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Survival Analysis of Triple Negative Breast Cancer Patients Based on Ki-67 Protein Expression in Prof. Dr. I.G.N.G Ngoerah General Hospital Denpasar

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ABSTRACT

Aim: To prove that 2-year mortality of triple-negative breast cancer (TNBC) patients with protein Ki-67 expression ≥ 40% is higher than patients with protein Ki-67 expression < 40% in Prof. dr. I.G.N.G. Ngoerah General Hospital Denpasar. ***Methods:*** This was a bidirectional cohort study with survival analysis. The end of follow-up was the mortality state (survived or deceased) of patients observed for 24 months (2 years) since the patient was diagnosed with TNBC. This study was conducted in the Surgical Oncology Department, Prof. dr. I.G.N.G. Ngoerah General Hospital Denpasar from January 2018 until January 2022. The sample was recruited by a consecutive sampling method. The Kaplan-Meier curve and log-rank test determined overall survival (OS) and its difference between the Ki-67 expression group. Multivariate analysis using Cox regression was also conducted. ***Results:*** 58 TNBC patients were included in this study. At the end of the study, 31 patients survived, with an OS of 53.4%. The mean OS time was 19 months (95%CI = 17.12-20.88). The two-year OS of TNBC patients with Ki-67 ≥ 40% group was 37.5%; meanwhile, in Ki-67 expression < 40% was 88.9%. It was statistically significant (p = 0.001). Multivariate analysis revealed that Ki-67 ≥ 40% expression was a significant and independent predictor factor for a high 2-year mortality rate (adjusted HR = 9.140; p = 0.008). Tumor-resection history also had a significant result in multivariate analysis (p < 0.05). ***Conclusion:*** TNBC patients with Ki-67 ≥ 40% have a higher 2-year mortality rate than patients with Ki-67 expression < 40%.

Keywords: Ki-67; survival; triple-negative breast cancer

INTRODUCTION

Breast cancer is one of the most important health problems in women in the world. Breast cancer is the cancer with the highest incidence in women in 2020. It also ranks as the fifth leading cause of cancer death in the world. Breast cancer accounts for about 40,000 deaths in the United States each year. Based on 2018 data, breast cancer has the highest incidence (24.2% of all new cancer cases) and mortality (15%) of all cancers in women in the United States. It is estimated that more than 600,000 new cases of breast cancer in 2012 in the Asian continent, accounting for 39% of all diagnosed breast malignancies in the world. The overall incidence rate of breast cancer in Asia is noticeably lower (29.1 per 100,000) compared to the global average incidence (43.1 per 100,000) and even lower when compared to other regions such as Europe (80.3 per 100,000) or the United States (92.9 per 100,000).

In Indonesia, breast cancer also accounts for the highest number of cancer cases, namely 65,858 newly diagnosed cases in 2020, with a prevalence of 148/100,000 population.

Indonesia is the fourth-ranked country in Asia with the most breast cancer patients (Ghoncheh *et al.*, 2017). Based on an epidemiologic study comparing breast cancer patients in Indonesia and Malaysia by Ng *et al.*, the median age of breast cancer patients in Indonesia at diagnosis was lower than in Malaysia, which is 47 years and 52 years. However, breast cancer patients in Indonesia had a more severe clinical presentation or had already metastasized when seeking medical attention at the hospital compared to patients in Malaysia (Ng *et al.*, 2011). Financial problems are one of the reasons why Indonesian women do not seek medical attention early. Other causes include high trust in traditional medicine and women's lack of autonomy in medical decision-making (Taib *et al.,* 2011).

The development of diagnostic examination, especially immunohistochemistry (IHK) in anatomical pathology examination, makes it easier to determine the diagnosis of various diseases. IHK is a modality that utilizes monoclonal and polyclonal antibodies to detect specific antigens in tissues.

These antibody-antigen interactions can be observed under a microscope by staining the antibodies with visualizable substances. IHK staining has been reported using several antibodies, such as Fluorescein isothiocyanate (FITC)-labelled with fluorescent stain, peroxidase, alkaline phosphatase, and gold label to view immunohistochemical reactions under both light and electron microscopes. Other markers, including radioactive elements and immunological reactions, can be seen by autoradiography. In addition to supporting diagnosis, IHK is also widely utilized as a marker of prognosis, predictor of therapeutic response, and confirmation of diseases such as infections, neurodegenerative diseases, brain trauma, and muscle diseases. This technique is also utilized for diagnosing and classifying breast cancer (Duraiyan *et al.,* 2012; Goldblum *et al*., 2020).

Breast cancer can be classified into five groups based on its genetic expression profile. Tumors with estrogen receptors are classified into luminal A or luminal B type. Estrogen receptor negative (ER-) tumors can be classified into basal type, HER2 positive and normal type (Thakur, Bordoloi and Kunnumakkara, 2018). Basal type tumors have a less or negative expression of ER, PR (progesterone receptor) and HER2, better known as triple-negative breast cancer (TNBC) (Hunt and Mittendorf, 2017). Triple-negative breast cancer (TNBC) is a molecular type of breast cancer that is commonly found in Indonesia. Research by Rahmawati et al. (2012) in Yogyakarta showed that TNBC ranked second (25.5%) as the most common molecular type of breast cancer after luminal A. The same study also showed that TNBC patients were younger, with 15.9% aged < 40 years and 30.1% aged between 40-50 years (Rahmawati *et al*., 2018).

TNBC tumors have several distinguishing characteristics in terms of therapy selection and prognosis. TNBC primary tumors are often larger, with higher grading and progress faster than other molecular subtypes (Tan and Dent, 2018). Research in the United States shows that TNBC breast cancer has a 4.34 times higher risk of death 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 are associated with worse survival (Del-la-Cruz-Ku et al., 2020). The poorer prognosis of patients with TNBC may be due to the fact that patients with TNBC cannot receive targeted therapy or endocrine therapy.

Biomarker expression is one of the essential factors in decision-making when determining therapeutic strategies. Currently, a panel of biomarkers has been found to provide prognostic information on breast cancer, one of which is Ki-67. Ki-67 protein is a nuclear antigen that can be found in proliferating cells. Ki-67 protein is expressed in the cell cycle's G1, S, G2 and M phases.

Ki-67 protein is also considered one of the indicators to determine the proliferation of tumor cells (Li et al., 2015). The role of Ki-67 protein as a predictor of breast cancer patient survival has been described in previous studies. A study by Soliman and Yussif (2016) showed that the survival and disease-free period of breast cancer patients with high Ki-67 protein expression (> 15%) were lower than those with low Ki-67 expression. A meta-analysis by Wu et al. (2019) explained the different cut-off points of Ki-67 expression. The study showed that Ki-67 protein expression > 40% had a higher risk of recurrence and death than Ki-67 20%-40% (Wu *et al*., 2019).

The Ki-67 expression cut-off point of 40% has not been commonly used in breast cancer survival research, especially TNBC. The consensus by St Gallen in 2009 classified Ki-67 protein expression into three groups: (1) low (< 15%), (2) intermediate (16-30%) and (3) high (> 30%). The cut-off point value of Ki-67 protein was then set at 20% to distinguish luminal subtypes A and B in hormonal breast cancer, where patients with Ki-67 protein expression > 20% have a shorter disease-free interval. This data refers to breast cancer in general and is not specific to TNBC (Goldhirsch et al., 2013). Miyashita et al. (2011) assessed TNBC prognosis factors by comparing Ki-67 expression cut-offs of 30% and 40%. The results showed that the use of a 40% cut-off gave better prognostic analysis results ($p = 0.01$ with Hazard Ratio [HR] 2.44) compared to the cut-off point of 30% ($p = 0.13$ with HR 1.82) (Miyashita et al., 2011). The International Ki-67 in Breast Cancer Working Group (IKWG) states that Ki-67 expression <5% or >30% from immunohistochemical examination in breast cancer patients can help in predicting the prognosis of early-stage patients (T1-2, N0-1). HER2-negative breast cancer patients who have Ki-67 < 10% have a lower 5-year absolute recurrence risk (8.4%) than patients with Ki-67 > 10% (21.5%) (Nielsen et al., 2021).

Based on the problems described above, the author feels it is essential to learn about biomarkers or markers to determine the prognosis and survival of TNBC patients. As evidenced by several previous studies, Ki-67 protein has good potential as a prognosis factor for TNBC patients. Unfortunately, the use of a Ki-67 cut-off of 40% has not been widely studied in TNBC patients to assess patient survival. In addition, research evaluating the use of Ki-67 expression on TNBC breast cancer survival has never been done in Indonesia, especially in Bali. Therefore, the author aims to study the survival of TNBC breast cancer patients based on Ki-67 protein expression with a cut-off point of 40% at Prof. dr. I.G.N.G. Ngoerah Hospital Denpasar.

METHODS

Design, time, and place of the study

This study used a bidirectional cohort study design with survival analysis to compare the survival of TNBC patients based on Ki-67 protein expression.

Ki-67 protein expression was classified into ≥ 40% and < 40%. The endpoint of observation was the patient's mortality status (survive or deceased) observed during a 24-month interval from the diagnosis of TNBC breast cancer. The study was conducted at the Department of Oncology Surgery, Faculty of Medicine, Udayana University / Prof. dr. I.G.N.G. Ngoerah Central General Hospital. This study was conducted from January 2018 - January 2022.

Sample characteristics

The target population in this study was all TNBC breast cancer patients diagnosed in Bali. The accessible population was all TNBC breast cancer patients with metastasis diagnosed at Prof. dr. I.G.N.G. Ngoerah Hospital from January 2018 to January 2022. The sample in this study was an affordable population that met the predetermined inclusion and exclusion criteria. The research sample was collected using a consecutive sampling technique; every patient diagnosed with TNBC breast cancer who met the inclusion and exclusion criteria in the cancer register of the Department of Oncology Surgery of Prof. dr. I.G.N.G. Ngoerah Hospital will be used as a research sample. Sample selection was carried out until the minimum sample size was met.

Data analysis

Descriptive analysis aims to describe the characteristics of research subjects and research variables. Categorical variables are displayed in frequency distribution and percentage. In contrast, numerical variables are displayed in the form of mean and standard deviation if normally distributed or median and interquartile range (IQR) if not normally distributed. Data normality test was performed using the Kolmogorov-Smirnov test.

Ki-67 expression in cancer tissues was classified into two groups: (1) Ki-67 ≥ 40% and (2) Ki-67 < 40%. Bivariate analysis aimed to assess the difference in the survival proportion between TNBC patients based on Ki-67 expression groups. Bivariate analysis was performed by making a 2 x 2 cross-tabulation (row x column). Differences in the proportion of survival of categorical variables were analyzed using the Chi-Square test or Fisher exact test if the Chi-Square test requirements were not met.

OS was compared between the two Ki-67 expression groups using a multivariable random intercept Cox regression model to estimate the hazard ratio (HR) and 95% confidence interval (95% CI). The OS distribution was assessed using the Kaplan-Meier method to obtain the mean survival by comparing the groups using the log-rank test. All hypothesis tests were two-way, with significance set as $p < 0.05$. Statistical analysis was performed using the statistical program SPSS ver 25 for Windows and R software version 3.5.3.

RESULTS

Characteristics of the study

A total of 58 patients were newly diagnosed with TNBC subtype breast cancer from January 2018 - January 2021 at Prof. dr. I G.N.G Ngoerah Hospital were included in the study. The mean age of the samples in this study was 50.41 (±11.14) years, with the youngest age of 25 years and the oldest age at diagnosis was 78 years. Most of the samples had high Ki-67 expression (≥ 40%), as much as 69%, and the remaining 18 patients (31%) had low Ki-67 expression (< 40%).

There was a significant difference in the proportion of survival based on the variables of lymph node spread, distant metastasis, lymphovascular invasion (LVI), and surgery ($p < 0.05$). Patients who died within two years of diagnosis had significantly more N2-N3 lymph node spread (48.1% vs 16.1%; $p = 0.009$), metastasis (M1) (59.3% vs 9.7%; $p = 0.000$), high LVI (70.4% vs 32.3%; $p = 0.004$), and no history of surgery (55.6% vs 22.6%; $p = 0.01$) than surviving patients.

There were no differences in 2-year mortality based on age group, menopausal status, tumor size, histopathology type, grade, TIL, and chemotherapy history ($p > 0.05$). Patients who died within two years after diagnosis were mostly < 50 years old (59.3%), pre-menopausal (59.3%), T4 tumor size (92.6%), miscellaneous histopathology type (14.8%), high grade (77.8%), and had a history of chemotherapy (96.3%) compared to patients who were still alive at the end of observation. The characteristics of this study sample can be seen in Table 1.

TABLE 1: Characteristics of the Participants.

Characteristics	2 Years Survival			P-value
	Total (N=58)	Deceased (N=27)	Survive (N=31)	
Age, mean (±SD), years	50.41 (±11.14)	49.26 (±10.88)	51.42 (±11.45)	0.466[c]
Age Group				
<50 years	29 (50%)	16 (59.3%)	13 (41.9%)	0.188[a]
≥ 50 years	29 (50%)	11 (40.7%)	18 (58.1%)	
Menopause Status				
Pre-menopause	31 (53.4%)	16 (59.3%)	15 (48.4%)	0.408[a]
Post-menopause	27 (46.6%)	11 (40.7%)	16 (51.6%)	

Characteristics	2 Years Survival			P-value
	Total (N=58)	Deceased (N=27)	Survive (N=31)	
Tumor Size (T)				
T3	9 (15.5%)	2 (7.4%)	7 (22.6%)	0.154[b]
T4	49 (84.5%)	25 (92.6%)	24 (77.4%)	
Lymph Node Spread (N)				
N0-1	40 (69%)	14 (51.9%)	26 (83.9%)	0.009[a]*
N2-3	18 (31%)	13 (48.1%)	5 (16.1%)	
Distant Metastasis (M)				
M0	39 (67.2%)	11 (40.7%)	28 (90.3%)	0.000[a]*
M1	19 (32.8%)	16 (59.3%)	3 (9.7%)	
Histopathology				
No special type (NST)	52 (89.7%)	23 (85.2%)	29 (93.5%)	0.402[b]
Others	6 (10.3%)	4 (14.8%)	2 (6.5%)	
Grade				
Low	19 (32.8%)	6 (22.2%)	13 (41.9%)	0.111[a]
High	39 (67.2%)	21 (77.8%)	18 (58.1%)	
Tumor Infiltrating Lympocyte (TIL)				
Low	32 (55.2%)	13 (48.1%)	19 (61.3%)	0.315[a]
High	26 (44.8%)	14 (51.9%)	12 (38.7%)	
Lymphovascular invasion (LVI)				
Low	29 (50%)	8 (29.6%)	21 (67.7%)	0.004[a]*
High	29 (50%)	19 (70.4%)	10 (32.3%)	
Surgery				
Yes	36 (62.1%)	12 (44.4%)	24 (77.4%)	0.010[a]*
No	22 (37.9%)	15 (55.6%)	7 (22.6%)	
Chemotherapy				
Yes	54 (93.1%)	26 (96.3%)	28 (90.3%)	0.615[b]
No	4 (6.9%)	1 (3.7%)	3 (9.7%)	

[a]Chi-Square test, [b]Fisher exact test, [c]T independent test, *significant if p-value < 0.05.

Differences in the Proportion of Survival Based on Ki-67 Expression

Bivariate analysis with a Chi-Square test was performed to see the difference in the survival proportion based on Ki-67 expression. The results showed a significant difference in the proportion of 2-year survival based on Ki-67 expression (p = 0.000). Patients with Ki-67 expression ≥ 40% had a significantly higher 2-year mortality rate than patients with Ki-67 expression < 40% group (92.6% vs. 7.2%).

TABLE 2: Differences in the Survival Proportion Based on Ki-67 Expression.

Ki-67 Expression	2 Years Survival			P-value
	Total (N=58	Deceased (N=27)	Survive (N=31)	
≥ 40%	40 (69%)	25 (92.6)	15 (48.4)	0.000*
< 40%	18 (31%)	2 (7.4)	16 (51.6)	

*significant if p-value < 0.05.

Analysis of 2-Year Survival of Triple Negative Breast Cancer Patients

Observation for 24 months showed that 31 samples were alive at the end of observation, with an OS of 53.4%. The mean OS time was 19 months (CI95% = 17.12 - 20.88). The 2-year overall survival curve of this study can be seen in Figure 1.

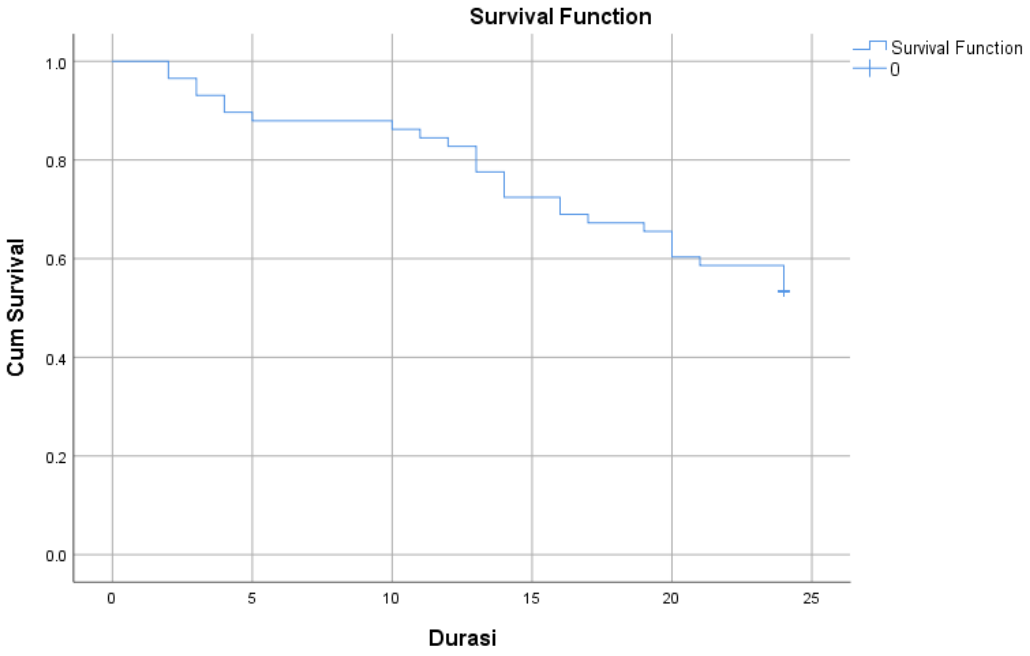

FIGURE 1: Kaplan-Meier 2-Year Overall Survival Curve.

OS distribution was assessed using the Kaplan-Meier method, and the comparison between groups was made using the log-rank test.TNBC patients with Ki-67 expression < 40% had a 2-year survival rate of 88.9%, while TNBC patients with Ki-67 expression ≥ 40% had a 2-year survival rate of 37.5%. This difference was statistically significant (p = 0.001).

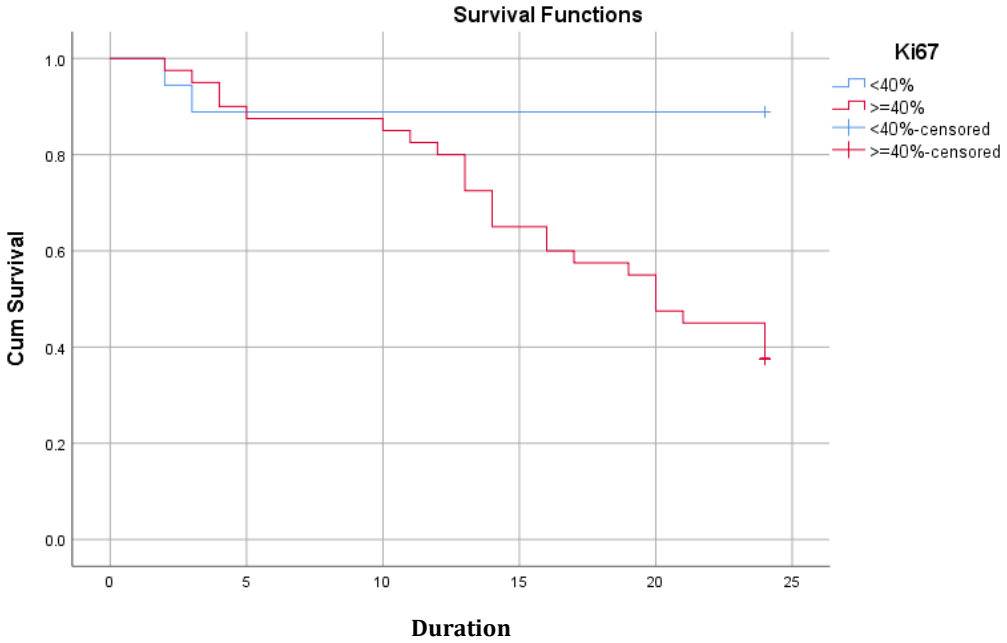

FIGURE 2: Kaplan Meier Survival Curve Based on Ki-67 Expression.

Multivariate Analysis

The bivariate analysis shown in Table 1 showed that KGB dissemination, distant metastasis, LVI and history of differentiation were significantly associated with 2-year survival, so they were included in the multivariate analysis. Multivariate analysis showed that Ki-67 expression was a significant independent predictor of 2-year survival (p = 0.005). TNBC patients with Ki-67 expression ≥ 40% had a 2-year post-diagnosis mortality rate 9.040 times greater than patients with Ki-67 expression < 40%. In addition to Ki-67 expression, history of tumor surgery was also a significant independent predictor of 2-year survival. Patients without a history of tumor surgery had a 2-year post-diagnosis mortality rate of 4.139 times greater than patients with a history of tumor surgery (p = 0.001). The results of this multivariate analysis can be seen in Table 3.

TABLE 3: Multivariate Analysis with Cox-regression Test of Factors Associated with 2-Year Mortality of TNBC Patients.

Variable	Hazard Ratio (HR)	CI 95%	P Value
Ki-67 (≥ 40%)	**9.040**	**1.925-42.446**	**0.005***
Lymph Node Spread (N2-N3)	0.449	0.169-1.189	0.449
Metastasis (M) (M1)	2.320	0.917-5.870	0.076
LVI (High)	2.304	0.882-6.015	0.088
Surgery (No)	**4.139**	**1.769-9.685**	**0.001***

*significant.

DISCUSSION

TNBC is known as a subtype of breast cancer that is aggressive and difficult to treat. This is related to the characteristics of TNBC, which under-expresses estrogen receptors (ER), progesterone (PR), and human epidermal growth factor 2 (HER2) so that it cannot be treated with targeted and hormonal or endocrine therapy modalities. TNBC subtypes are also reported to have a high recurrence rate and incidence of metastasis at diagnosis, contributing to the poor prognosis of TNBC (Zhu et al., 2022).

This study included 58 patients who were newly diagnosed with TNBC subtype breast cancer from January 2018 - January 2021 at Prof. Dr. I G.N.G Ngoerah Hospital. Observation for 24 months (2 years) showed that 31 samples were still alive at the end of observation with a 2-year overall survival (OS) of 53.4%. The mean OS was 19 months (95% CI=17.12-20.88). The median OS could not be determined in this study because it coincided with the end of follow-up or observation, which was 24 months.

The 2-year survival observed in this study was lower than in previous studies. The results of the study by Bajpai et al. (2022), which had a median follow-up of 54 months, also did not reach the median OS. However, the 3- and 5-year OS reported were higher than our study, 84.3% and 80.3%, respectively. A study in Peru showed that the overall survival (OS) in 3, 5 and 10 years was 64%, 56% and 47%, respectively (Del-la-Cruz-Ku et al., 2020). Research by Hsu et al. (2022) in Taiwan on 50,856 subjects diagnosed with breast cancer showed that the 5-year OS rate in TNBC patients was 81.28%, while in non-TNBC, it was 86.50%.

This difference may be due to the large number of patients in this study who were diagnosed at an advanced stage, with 31% already having distant metastases at diagnosis. This percentage is higher than the study by Bajpai et al. (2022), where the majority of patients were at stage II and III, 46.7% and 45.7%, respectively. Hsu et al. (2022) also reported that the majority of TNBC patients were in stages I and II, namely 20.34% and 20.80%, respectively, and only 10.8% were diagnosed in stage IV.

A panel of biomarkers has been compiled and used to provide information on breast cancer prognosis. One component is the Ki-67 expression.

The Ki-67 protein is a nuclear antigen found in proliferating cells. The Ki-67 protein is expressed in the cell cycle's G1, S, G2 and M pha. The Ki-67 protein is also considered one of the indicators of tumor cell proliferation (Li et al., 2015). Several diagnostic applications of Ki-67 expression have been reported, where Ki-67 expression is significantly higher in malignancies than in normal tissues (Koca et al., 2021; Davey et al., 2021). High Ki-67 expression (>30%) was reported to be associated with senile lymphonodi metastases, higher nuclear grade, more advanced clinical stage, poorer survival, invasive tumor diagnosis, and failure to achieve pathological remission (Arafah et al., 2021).

The baseline value of Ki-67 protein in TNBC patients is still very diverse and controversial, ranging from 10-61% (Zhu et al., 2020). The first baseline was set in the St Gallen consensus in 2009, where Ki-67 expression was grouped into three categories, namely: low (<15%), intermediate (16-30%) and high (>30%). St Gallen set a Ki-67 cut-off value of 20% to distinguish luminal A and luminal B subtypes of breast cancer in 2013 (Goldhirsch et al., 2013). A meta-analysis by Petrelli et al. (2015) involving 25 studies with more than 64,000 patients mentioned that a cut-off of 25% was significant in predicting OS (HR = 2.05, 95% CI=1.66 - 2.53, p<0.001) (Petrelli et al., 2015). However, setting the same Ki-67 expression cut-off number for all purposes and conditions is considered idealistic, given the complexity of the Ki-67 expression in different situations (Penault-Llorca and Radosevic-Robin, 2017). As baseline Ki-67 values for TNBC and HER2-positive tumors are higher than those for luminal tumors, the selection of Ki-67 cut-off values is suggested to be tailored to each breast cancer subtype (Wang et al., 2016).

This study used a cut-off point of 40% to classify Ki-67 expression into high (≥ 40%) and low (< 40%). Most of the samples had high Ki-67 expression, 69%. TNBC patients with Ki-67 expression < 40% had a 2-year survival rate of 88.9%, while TNBC patients with Ki-67 expression ≥ 40% had a 2-year survival rate of 37.5%. This difference was statistically significant (p = 0.001). Multivariate analysis also showed that Ki-67 was a significant independent predictor of 2-year survival (HR = 9.040; CI95% = 1.925-42.446; p = 0.005).

Previous studies using similar cut-offs have also shown the role of Ki-67 expression as a predictor of 2-year survival. Research by Wang et al. (2016), with a median follow-up of 34 (15-12) months, showed that 9.1% of breast cancer patients experienced death. Multivariate analysis showed that high Ki-67 (> 40%) was an independent risk factor of poorer prognosis (disease-free survival [DFS] and low OS) in TNBC patients, regardless of tumor size and lymph node status. A meta-analysis by Wu et al. (2019) on 35 studies with 7,716 breast cancer patients showed that a Ki-67 cut-off of ≥ 40% was associated with the highest risk of recurrence and mortality compared to lower cut-offs. High Ki-67 expression (≥ 40%) was significantly associated with worse OS (HR=2.95) (Wu et al., 2019).

Some previous studies reported different results. High Ki-67 index expression (> 30%) showed no significant association with OS in breast cancer patients with hormone receptor-negative expression. However, this study assessed Ki-67 expression post-NAC, so it may not represent breast cancer prognosis (Tan et al., 2014). Another study by Dokcu et al. (2023) reported that patients with low Ki-67 expression (< 20%) were significantly associated with longer DFS and OS compared to the high Ki-67 group on bivariate analysis, but not significant in multivariate analysis, in luminal subtype patients. Expression of Ki-67 was also reported to be not significantly associated with recurrence rate and distant metastasis in a cross-sectional study across different breast cancer subtypes (Mohammed, 2019). This difference may be influenced by differences in breast cancer subtypes used as research samples. Luminal breast cancer subtypes tend to survive longer, so they require more extended observations to get representative results. Research by Vihervuori et al. (2022) showed that Ki-67 is a significant prognosis factor in the age group >57 years but insignificant for the age group ≤ 57 years.

The diversity of patient populations, sample sizes, and differences in therapies administered may affect the heterogeneity of cut-off selection and results from previous studies. A high baseline Ki-67 indicates that tumor cells have a high proliferation rate, are potentially more chemosensitive to NAC, and have a higher chance of achieving a pathological complete response (pCR). This indicates a better outcome and prognosis. However, Ki-67 expression is also associated with more aggressive cancer cell properties and higher recurrence rates, despite achieving pCR. This has led to low TNBC patient survival in patients with high Ki-67 expression (Miyashita et al., 2011).

In addition to Ki-67 expression, tumor surgery history was also a significant independent predictor of 2-year survival of TNBC patients in this study ($p < 0.05$). Surgery is one of the therapeutic options in TNBC cases in addition to chemotherapy. This study showed that a history of surgery was significantly associated with 2-year survival of TNBC patients. Patients without a history of tumor surgery have a 2-year survival chance of 4.139 times greater than patients with a history of tumor surgery ($p = 0.001$). Research by Pal et al. (2014), which assessed the relationship between therapy and the survival of TNBC patients, reported that the best survival was reported in the group that received chemotherapy (OR = 4.21) followed by the surgery plus chemotherapy group (OR = 2.52). Patients with a better prognosis tend to be selected for more aggressive therapy, so this needs to be considered when interpreting the survival results. Another study by Vuger et al. (2020) reported that TNBC patients with a history of radical surgery were significantly associated with better 5-year survival than the conservative surgery group based on bivariate analysis but not significant in multivariate analysis. However, this study did not differentiate between radical and conservative surgery, as the majority of patients underwent radical mastectomy surgery. However, this study did not differentiate between radical and conservative surgery, as the majority of patients underwent radical mastectomy surgery. This study found no significant association between other confounding variables and 2-year survival in this study after being analyzed by multivariate test.

This study has several limitations. First, the short observation time of 2 years was characterized by the non-measurement of median OS from this study. Second, this study did not observe some prognosis parameters, such as DFS and RFS, due to the unavailability of recurrence time data. Third, this study did not differentiate the type of chemotherapy given, namely neoadjuvant and adjuvant, as more aggressive therapy may affect the prognosis of TNBC patients. Further studies with longer observation times, such as 5 and 10 years, are needed to measure median survival. In addition, assessing and recording recurrence/relapse and disease-free survival (DFS) is necessary to provide a more comprehensive prognosis.

CONCLUSION

TNBC patients with Ki-67 ≥ 40% expression have a higher 2-year mortality rate than patients with Ki-67 < 40% expression.

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