

Survival Analysis of TNBC Subtype Breast Cancer Based on Clinicopathology at Prof. Dr. I.G.N.G Ngoerah Hospital Denpasar

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ABSTRACT

Introduction: Triple-negative breast cancer (TNBC) is a subtype of breast cancer that has worse clinical outcomes and contributes to 30% of breast cancer deaths. Management targets focus on inhibiting progression and improving patient survival. Therefore, this study aims to identify factors that influence the survival of TNBC subtype breast cancer patients at Prof. Dr. IGNG Ngoerah Hospital Denpasar. **Methods:** This study used a retrospective cohort design, using medical record data and the Cancer Registry of TNBC subtype breast cancer patients who were treated at Prof. Dr. IGNG Ngoerah Denpasar Hospital from January 1, 2017, to December 31, 2021. The variables studied included age, menstrual status, tumor size, lymph node status, metastasis, tumor stage, tumor grading, lymphovascular invasion (LVI), and tumor-infiltrating lymphocyte (TIL). Data analysis was performed using Kaplan-Meier and Cox regression methods. **Result:** A total of 113 patients were included in this study. The majority of patients were >40 years old (85%). The median survival of TNBC subtype breast cancer patients was 42 months (95% confidence interval [CI] = 38.31-46.32). Factors associated with TNBC subtype breast cancer patient survival were T stage (hazard ratio [HR] = 3.10; 95% CI = 1.393-6.904; p=0.006), N stage (HR=1.56; 95% CI=1.003-2.443; p=0.048), metastasis (HR=4.07; 95% CI=2.310-7.191; p<0.001), and tumor stage (HR=1.57; 95% CI=1.312-1.897; p<0.001). Age, menstrual status, tumor grading, LVI, and TIL were found to have no significant effect on patient survival. **Conclusion:** Age, tumor size, lymph node status, metastasis, stage, grading, and LVI are factors that influence the survival of TNBC subtype breast cancer patients in TNBC subtype breast cancer patients treated at Prof. Dr. IGNG Ngoerah Hospital Denpasar.

Keywords: breast cancer; prognostic factors; survival; TNBC.

INTRODUCTION

Triple-negative breast cancer (TNBC) occurs in 10%-20% of breast cancers, tends to occur in younger women, and has the poorest prognosis when compared to ER-positive (and/or PR-positive) and HER2-positive. TNBC is a highly differentiated, aggressive breast cancer with a high incidence of metastasis and is associated with poorer outcomes than other breast cancer subtypes. Every year, about half a million women die from breast cancer, and 150,000 of them are estimated to be TNBC cases, representing about 30% of deaths caused by breast cancer. The high mortality rate in TNBC cases may be due to the fact that this type of breast cancer is the only one that does not have a recognized adjuvant therapy. When faced with a case of TNBC, the therapeutic management performed by the oncology surgeon will be limited to surgery, radiotherapy, and chemotherapy (Saraiva et al., 2017). Manipulation of the primary tumor can trigger metastasis; therefore, focusing on inhibiting progression and improving patient survival is the target of TNBC management that is currently receiving attention from medical personnel and researchers (Mori et al., 2017).

Patient age at first diagnosis is an important prognostic factor for breast cancer in general. TNBC primary tumors are often larger, with higher grading, and progress more rapidly compared to other molecular subtypes. Research in the United States shows that TNBC breast cancer has a 4.34 times higher mortality risk than non-TNBC patients (Xiao et al., 2016). Data centers in Peru showed that event-free survival (EFS) in 3, 5 and 10 years was 55%, 49%, and 41%, with overall survival (OS) of 64%, 56%, and 47%. Higher lymph node (N) and tumor (T) status and older age at diagnosis were associated with worse survival (Del-la-Cruz-Ku et al., 2020).

TNBC develops in younger women and is biologically and clinically different from TNBC in older women. The prognosis of TNBC has also not been clearly analyzed, whether there are differences based on age at initial diagnosis. Some previous studies have shown that age can be a prognostic factor for patients with TNBC subtype breast cancer. However, some studies cannot prove age is an independent prognostic factor in all breast cancers.

Given the poor prognosis of TNBC subtype breast cancer and the association of early detection with patient length of life, this study is important to assess the length of life and prognosis factors associated with the survival of breast cancer patients with TNBC subtype. These various reasons make the author interested in conducting research at Prof. Dr. IGNG Ngoerah Hospital Denpasar.

METHODS

This study is an analytical observational study with a retrospective cohort design. The data used in this study are secondary data obtained from medical record data and data from the Bali Cancer Registry Data for triple-negative breast cancer patients undergoing treatment at Prof. Dr. IGNG Ngoerah Hospital Denpasar from January 1, 2017, to December 31, 2021.

The research sample is a subject taken from an affordable population that meets the inclusion criteria and is not included in the exclusion criteria. The inclusion criteria were all patients with TNBC subtype breast cancer from January 1, 2017, to December 31, 2021, who had complete data and were confirmed by histopathological and immunohistochemical examinations. Exclusion criteria were patients with incomplete clinical and histopathological data in medical records, having a history of other malignancies, subjects who could not be contacted for data completeness, and mortality caused by other diseases.

The independent variables in this study were age, menstrual status, tumor size, nodes, metastases, stage, tumor grading, LVI, and TIL. The dependent variables in this study were mortality status and length of survival. Triple-negative breast cancer was defined as breast cancer with subtypes of estrogen receptor-negative, progesterone receptor-negative, and HER2-negative. Tumor size was the length of the breast lump measured by physical examination or radiological examination using the AJCC classification.

Lymph node enlargement is the presence of lymph node enlargement from physical examination or radiologic examination. Tumor grading is a scoring system that states the level of appearance of cancer cells compared to normal cells. Tumor-infiltrating lymphocyte (TIL) is a T cell-mediated tumor cell recognition of tumor antigens. Lymphovascular invasion (LVI) is the invasion of cancer into blood and/or lymphatic vessels.

Univariate analysis was performed to see the frequency distribution of characteristics of TNBC subtype breast cancer patients, and all research variables were displayed in the form of frequency and percentage tables. Data analysis was performed with the SPSS and R programs. Median survival was determined by the Kaplan-Meier method; analysis to assess prognostic factors was carried out using the Cox proportional hazard regression model with 95%CI confidence limits, and statistical calculations were carried out with the SPSS program. Of all the prognostic factors studied, only significant factors ($p < 0.05$) were taken. Then, calculations were carried out again on the influential factors only to obtain a survival model. All statistical analyses were performed using SPSS software (version 25.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of Research Subjects

This study obtained a total of 217 patients, including 113 patients with TNBC subtype breast cancer who underwent treatment at Prof. Dr. IGNG Ngoerah Hospital in the period January 1, 2017-December 31, 2021. The characteristics of the study subjects can be seen in Table 1. The study subjects were dominated by age over 40 years (85%), postmenopause (50.4%), stage T4 (44.2%), N1 (59.3%), M0 (77.0%), stage III B (29.2%), negative LVI (61.9%), and low positive TIL (40.7%). The 5-year survival of the study subjects was 55.8%.

TABLE 1: Characteristics of Research Subjects.

Variable	n=113
Age, n (%)	
<40 years	17 (15,0)
>40 years	96 (85,0)
Menopausal Status, n (%)	
Premenopause	56 (49,6)
Postmenopause	57 (50,4)
T Stage, n (%)	
1	2 (1,8)
2	30 (26,5)
3	31 (27,4)
4	50 (44,2)
N Stage, n (%)	
0	24 (21,2)
1	67 (59,3)
2	22 (19,5)

Variable	n=113
M Stage, n (%)	
0	87 (77,0)
1	26 (23,0)
Clinical Stage, n (%)	
Stage I	2 (1,8)
Stage II A	12 (10,6)
Stage II B	18 (15,9)
Stage III A	20 (17,7)
Stage III B	33 (29,2)
Stage III C	2 (1,8)
Stage IV	26 (23,0)
Grade, n (%)	
Grade I	14 (10,3)
Grade II	43 (31,6)
Grade III	79 (58,1)
LVI, n (%)	
Negative	70 (61,9)
Positive	43 (38,1)
TIL, n (%)	
Negative	20 (17,7)
Low positive	46 (40,7)
Medium positive	29 (26,7)
Strong positive	18 (15,9)
Survival, n (%)	
Alive	63 (55,8)
Deceased	50 (44,2)

TNBC Subtype Breast Cancer Survival

During the 60-month study period, there were 50 deaths (44.2%), which in this survival study was the event assessed as the final outcome. The remaining 63 (55.8%) subjects completed the observation period alive and were censored due to the end of the study period. The mean life expectancy of TNBC subtype breast cancer patients in this study was 42 months (95%CI = 38.31-46.32). Five-year life

expectancy can be directly obtained from the cumulative survival proportion until the fifth observation (60 months). Five-year survival in TNBC subtype breast cancer patients in this study was 55.8%. The Kaplan-Meyer survival curve for the entire sample can be seen in Figure 1. The mean duration of survival in the entire sample of women with TNBC subtype breast cancer was 42 months (95%CI = 38.31-46.32).

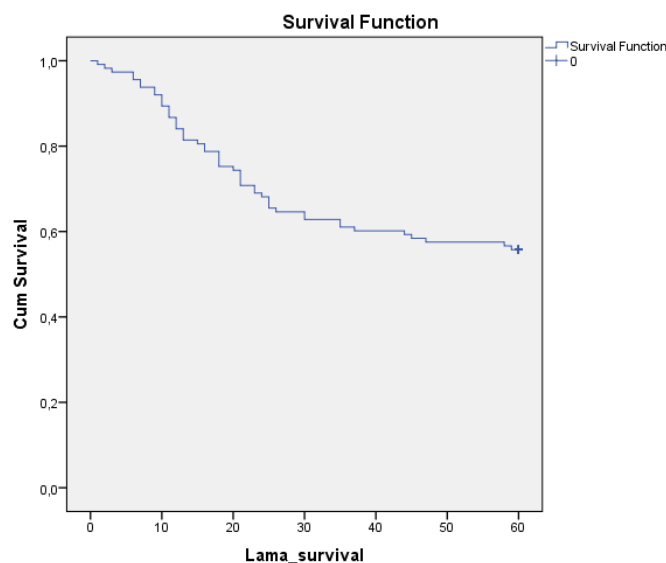


FIGURE 1: Overall survival Kaplan-Meyer curve for the whole sample.

Influence of Clinicopathologic Characteristics on TNBC Survival

The effect of clinicopathologic characteristics on the survival of TNBC subtype breast cancer can be seen in Figure 2. Stage T1 and T2 have more prolonged survival than patients with stage T3 and T4 (52.68 months vs 38.22 months; $p=0.003$). Patients without metastasis had more prolonged survival than patients with metastasis (47.10 months vs 26.30 months; $p<0.001$).

Patients with clinical stage I-II had more prolonged survival than patients with clinical stage III-IV (53.93 months vs 37.72 months; $p=0.001$). Patients with age <40 years, premenopause in menopausal status, stage N0, grade I, LVI negative, and TIL negative had more prolonged survival but were not statistically significant ($p>0.05$).

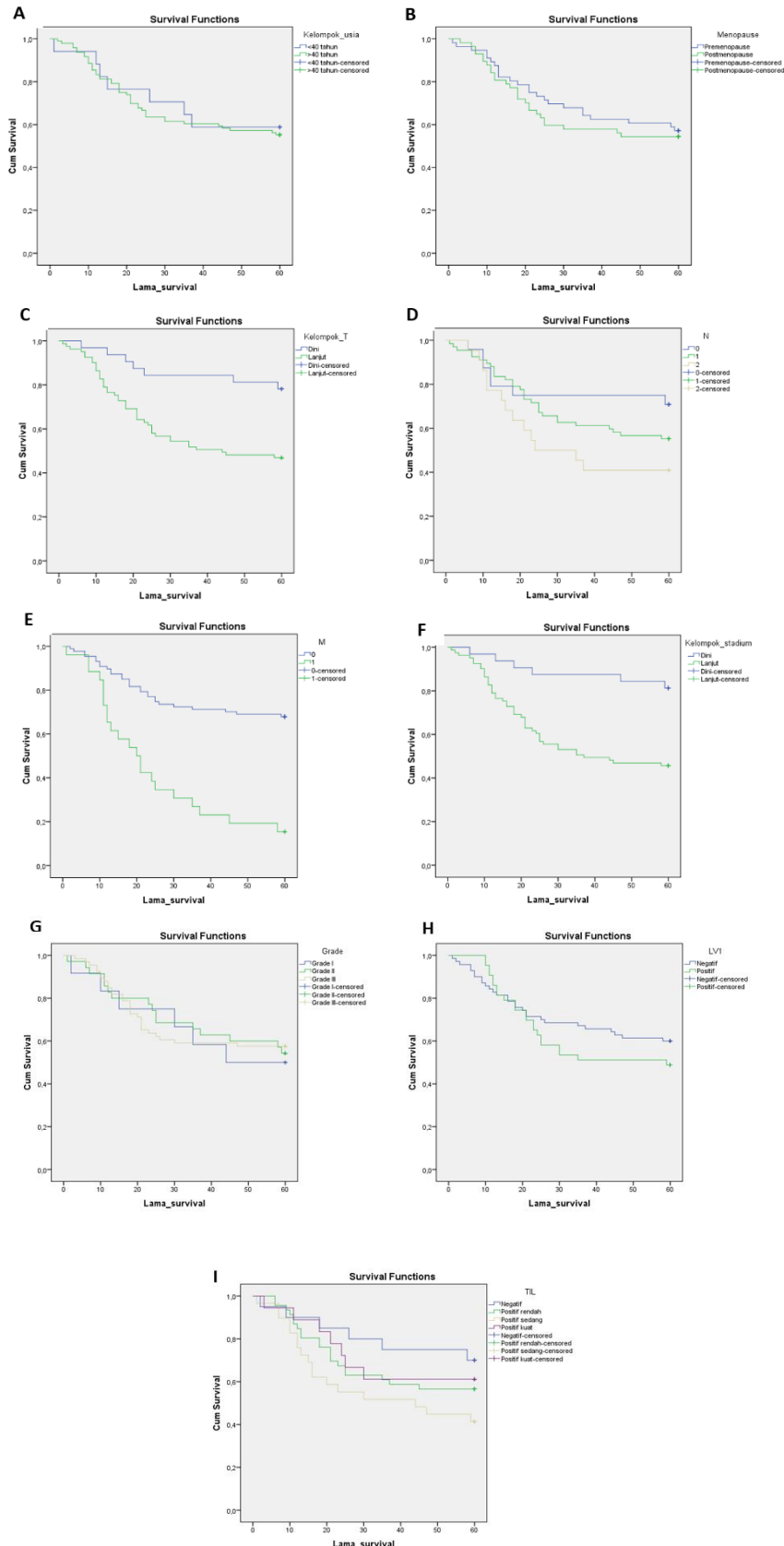


FIGURE 2: Kaplan-Meier survival curves stratified by A) age, B) menopausal status, C) stage T, D) stage N, E) stage M, F) stage, G) grade, H) LVI, I) TIL.

Cox-Regression Analysis

The results of Cox-Regression analysis showed that the factors affecting the survival of TNBC subtype breast cancer patients were T status (HR=3.101 [95%CI=1.393-6.904], p=0, 004), N status (HR=1.566 [95%CI=0.048-2.443], p=0.048), M status (HR=4.076 [95%CI=2.310-1.191], p<0.001), and clinical stage (HR=1.578 [95%CI=1.312-1.897], p<0.001). Patients with T3-T4 tumor status experienced faster mortality

by 3.1 times than patients with T1-T2 tumor status. Patients with N2 nodule status had a faster mortality of 1.5 times than patients with N0 nodule status. Patients with metastasis had a faster mortality of 4 times than patients without metastasis. Patients with stage III-IV had a faster mortality of 1.5 times than patients with stage I-II. There is no effect of age, menopausal status, grade, LVI, and TIL on the survival of TNBC subtype breast cancer (Table 2).

TABLE 2: Results of Cox-Regression Analysis of the effect of age, menopausal status, T stage, N stage, M stage, stage, grade, LVI, and TIL on survival of TNBC subtype breast cancer patients.

Variable	HR	95%CI		P value
		Lower limit	Upper limit	
Age (<40 years)	1,132	0,509	2,516	0,761
Premenopause	1,144	0,657	1,994	0,634
Tumor (T3-T4)	3,101	1,393	6,904	0,006
Nodule (N2)	1,566	1,003	2,443	0,048
Metastasis (M1)	4,076	2,310	7,191	<0,001
Stage (IV)	1,578	1,312	1,897	<0,001
Grade (III)	0,937	0,627	1,400	0,751
LVI (positive)	1,312	0,750	2,296	0,341
TIL (positive)	1,151	0,872	1,521	0,320

DISCUSSION

The subjects of TNBC subtype breast cancer patients in this study were dominated by women who were diagnosed at the age of > 40 years (85%). These results are in accordance with research by Li et al. (2016), which showed that the average age at diagnosis was 58.9 years. Most menopausal status in this study was post-menopausal (50.4%). These results are similar to studies in India, which state that TNBC breast cancer patients are mostly post-menopausal (51.36%) (Akhtar et al., 2015). The stage at diagnosis in this study was III B (29.2%). These results are in accordance with studies in India, where TNBC subtype breast cancer patients are mostly found at stage III by 45.7% (Bajpai et al., 2022). The most common TNBC grade in this study was grade III (58.1%). These results are in accordance with research in China, where the most common grade of TNBC subtype breast cancer is grade III (68%) (Li et al., 2016). Lympho-vascular invasion in this study was mostly negative (61.9%). This result is similar to a study in India, where only 16% of LVI were positive (Bajpai et al., 2022).

The 5-year survival rate in this study was 55.8%. This result is similar to the study by Goncalves et al. in Brazil, which stated the 5-year overall survival of TNBC subtype breast cancer patients was 62.1%. The TNBC subtype breast cancer survival rate is significantly lower than the 5-year survival of non-TNBC breast cancer patients, which is 80.8% (Goncalves et al., 2018).

TNBC cases in Indonesia are reported to have a high risk of death, with a 5-year survival rate of 11.4% (Khambri and Harahap, 2017). The 5-year survival rate in this study is still higher than the study by Khambri and Harahap, possibly because the study by Khambri and Harahap only included advanced-stage

TNBC subtype breast cancer patients, while this study included all stages.

Age at diagnosis was found to have no significant effect on TNBC subtype breast cancer survival in this study. Fredholm et al.'s study reported patients aged 35 years or younger at diagnosis had worse 5-year absolute survival than women aged 35 to 69 years (74.7% vs. 83.8%), even after controlling for tumor stage, characteristics, and histopathological factors (Fredholm et al., 2009). In Liedtke et al.'s study, patients with TNBC subtype breast cancer under 40 years of age were also reported to have poorer survival despite more aggressive systemic therapy (Liedtke et al., 2013).

Menopausal status in this study was found to have no effect on TNBC subtype breast cancer survival. Based on previous studies, the postmenopausal phase becomes a risk when there is a hormonal imbalance, and metabolism becomes stronger and weakens the body's defense mechanisms. The peri-menopausal phase becomes a risk when there is a decrease in sexual steroid synthesis in the ovaries. Boyle stated that the risk of having TNBC in peri-menopausal women is three times higher than post-menopausal and has a worse prognosis (Boyle, 2012).

Menopausal status did not have a significant effect in this study, possibly because although perimenopausal women are reported to have a lower risk of survival, post-menopausal patients are generally elderly who are prone to comorbid diseases and physically weaker than younger women, so they also have a high mortality rate. In addition, there can be a delay in diagnosis where breast cancer has actually developed at peri-menopausal age but is only detected at post-menopausal age and with an advanced stage.

This emphasizes the importance of early diagnosis of breast cancer (Nimbalkar et al., 2023).

Primary tumor size (T) influenced the survival of TNBC subtype breast cancer in this study. The 5-year survival increase for breast cancer < 2 cm was (91%), much higher than breast cancer with size > 5 cm (63%) (Carter et al., 1989). 5-year survival was increased for breast cancer < 2 cm.

Lymphatic spread (N) affects the survival of TNBC subtype breast cancer in this study. This result is consistent with the theory that the lymphatic system plays an important role in the spread of breast cancer, both in the macro and microenvironment. When lymph flows into the systemic circulation through the thoracic lymphovascular system, metastasis can spread from the lymph node with or without hematogenous pathways (Kawada et al., 2011).

Metastatic status (M) influenced the survival of TNBC subtype breast cancer in this study. TNBC patients who experienced metastasis only had a mean 5-year survival of 26.30 months, while patients without metastasis had a mean 5-year survival of 47.10 months. The incidence of metastasis is influenced by various factors, with a poor prognosis with an average survival time of 2-3 years (Marrionto et al., 2017; Wang et al., 2019).

Metastasis is reported to be the cause of death in more than 90% of patients with cancer. Gerratana et al. (2015) reported that breast cancer patients with the lung as the first site of distant metastasis had the best survival outcome (58.5 months) compared to populations with bone (44.4 months), liver (36.7 months), or brain (7.35 months) metastases.

The clinical stage based on AJCC influenced the survival of the TNBC subtype breast cancer in this study. This result is consistent with the study of Urru et al., who stated that the TNM staging system is a significant independent prognostic factor for TNBC mortality. The hazard ratio (HR) for Stage II is 3.13 times higher than for Stage I, stage III is 9.65 times, and Stage IV is 29 times (Urru et al., 2018).

LVI is a biomarker that indicates the presence of tumor cells in the lymphatic space, blood vessels, or both in the peritumoral region. It is identified morphologically by microscopic examination of the primary tumor with or without endothelial-specific markers. In a previous study of 3,812 breast cancer cases, LVI was shown to be an independent prognostic variable of breast cancer (Rakha et al., 2010).

Tumor-infiltrating lymphocytes (TILs) were found to not affect the survival of TNBC subtype breast cancer in this study. Tumors are usually infiltrated by leukocytes or TILs. However, it remains unclear whether the density and type of individual TILs have a direct correlative role with poor prognosis in breast cancer patients. TILs may be a potential biomarker for immune checkpoint inhibitors in

some studies (Sawe et al., 2017; Kurozumi et al., 2018; Fujimoto et al., 2019).

This study has been able to describe patient survival for 5 years in TNBC subtype breast cancer at Prof. Dr. IGNG Ngoerah Denpasar Hospital so that it can be used as a reference for further literature review. The limitation of this study is that it uses retrospective data, and we have not been able to control other variables that can affect patient survival, such as comorbid diseases suffered, causes of death, treatment history in the form of chemotherapy and its regimen, surgery, radiotherapy, and response to treatment.

CONCLUSION

Based on the results and discussion above, it can be concluded as follows. Age and menopausal status were found to have no significant effect on TNBC subtype breast cancer survival. High tumor size has a worse survival rate compared to low tumor size (T) in TNBC subtype breast cancer patients. High node (N) has a worse survival rate compared to low node (N) in TNBC subtype breast cancer patients. Tumor spread (M) has a worse survival rate compared to no tumor spread in TNBC subtype breast cancer patients. The high stage has a worse survival rate compared to the lower tumor stage in TNBC subtype breast cancer patients. LVI was found to have no significant effect on TNBC subtype breast cancer survival. TIL was found to have no significant impact on TNBC subtype breast cancer survival.

Based on the results and discussion above, the results of this study can be used as a reference in providing counseling, education, and information (IEC) regarding the prognosis of survival estimates in TNBC subtype breast cancer patients based on stages T, N, and M. Further research should be other variables that can affect patient survival such as comorbid diseases suffered, causes of death, treatment history in the form of chemotherapy and its regimens, surgery, radiotherapy, and response to treatment. Due to the type of research using secondary data sourced from medical records and Cancer Registry Bali, it is recommended that data filling is complete and more updated at any time.

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