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Low Immunoscores CD3/CD8 and CD3/CD45RO are Associated with The Low Survival Rate of Triple Negative Breast Cancer Patients

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ABSTRACT

Aim: Triple-negative breast cancer (TNBC) is associated with a highly aggressive clinical course, contributing to poorer patient outcomes and higher mortality rates. Current prognostic tools do not fully capture the complexities of the tumor immune microenvironment, particularly the role of effector lymphocytes (CD3, CD8, and CD45RO). Therefore, this study was conducted to investigate the prognostic significance of the immune markers CD3, CD8, and CD45RO within the tumor microenvironment of TNBC patients. **Methods:** This retrospective cohort study involved women aged >18 years old diagnosed with TNBC. Immunohistochemistry (IHC) for CD3, CD8, and CD45RO was performed using the Novolink system. Two pathologists independently assessed cell density in the tumor center (CT) and invasive margin (IM). Densities were classified as high or low using ROC curves, and the immunoscores (CD3/CD8, CD3/CD45RO) were grouped into low (I0, I1) and high (I2, I3, I4). Two-year mortality and clinical data were collected from medical records. Survival rates were analyzed using Kaplan-Meier and compared with the log-rank test. **Results:** The 2-year survival rate for TNBC patients was 58.3%, with a mean survival time of 18.95 months. Low CD3/CD8 was associated with significantly lower survival compared to high CD3/CD8 (42.9% vs. 73%; p=0.013), with mean survival times of 17.03 vs. 20.80 months. Similarly, low CD3/CD45RO had lower survival than high CD3/CD45RO (38.5% vs. 69.6%; p=0.01), with mean survival times of 16.37 vs. 20.43 months. **Conclusion:** Low CD3/CD8 and CD3/CD45RO immunoscores are associated with low survival in TNBC patients.

Keywords: CD3/CD8 immunoscore, CD3/CD45RO immunoscore, survival, triple negative breast cancer.

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INTRODUCTION

Breast cancer is one of the most common cancer in women with a high mortality rate. Globocan data in 2020 showed that about 2.2 million new cases of breast cancer were diagnosed globally[1], which represents around 11.7% of all cancer cases. As many as 24% of all breast cancer cases in the world were reported in Asia Pacific with an incidence rate of 30 cases per 100,000 population. Indonesia ranks third in Asia by accounting for 12% of breast cancer cases.[2]

Triple negative breast cancer (TNBC) is a subtype of breast cancer with no expression of estrogen, progesterone, and human epidermal receptor-2 (HER-2). This subtype not only has more aggressive characteristics than the others but also has a poorer prognosis.[3] This is also supported by the theory that TNBC is the most immunogenic breast cancer with the fastest evolving and adapting capability.[4] There are several studies which designed predictive models for survival of TNBC, including clinicopathological criteria and the American

Joint Committee on Cancer (AJCC) TNM. However, the diagnostic values of these model were less significant.[5]

A more specific prognosis predictor system based on immunity profile is needed, especially to predict mortality of TNBC patients. The immune profile of the cancer microenvironment is an important factor to progressivity and prognosis of TNBC through increased effectiveness of chemotherapy. In TBNC cases, hormonal therapies and HER2-targeted treatments tends to be unresponsive due to the absence of estrogen receptors, progesterone receptors, and HER2 amplification.[6]

Tumor immune microenvironment plays a critical role in the progression and treatment response of TNBC. Within the tumor environment, neutrophils (as well-recognized important regulators of cancer progression) impact the immune response by switching between pro-tumor and anti-tumor activities. Other leukocyte types then gather neoantigens from the destroyed cancer cells, triggering an immune response against the tumor. These immune cells work together in a complex way to influence cancer development and patient prognosis.[6] One type of leukocyte, lymphocyte, has become a strong candidate in the development of TNBC mortality predictor models.[4]

Effector lymphocytes can be identified by three key CD markers: CD3 (a general lymphocyte marker), CD8 (cytotoxic T-lymphocytes), and CD45RO (memory T-cells). The combination of CD3/CD8 and CD3/CD45RO is commonly referred to as the immunoscore. In particular, tumor-infiltrating lymphocytes (TILs), including CD3+ T cells, CD8+ cytotoxic T cells, and memory T cells marked by CD45RO, are important indicators of the immune response against the tumor. Higher levels of these lymphocytes, especially CD8+ T cells, have been associated with better clinical outcomes, as they contribute to the immune system's ability to recognize and eliminate cancer cells. Evaluating the presence and activity of lymphocytes in TNBC tumors may help guide prognosis and therapeutic strategies, as immunotherapy emerges as a promising approach for treating this challenging cancer.[6]

Even though several biomarkers have been reported to help clinician to making prognosis and determining the potential treatment modalities for TNBC cases. Unfortunately, currently available prognostic tools do not fully capture the complexities of the tumor immune microenvironment, particularly the role of effector lymphocytes (CD3, CD8, and CD45RO), and there were only limited information regarding this issue. This creates an urgent need to explore alternative prognostic tools, such as the role of the immune system in TNBC progression. Given the potential benefits of utilizing immunoscores in TNBC, further research is essential to investigate how CD3/CD8 and CD3/CD45RO immunoscores might impact the survival of TNBC patients. Therefore, this study was conducted to address this gap and evaluate the prognostic value of these markers in TNBC patients' survival.

METHODS

This retrospective cohort study was conducted to evaluate the survival of TNBC patients receiving neoadjuvant chemotherapy, based on CD3/CD8 and CD3/CD45RO immunoscores. The study was carried out at Prof. Dr. I.G.N.G. Ngoerah Denpasar General Hospital and Prima Medika Private Hospital in Denpasar, Bali. Subjects were observed from diagnosis for up to 24 months, with data collected from medical records and the Indonesian Surgical Oncology Society cancer registry. The recruitment period spanned from

January 2020 to January 2022, while subject observation was conducted from 2022 to 2024.

The study included women aged >18 years old who were diagnosed with TNBC based on histopathological and immunohistochemical examinations, had received neoadjuvant chemotherapy, and had paraffin blocks that was readable and not defective. Subjects with relapse cases, a history of other malignancies, immunodeficiency disorders, and death caused by other diseases were excluded from the study. The protocol of this study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Udayana (No. 1045/UNI4.2.2.VII.14/LT/2023).

The tumor samples from both the tumor center (CT) and invasive margin (IM) were processed for immunohistochemical examinations using primary antibodies against CD3 (catalogue number: [PA0553], monoclonal, mouse), CD8 (catalogue number: [PA0183], monoclonal, mouse), and CD45RO (catalogue number: [PA0146], polyclonal, rabbit) based on the Novolink Min Polymer Detection system (Novacastra, Leica Biosystem Newcastle Ltd, UK). Chromogen DAB (3,3'-diaminobenzidine tetrahydrochloride) was applied to the specimens, followed by staining with hematoxylin.

Density evaluation of CD3, CD8, and CD45RO on CT and IM was performed independently by two certified pathologists at 40x magnification. The area for density measurement was selected based on the most representative regions of the tumor as identified by the pathologists. For this, the double-blind process involved the pathologist collecting data without knowledge of the subjects' outcome (whether they survived or not). The selected spots were then photographed using a lens connected to the microscope. From these photographs, the analysis was performed and the density was quantified by counting the number of cells per mm^2.

The data was provided as a single dataset from the pathology lab of Prof. Dr. I.G.N.G. Ngoerah Denpasar General Hospital, as the hospital issues one result per examination. A ROC curve was used to classify CD3, CD8, and CD45RO densities in CT and IM as high or low. The cut-off values used for categorizing immunoscores into high and low groups were defined as follows: CD3 in the CT at 16.5 cells/mm^2, CD3 in the IM at 41 cells/mm^2, CD8 in the CT at

15.5 cells/mm^2, CD8 in the IM at 24.5 cells/mm^2, CD45RO in the CT at 30.5 cells/mm^2, and CD45RO in the IM at 23 cells/mm^2. The optimal cut-off value was determined using the Youden Index, and sensitivity, specificity, area under the curve (AUC), and 95% confidence interval (95% CI) values were reported (Table 1). Immunoscores for CD3/CD8 and CD3/CD45RO were classified into two groups: low values (I0 and I1) and high values (I2, I3, and I4). To ensure accuracy and minimize bias, both pathologists underwent certification and were blinded to the clinical outcomes during their evaluations, and it was confirmed that the hospital laboratory is certified and standardized for CD3, CD8, and CD45RO measurements

The assessment of 2-year mortality status was conducted based on medical record. The mortality data was collected from the subjects' medical records during their last visit to the clinic or hospital. This data included death certificates, and in some cases, coordination was done by contacting the subjects' family by phone to confirm whether the patient was still alive or had passed away.

Other data such as age, menopausal status, number of parities, stage, tumor size, lymph node spread, distant metastases, histopathologic type, grade, TIL and

lymphovascular invasion (LVI) were also collected from medical records.

All statistical analysis processes were carried out with the Statistical Package for Social Science (SPSS) program. In this study, data analysis consisted of univariate, bivariate, and multivariate analysis. Descriptive analysis was conducted to describe the characteristics data of TNBC patient. Kaplan-Meier analysis was used to calculate survival rate. The comparison of survival rate was calculated using log-rank test.

The cox proportional hazard regression test aimed to assess the association (adjusted) of each independent variable to the survival of TNBC patients by controlling for confounding variables. Hazard Ratio was presented as a measurement of risk. The inference process was initiated with a confidence level of 95% and a value of $p<0.05$.

RESULTS

This study included 72 TNBC patients, with 30 dying and 42 surviving over a 2-year survival period. There were no significant differences in age, parity, menopausal status, tumor size, lymph node involvement, distant metastases, histopathologic type, grade, TIL, LVI based on mortality status within 2 years ($p>0.05$). The basic characteristics of the sample were presented in **Table 1**. Additionally, the immunoscore was calculated by comparing intratumoral and tumor margin samples. However, no data on significant differences in immunoscore between these two populations is presented in this study. For future research, it would be valuable to assess whether there are significant differences in immunoscore between intratumoral and tumor margin samples to improve sampling strategies and better understand the tumor's immune environment.

Table 1. Characteristics of Research Sample.

Variables	Mortality		P value
	Died (N=30)	Alive (N=42)	
Age			0.732
≥40 years	25 (83.3%)	37 (88.1%)	
<40 years	5 (16.7%)	5 (11.9%)	
Parity			0.214
1-3	13 (43.3%)	10 (23.8%)	
>3	13 (43.3%)	25 (59.5%)	
Missing data	4 (13.3%)	7 (16.7%)	
Menopause			0.513
Pre-menopause	17 (56.7%)	27 (64.3%)	
Post-menopause	13 (43.3%)	15 (35.7%)	
Tumor size (T)			1.000
T1-T2	3 (10%)	5 (11.9%)	
T3-T4	27 (90%)	37 (88.1%)	
Lymph node involvement (N)			1.000
N0	2 (6.7%)	3 (7.1%)	
N1-2	28 (93.3%)	39 (92.9%)	
Distant metastasis (M)			0.848
M0	23 (76.7%)	33 (78.6%)	
M1	7 (23.3%)	9 (21.4%)	
Histopathological type			0.288
NST	28 (93.3%)	35 (83.3%)	
Others	2 (6.7%)	7 (16.7%)	

Grade			0.765
Low (1-2)	9 (30%)	14 (33.3%)	
High (3)	21 (70%)	28 (66.7%)	
TIL			0.814
Positive	26 (86.7%)	34 (81%)	
Negative	2 (6.7%)	4 (9.5%)	
Missing data	2 (6.7%)	4 (9.5%)	
LVI			0.214
Positive	13 (43.3%)	10 (23.8%)	
Negative	13 (43.3%)	25 (59.5%)	
Missing data	4 (13.3%)	7 (16.7%)	

The 2-years overall survival (OS) of TNBC patients in this study was 58.3%. The mean survival time was 18.95 months. The low immunoscore CD3/CD8 group had a significantly lower 2-year survival than the high immunoscore CD3/CD8 group (42.9% vs. 73%; p=0.013).

The mean survival time of the high immunoscore CD3/CD8 group was 20.80 months and the low immunoscore CD3/CD8 group was 17.03 months (Figure 1). The low immunoscore CD3/CD45RO group also had significantly lower 2-year survival than the the high immunoscore CD3/CD45RO group (38.5% vs 69.6%; p=0.01). The mean survival time in the high immunoscore CD3/CD45RO group was 20.43 months, while in the low immunoscore CD3/CD45RO group it was 16.37 months (**Figure 1**).

Figures 3 and **Figure 4** illustrate the density evaluation of CD3-positive cells under 40x magnification, with red arrows indicating stained cells. These figures demonstrate the histological differences in CD3-positive cell infiltration, which were quantified to determine the immunoscores used in the survival analyses.

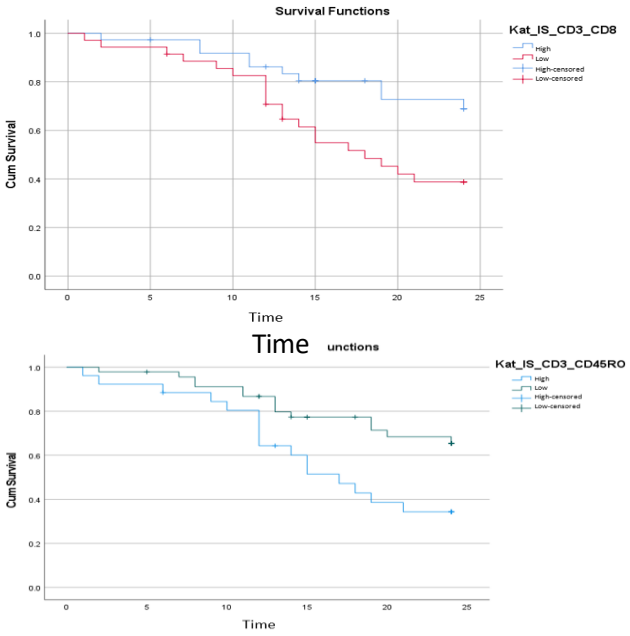

Figure 1. Kaplan Meier Survival Curve Based on Immunoscore CD3/CD8 and CD3/CD45RO

Table 2. Immunoscore CD3/CD8 and CD3/CD45RO Based on 2-Years Mortality.

Variable	2-Years Mortality		P value
	Died (N=30)	Alive (N=42)	
Immunoscore CD3/CD8			0.01
Low	20 (66.7%)	15 (35.7%)	
High	10 (33.3%)	27 (64.3%)	
Immunoscore CD3/CD45RO			0.01
Low	16 (53.3%)	10 (23.8%)	
High	14 (46.7%)	32 (76.2%)	

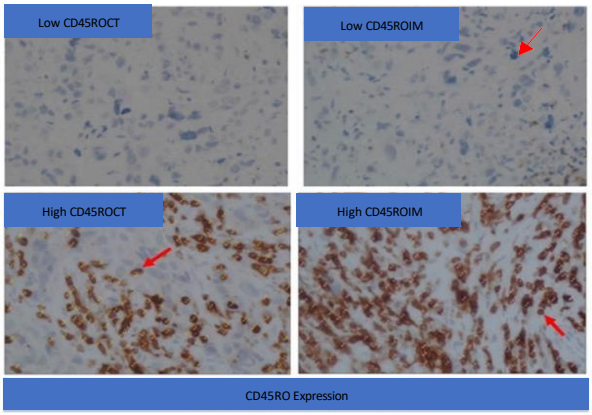

Figure 2. Density evaluation of CD45RO at 40x magnification. The red arrow indicates stained cells.

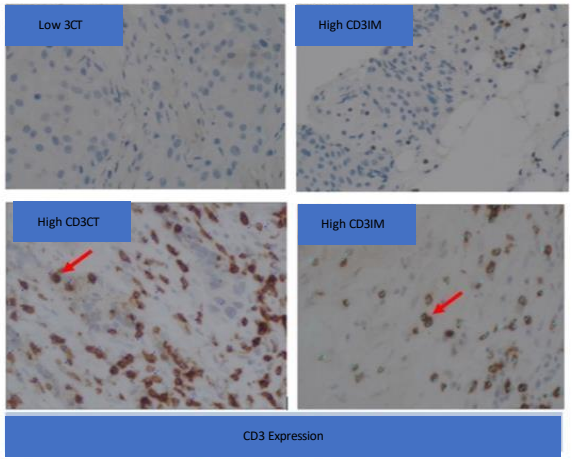

Figure 3. Density evaluation of CD3 at 40x magnification. The red arrow indicates stained cells.

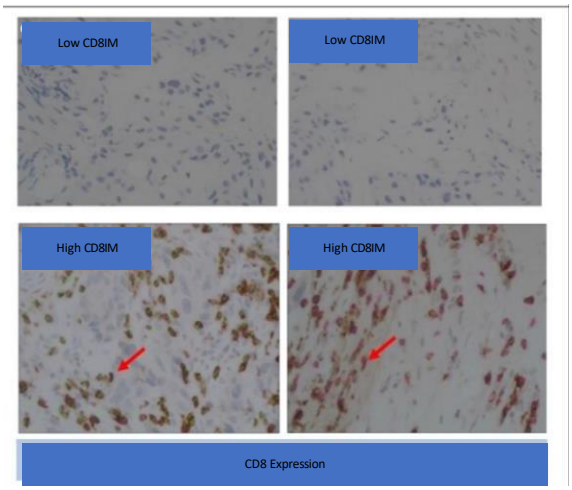

Figure 4. Density evaluation of CD3 at 40x magnification. The red arrow indicates stained cells.

Bivariate analysis revealed the significant association between CD3/CD8 and CD3/CD45RO immunoscores and 2-year mortality of patients (**Table 2**).

We cannot perform further statistical analysis by classifying the 72 subjects based on combinations of Low CD3/CD8, High CD3/CD8, Low CD3/CD45RO, and High CD3/CD45RO, and then determining whether those subjects were alive or deceased within 2 years, cannot be fulfilled due to the small sample size in the mortality group (n=30). Conducting this classification with such a limited number of subjects would yield insufficient data for meaningful statistical analysis. Additionally, the suggestion to perform similar analysis for Table 2 by separating the dead (n=30) and alive (n=42) subjects based on clinical variables faces the same limitation. Instead, we have relied on the existing tables and analyses, which provide a more comprehensive and statistically valid representation of the data. This ensures that the findings remain reliable without over-fragmenting the sample.

DISCUSSION

Triple Negative Breast Cancer (TNBC) is characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and HER-2 receptors, making it resistant to hormonal and HER-2 targeted therapies.[11] In this study, survival rate in TNBC patients was lower than in previous studies. A study with 133 months of follow-up noted 30.9% mortality and 38% disease progression.[12] Another found 5-year overall survival (OS) and disease-free survival (DFS) rates of 73.7% and 67%, respectively, with age, tumor size, and lymph node involvement significantly affecting outcomes.[13]

CD8 T cells are key players in the tumor-infiltrating lymphocyte (TIL) population and tumor immune microenvironment (TIME).

They act as cytotoxic cells, directly killing cancer cells, while CD4 T cells regulate their function. TNBC tumors have higher CD8 expression, which correlates with increased interferon (IFN)-γ responses and enhanced anti-tumor immune activity. IFN-γ also induces apoptosis, inhibits angiogenesis, and activates macrophages.[14,15,16] CD8 T cells eliminate tumor cells through granule release—containing granzyme, perforin, and granulysin—that penetrate target cell membranes, either via direct fusion or endocytosis. Additionally, they express Fas ligand (FASL), which activates apoptosis by engaging with Fas receptors on target cells, leading to caspase activation and DNA fragmentation.[16,17]

In addition to CD8, CD3 T cells are also directly related to tumor microinvasion status.4,18 This study observed that patients with low CD3/CD8 immunoscores had worse 2- year survival compared to those with high immunoscores, contrasting with earlier studies where immunoscores showed no significant correlation with survival. A limited sample size, especially in stages IIB and III, might explain these discrepancies.[19] Higher pathological complete response (pCR) rates were observed in patients with high CD3/CD8 immunoscores, reinforcing their prognostic value.[20]

CD45RO memory T cells are another crucial component of TIL.[21] They help generate long-term immune memory after antigen recognition by converting naïve CD45RA T cells into mature CD45RO T cells. These memory cells can be classified into central memory (Tcm) and effector memory (Tem) cells, with Tcm migrating to lymph nodes and Tem remaining in tumor sites for immediate response.[22,23,24] When cancer antigens are detected, these Tem cells can immediately perform effector functions to kill tumor cells without the need for further differentiation. Conversely, Tcm cells lack of effector function, therefore it differrentiate immediately into Tem cells after restimulation by antigens.[25] This mechanism confirms that the role of CD45RO memory T cells is highly dependent on CD8 T cells as effector cells.

In this study, patients with low CD3/CD45RO immunoscores had worse 2-year survival compared to those with high scores, consistent with prior research linking higher CD45RO density to better OS and DFS.[25,26] High expression of CD45RO has been associated with improved immune responses, reducing the likelihood of residual tumors or metastases.[27] However, CD45RO density is not universally predictive. For example, in renal cell carcinoma (RCC), higher CD45RO density correlated with poorer prognosis, likely due to dysfunctional TILs unable to mount effective anti-tumor responses.[27,29]

This study faced several limitations. Incomplete data introduced potential bias, as missing data were not excluded to preserve sample size. Manual calculation of CD3, CD8, and CD45RO densities—despite efforts to minimize discrepancies—may have introduced variability. Additionally, the lack of sufficient follow-up prevented the evaluation of DFS and RFS. Future research should address these limitations by increasing sample sizes and conducting multi-center collaborations. Automated immune cell quantification techniques would improve accuracy, reducing bias. Longitudinal studies are needed to better assess survival outcomes and understand the role of TILs, especially CD8+ T cells. Exploring immune checkpoint inhibitors could also provide insights into novel therapeutic strategies for TNBC.

CONCLUSION

Low CD3/CD8 was associated with significantly lower survival compared to high

CD3/CD8. Similarly, low CD3/CD45RO had lower survival than high CD3/CD45RO. This study proves that immunoscores CD3/CD8 and CD3/CD45RO can predict the survival in TNBC patients.

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DISCLOSURE

The author stated that there was no conflict of interest. SVM, IBS, and PATA were involved in concepting and planning the research, SVM performed the data acquisition/collection, calculated the experimental data and performed the analysis. SVM and IGBS drafted the manuscript and designed the figures, interpreting the results. IBS, PATA, IGBS, took parts in giving critical revision of the manuscript.

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