the previously mentioned minimum eligibility criteria for screening at full text review stage were applied, eight studies were left for full text review. Two studies were excluded based on the absence of histopathological data. Therefore, six studies were included that met every criterion for qualitative and quantitative assessment **(Figure 1)**.

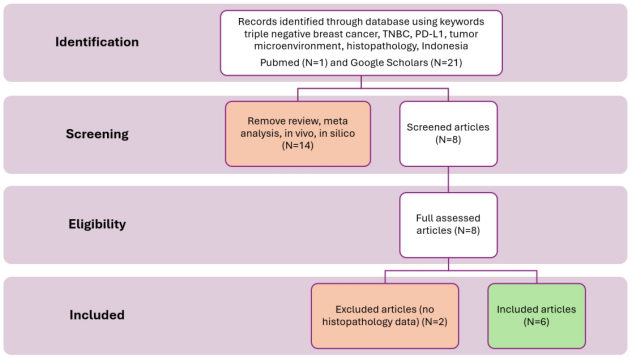

Figure 1. PRISMA flow diagram of the study selection process

This multicenter study took place from 2019-2024 in general referral hospitals spanning the area from Sanglah General Hospital (Bali) to Dr. Sardjito Hospital (Yogyakarta) to RSUP Dr. Mohammad Hoesin (Palembang) to Universitas Sumatera Utara Teaching Hospital (Medan) to Cipto Mangunkusumo and Dharmais Cancer Center (Jakarta) to Semarang. A total of 370 TNBC patients were registered with a mean age of 50.3 years old at diagnosis **(Figure 2)**. All patients were diagnosed with TNBC based on ER-, PR-, HER2- immunohistochemistry; FISH was conducted when indicated to ascertain HER2 status.

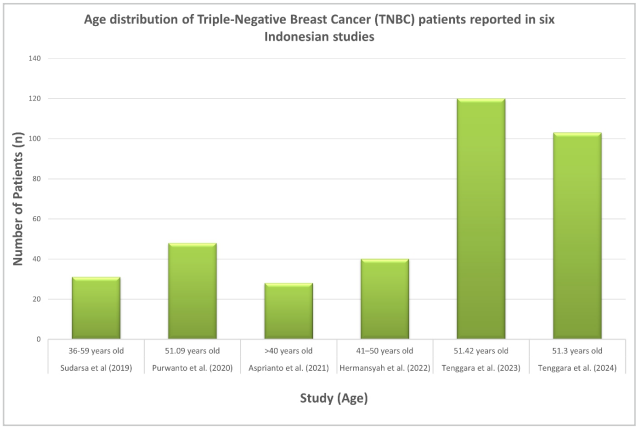

Figure 2. Age distribution of Triple-Negative Breast Cancer (TNBC) patients reported in six Indonesian studies

The PECO synthesis of six studies **(Table 1.)** demonstrated identical patterns regarding PD-L1 expression and immune microenvironment features and TNBC histopathological severity in Indonesian patients. The PD-L1 expression levels showed broad variation because of different testing methods, yet studies found that higher PD-L1 expression through mRNA or protein measurement linked to worse patient results, higher metastasis rates, and shorter survival times.

Table 1. PECO Analysis Indonesian TNBC Studies (2019–2024)

No	Study (Year)	Setting / Design	Population (P)	Exposure (E)	Comparator (C)	Outcomes (O)	Key PECO Finding
1	**Sudarsa et al. (2019)**	Sanglah General Hospital, Bali; cross-sectional study	Female TNBC patients diagnosed at Sanglah Hospital, Denpasar, Indonesia (n = 31)	High stromal PD-L1 expression and low TIL density (IHC Ventana SP263)	Low PD-L1 stromal expression or high TIL density	Presence of distant metastasis (lung, brain)	High PD-L1 stromal expression with low TIL density was significantly associated with distant metastasis (p = 0.043), indicating an immunosuppressive TME.
2	**Purwanto et al. (2020)**	Dr. Sardjito Hospital, Yogyakarta; retrospective cohort	Stage I–III TNBC patients with available FFPE tissue (n = 48)	PD-L1 mRNA overexpression (qRT-PCR)	PD-L1 mRNA underexpression	Three-year overall survival (OS) and clinicopathological correlations	PD-L1 mRNA overexpression was significantly associated with worse 3-year OS (p < 0.01) and was independent of age, grade, and stage.
3	**Tenggara et al. (2023)**	Multicenter cross-sectional study (Jakarta, Yogyakarta, Semarang)	De novo metastatic TNBC patients (n = 127)	High PD-L1 expression and immune ratios (CD4/FOXP3, CD8/CD163)	Low PD-L1 or low immune ratios	Presence of visceral and bone metastases; histologic grade and Ki-67	High CD4/FOXP3 and CD8/CD163 ratios were associated with reduced visceral and bone metastases. PD-L1 positivity rate was 30.8%.

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4	**Tenggara et al. (2024)**	Multicenter prospective cohort (Jakarta tertiary hospitals)	De novo metastatic TNBC patients (n = 128)	High CD4/FOXP3 and CD8/CD163 ratios (immune profiling by IHC)	Low immune ratios	One year overall survival (OS); metastasis distribution	High immune ratios were independently associated with improved 1-year OS (HR 1.8–2.0; p < 0.05). Metastasis sites included lungs (56.3%), bones (49.5%), liver (29.1%), and brain (10.7%).
5	**Asprianto et al. (2021)**	RSUP Dr. Mohammad Hoesin Hospital, Palembang; cross-sectional study	TNBC and HER2-enriched breast cancer cases (n = 42 TNBC)	PD-L1 protein expression (SP142 clone) and TIL density (H&E, intratumoral and stromal)	Lower PD-L1 or lower TILs	Association between PD-L1, TILs, and histopathological grade	High TILs were found in 75% of TNBC but showed no correlation with PD-L1 expression; the HER2-enriched subtype had higher PD-L1 positivity (p = 0.021).
6	**Hermansyah et al. (2022)**	Universitas Sumatera Utara Teaching Hospital, Medan; descriptive cross-sectional	Female TNBC patients with complete clinicopathological data (n = 40)	PD-L1 IHC positivity (clone 22C3)	PD-L1 negative	PD-L1 positivity rate; histological grade, LVSI, nodal involvement, TILs	PD-L1 positivity rate was 45%. Most tumors were grade III (77.5%) with LVSI (57.5%) and lymph node metastasis (62.5%); moderate TILs (62.5%) were common.

The immune-related parameters, which included elevated CD4/FOXP3 and CD8/CD163 ratios, showed a direct link to better treatment outcomes. The ratios indicated that the tumor environment contained active immune cells that fought against cancer cells. The studies showed that TILs appeared at moderate to high concentrations throughout all research findings. The relationship between TILs and PD-L1 expression and clinical results in TNBC showed inconsistent results because of its complex and diverse immune environment. The clinicopathological features of TNBC showed identical aggressive characteristics throughout all studies, which included high-grade tissue appearance, increased cell growth rates, and regular occurrence of lymphatic vessel and lymph node metastases. The metastatic spread of TNBC tumors primarily affected the lungs, bones, liver, and brain tissues according to worldwide research findings.

The research findings about PD-L1 expression showed wide differences between studies which reported tumor cell expression from 21% to 93.5% and stromal cell expression at 61.3%. The study by Sudarsa et al. (2019) in Bali reported the highest PD-L1 expression but Purwanto et al. (2020) in Yogyakarta and Tenggara et al. (2023–2024) in Jakarta multicenter found lower expression levels between 21% and 31%. The different results between studies probably stem from antibody selection (SP263 vs. SP142) and the criteria used to determine positive results. The studies demonstrated that PD-L1 expression or mRNA overexpression led to worse survival results which established its status as a poor prognostic marker for Indonesian TNBC patients **(Table 2)**.

Table 2. Histopathological features and Programmed Death-Ligand 1 (PD-L1) Expression in Triple-Negative Breast Cancer (TNBC) patient samples in six Indonesian studies

Article	Study Location	Study Design	Programmed Death-Ligand 1 (PD-L1) expression	Histopathological Grade	Metastasis	Tumor Microenvironment
Sudarsa et al (2019) (16)	Sanglah General Hospital, Bali	Cross-sectional	93,5% in tumor tissue 61,3% in stromal	High grade 41.9%	Lungs, brain	Low TILs level, high stromal PD-L1
Purwanto et al (2020) (14)	Dr. Sardjito Hospital, Yogyakarta	Retrospective cohort	21% (not specified in tumor or stromal tissue)	Grade III 62.5%	Not reported	Not assessed (no TILs or immune marker quantification)
Asprianto et al (2021) (15)	Dr. Mohammad Hoesin Hospital, Palembang	Cross-sectional	28.6% (not specified in tumor or stromal tissue)	Grade III 87.5% ILV positive 81.5%	Not reported	TILs high in 75% (intratumoral), 75% (intrastromal); no significant correlation with PD-L1

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Hermansyah et al (2022) (17)	USU Teaching Hospital, Medan	Descriptive cross-sectional	45% (not specified in tumor or stromal tissue)	Grade 3: 77.5% LVSI: 57.5% Angioinvasion: 60% LN+: 62.5%	Lymph nodes	TILs level 62.5%
Tenggara et al (2023) (18)	Multiple hospitals in Jakarta, Yogyakarta , and Semarang	Cross-sectional	30.8% (not specified in tumor or stromal tissue)	Grade 3 56.7% High Ki-67 (≥20%) 85.8%	Visceral organ (75.8%) Lung (56.7%) Bone (49.2%)	CD4, CD8, FOXP3, CD163; significant ratios (CD8/FOXP3, CD4/FOXP3) linked to bone and visceral metastasis
Tenggara et al (2024) (19)	Multiple hospitals in Jakarta	Cohort	45.6% (not specified in tumor or stromal tissue)	Grade 3 54.4%, High Ki-67 (≥20%) 86.4%,	Lung (56.3%) Bone (49.5%) Liver (29.1%) Brain (10.7%)	CD4, CD8, CD163, FOXP3; high CD4/FOXP3 and CD8/CD163 ratios associated with better 1-year OS

Histopathologically, most tumors were high grade (Grade III), around 41.9-87.5% and the Ki-67 index ≥ 20% was found in more than 80% of cases, which highlights the standard proliferative characteristics of TNBC. Similarly, metastasis patterns occurred as they did abroad: lungs and brain metastases were most common in the Bali population (Sudarsa et al., 2019), while bone, lung, liver, and brain were most common in the Jakarta multicenter study (Tenggara et al., 2024). Lymph node metastasis occurred in 62.5% of patients in the Medan cohort (Hermansyah et al., 2022), emphasizing the high metastatic potential at presentation.

In the TME, TILs and CD4/FOXP3 and CD8/CD163 ratios are significant prognostic factors ($p<0.05$). The density of TILs was found to be 62.5%-75%, and there exists significant biological heterogeneity from intratumoral to peritumoral locations. For example, Asprianto et al. (2021, Palembang) found similar findings of high TILs but no association with PD-L1 expression significance. However, the results show that CD4/FOXP3 and CD8/CD163 ratios are higher and an independent factor of 1-year overall survival (hazard ratio 1.8-2.0; $p < 0.05$). On the other hand, Sudarsa et al. (2019) reported that PD-L1 high in the stroma + TILs low were a causative factor of distant metastasis, which ultimately means that there is an improperly regulated immunosuppressive component to the TME.

The PECO framework **(Table 1)** enables the combination of study results which show Indonesian women with confirmed TNBC as the population, while IHC and molecular PD-L1 evaluation and immune-cell profiling serve as interventions for comparing PD-L1 expression levels and immune ratios to achieve survival results. These findings show that Indonesian TNBC patients present with high-grade tumors with variable PD-L1 expression and specific immune infiltrate distributions. Patients have better survival outcomes when $FOXP3^+$, $Cd163^+$ immune cells are proportionally lower relative to $CD4^+$, $CD8^+$ immune cells, regardless of PD-L1 expression **(Figure 3)**.

In conclusion, Indonesian TNBC populations demonstrate a reproducible relationship between immune equilibrium and survival wherein PD-L1 expression and immune cell ratios may serve as clinically translatable biomarkers for personalized immunotherapy risk stratification. These data converge to create a strong national basis for translating precision oncology efforts in the management of TNBC.

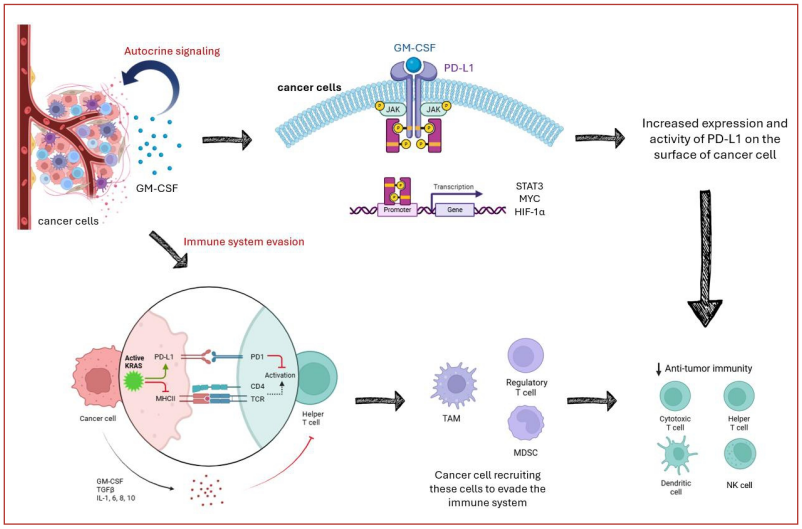

Figure 3. Mechanisms of programmed death-ligand 1 (PD-L1) upregulation and major signaling pathways including HIF-1, MYC, CSF-1/CSF-1R, ICAM-1–EGFR–STAT3, and immune evasion by TNBC cells. This illustration was created using Biorender.

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DISCUSSION

Clinicopathological Aggressiveness of Indonesian TNBC

The clinicopathological profiles of Indonesian TNBC patients show different levels of aggressiveness because they present at a younger age (47–49 years) and have many grade III tumors with necrosis and lymphovascular invasion. The study supports previous regional findings which show breast cancer affects young women predominantly and TNBC occurs frequently in women under 40 years old.[9] Studies from Yogyakarta and Jakarta confirm that more than 60% of TNBC cases are diagnosed at advanced stages, indicating that delayed detection, combined with biologically aggressive subtypes, contributes to poor prognosis among Indonesian women.[20] These clinicopathological traits resemble global data in which TNBC commonly shows a high mitotic index, poor differentiation, and early visceral metastasis to the lungs and brain.[2] The international datasets show TNBC diagnosis at age 50, but Indonesian studies show TNBC cases appear at ages 45 to 49, with many cases developing before age 40.[8] Differences in age at diagnosis observed between Western populations and Indonesian patients could result from genetic, environmental, reproductive, and health system access factors. In addition to these clinicopathological features, histologic heterogeneity is a strong determinant of prognosis and treatment response. Solid, medullary, apocrine, and metaplastic types of TNBC have varying levels of immune cell infiltration and PD-L1 expression.[21] For example, what is known as Medullary-like TNBC shows very dense lymphocytic infiltration as well as very strong expression of PD-L1, Conversely, metaplastic subtypes tend to have very little immune infiltration and show high frequencies of immune checkpoint therapy resistance. The morphological diversity seen is what makes it necessary to combine both the histological and molecular approaches to checking the expression of PD-L1 in the Indonesian population of TNBC cases.

Heterogeneity of PD-L1 Expression and Immune Landscape

PD-L1 expression in TNBC varies widely from 21% to 58% among Indonesian cohorts, consistent with international findings.[22] Such heterogeneity manifests a feature observed in TNBC at the molecular level, where TNBC is composed of various subtypes such the BLIA, BLIS, MES, and LAR subtypes.[4] PD-L1 expression is typically higher in basal-like immune-activated tumors and is correlated with greater TIL activity and improved outcomes in patients receiving immune checkpoint inhibitors.[23]

However, the degree of PD-L1 variability in space and time, for example, as it relates to diagnosis, should be taken into consideration. In 2022, a multicenter study demonstrated that about 30% of TNBC patients who tested PD-L1 negative on their core biopsies would test PD-L1 positive by excisional specimen. This study demonstrates that when considering the type of tissue sample used to assess PD-L1 via IHC, the results could be altered due to the differences in the samples.[24] Additionally, PD-L1 has also been shown to have a relationship between tumor grade and CD8+ TILs density; however, the levels of circulating sPD-L1 do not have a significant association with tissue PD-L1 expression, indicating that PD-L1 levels are indicative of systemic inflammation versus tumor-specific PD-L1 expression.[25] Therefore, these studies emphasize the importance of selecting tissues carefully, using validated antibodies, and implementing a standard method of scoring PD-L1 in order to evaluate PD-L1 consistently. It is critical to standardize methods of evaluating PD-L1 in various laboratories across Indonesia in order to make comparisons possible. Across Indonesian studies, higher PD-L1 expression frequently accompanies aggressive pathological features, but PD-L1 alone is not a consistent prognostic marker. Its clinical relevance becomes clearer when evaluated together with TILs density and immune-cell ratios, which better reflect the balance between effector and suppressive immunity.

Tumor Microenvironment Composition and Immune Ratios

TNBC, the immune microenvironment reveals a complex equilibrium between immune suppressors and immune killers. More prolonged disease-free survival in Indonesian cohorts with TNBC has been associated with increased CD8/CD163 and CD4/FOXP3 immune cell ratios, suggesting the relative balance between cytotoxic and immune-suppressor players may impact prognosis.[26] The density of TILs continues to be a strong prognostic factor in numerous studies.[27]

The process of how macrophage polarization affects the tumor micro-environment has been extensively studied recently. Activation of M1 type macrophages, mediated by up-regulated levels of IFI35, PSMB9, and SAMD9L gene expression, can improve the body's anti-tumor immunity.[28] Conversely, the function of MCSF-1 for attracting M2 type macrophages, associated with tumor progression and immune suppression, is well established.[29]

In addition to T-cells and macrophages, B-lymphocytes also regulate the immune response in various ways. Clonal, antigen-specific expansion of tumor-infiltrating B-cells (TIL-B) into tertiary lymphoid structures contributes to the humoral immune response and improved prognosis.[30] These clusters indicate organized lymphoid development, including the cooperation between T and B cell populations, suggesting TNBC is an immunogenic tumor subtype.

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Integrative Links Between Histopathology, PD-L1, and Tumor Microenvironment

An integrated model of PD-L1 expression, histological characteristics, and tumor immune infiltration provides the basis for understanding how TNBC progresses. High-grade tumors show immune infiltration and increased PD-L1 expression, indicative of exhausted immune responses.[23] Regions of necrosis and peritumor inflammation are associated with localized increases in PD-L1 expression.[2]

Subtyping of TNBC based on androgen receptor (AR), CD8, FOX C1 and DCLK1 by immunohistochemistry can classify tumors into four types, LAR (luminal androgen receptor), IM (immunomodulatory), BLIS and MES. The frequent presence of necrosis and lymphovascular invasion in Indonesian TNBC cases suggests chronic intratumoral hypoxia, which aligns with HIF-1α–mediated upregulation of PD-L1 and supports an immunosuppressive microenvironment. The IHC classification corresponds with previously established transcriptome-based classifications and provides prognostic information.[31] A similar pattern was seen in Indonesian samples, where BLIA tumors demonstrated high levels of PD-L1 expression and strong lymphocytic infiltration.[32] These data support the utility of IHC-based molecular subtyping as a practical and cost-effective means to replace genomic testing in clinical settings in developing countries.

Molecular Mechanisms of PD-L1 Upregulation and Immune Evasion

Oncogenic signaling pathways, as well as the microenvironment of the tumor, both have a part in the regulation of PD-L1 expression. HIF-1α, an important mediator of hypoxic responses, binds to the PD-L1 gene promoter, leading to the increased transcription of PD-L1 and consequent immune escape.[33,34] The oncogene MYC has a bidirectional function by simultaneously increasing PD-L1 and CD47 expression, which results in the blockade of T cell cytotoxicity and macrophage phagocytosis.[35] Activation of the PD-1 pathway results in exhaustion of T cells and a decrease in their anti-tumor activity.[36] Moreover, the CSF-1/CSF-1R axis attracts immune suppressive macrophages into the tumor microenvironment, which helps the tumor maintain immune evasion.[29]

Correlation Between Histopathological Features, PD-L1 Expression, and Metastatic Profiles

Triple Negative Breast Cancer (TNBC) has a high propensity to cause an early metastasis to a variety of organs and tissues at distant sites by creating premetastatic niches through a process that is poorly understood; PD-L1 supports immune evasion of disseminated circulating tumor cells.[38] Genomic analysis suggests that TNBC can undergo EMT at an early stage and thus lead to widespread metastasis throughout the body prior to the primary site becoming enlarged.[39] It appears that basal-like types of TNBC have a predilection for metastasizing to the lungs and brain, suggesting regional and global metastasis.[2,20]

Inter-cellular adhesion molecule-1 (ICAM-1) has been shown recently to be a critical component in the metastatic process of TNBC. ICAM-1 contributes to metastasis via two mechanisms: 1) direct interaction with EGFR, activating JAK1/STAT3 signaling and causing EMT, increasing migration and invasion of TNBC cells[40]; and 2) integrin-mediated TGF-β/EMT signaling promoting bone tropism and osteolytic lesions seen in TNBC metastasis.[41] These ICAM-1–driven pathways correspond with the metastatic patterns reported in Indonesian cohorts, where lung and bone involvement predominate, suggesting that EMT activation and integrin-mediated niche formation may underlie organ-specific dissemination in these patients. These mechanisms provide a biological rationale for the predominance of lung and bone metastasis seen in Indonesian TNBC patients, and identify ICAM-1 as a potential target for therapy to prevent metastatic disease.

Therapeutic Implications and Immunotherapy Response

Translational medicine has created new therapeutic opportunities for TNBC. For instance, PD-L1 positive patients respond well to immune checkpoint inhibitors atezolizumab and pembrolizumab with a focus on chemotherapy.[42,43] Similarly, poly-ADP ribose polymerase (PARP) inhibitors olaparib and talazoparib are most effective in patients with BRCA1 or BRCA2 mutations .[44,45]

The more exclusive the therapeutic options can be, the more effective they will be when utilizing molecular subtyping and genomic profiling. For example, one study found that the immunomodulatory TNBC subtype is more responsive to programmed death-1 (PD-1) blockade than other subtypes.[46] Additionally, there may be alternative combinations of immunotherapy and PARP inhibitors or M1 phenotype macrophage repolarization.[28]

Current Gaps and Future Directions for TNBC Research in Indonesia

The research on TNBC in Indonesia faces challenges because of the absence of standardized PD-L1 testing protocols and irregular molecular subtyping practices. The implementation of immunohistochemical panels, which include AR, CD8, FOXC1, and DCLK1 markers, together with immune ratio assessments of CD8/CD163 and CD4/FOXP3, will enhance both predictive value and treatment selection for patients. The addition of macrophage and B-cell markers, including IFI35 and IgG-biased TIL-B profiles, to future biomarker panels will help scientists better understand immune system patterns.

Standardization of tissue processing, antibody selection, and PD-L1 scoring across Indonesian laboratories is critical to achieve better data consistency and determine

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treatment eligibility. The upcoming research on TNBC in Indonesia needs to focus on programmed death-ligand 1 (PD-L1) and tumor microenvironment analysis as its main research objectives. The evaluation of PD-L1 expression combined with spatial and functional immune mapping could reveal biomarkers which predict how patients will respond to immunotherapy. The standardization of PD-L1 testing across multiple centers together with molecular subtype analysis and clinical outcome assessment will enhance Indonesia's role in worldwide TNBC research.

CONCLUSION

Indonesian TNBC cases demonstrate aggressive pathological characteristics, including high-grade morphology, rapid proliferation, and a strong tendency for early and widespread metastasis. Although PD-L1 expression varies widely across studies, this variability reflects differences in tumor biology as well as methodological variations in antibody selection and scoring systems. The prognostic impact of PD-L1 is limited when used in isolation; its interpretation becomes more clinically meaningful when evaluated together with immune-cell ratios such as CD8/CD163 and CD4/FOXP3, which better represent the functional balance within the tumor microenvironment. Future research in Indonesia should integrate PD-L1 assessment with spatial and functional immune profiling to develop more reliable biomarkers for immunotherapy. Establishing standardized PD-L1 testing protocols and incorporating immune-based molecular classification will be essential to advance precision oncology for TNBC patients in Indonesia.

IMPLICATION

The research results demonstrate that Indonesian TNBC requires standardized biomarker evaluation methods. The wide variation between PD-L1 expression levels and immune microenvironment components makes PD-L1 an inadequate prognostic marker when used without measuring CD4/FOXP3 and CD8/CD163 immune cell ratios. The implementation of standardized PD-L1 testing methods together with immune-based molecular classification will enhance both prognostic results and immunotherapy treatment selection. The research findings demonstrate the need to establish PD-L1 profiling and immune ratio evaluation and standardized histopathological reporting as standard clinical procedures to enhance precision oncology in Indonesia.

STRENGTHS AND LIMITATIONS

This review provides a comprehensive synthesis of TNBC data from multiple regions in Indonesia, o create a national understanding of PD-L1 expression patterns and tumor characteristics and immune cell distributions. The review process achieves better methodological clarity through the use of PRISMA and PECO frameworks. The results from different studies become difficult to compare because researchers used different methods to evaluate PD-L1 and report immune marker results. The review faces challenges because different study approaches and available data points make it difficult to create equivalent comparison points. Future Indonesian TNBC research needs to establish standardized biomarker testing and reporting methods because current limitations affect study results.

CONFLICT OF INTEREST

The authors declare no conflict of interest. There are no financial or personal relationships that could have influenced the work reported in this manuscript.

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DECLARATION OF USING AI

Artificial intelligence (AI) tools were used only for language refinement and formatting, not for scientific content. All scientific content, interpretation, and conclusions were developed entirely by the authors.

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