

The Role of the Nottingham Prognostic Index in Determining Survival Outcomes of Triple Negative Breast Cancer Patients at Prof. Dr. I.G.N.G. Ngoerah Hospital

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ABSTRACT

Background: Triple Negative Breast Cancer (TNBC) is a subtype of breast cancer that does not express the hormones Estrogen receptor (ER), Progesterone receptor (PR), and Human Epidermal growth factor Receptor 2 (HER2). In cases of breast cancer, approximately 15-20% of patients are classified as the TNBC subtype. The Nottingham Prognostic Index has been widely used and validated in various countries to indicate a poor prognosis in TNBC patients. Still, there has been no research on using this NPI score as a validation standard to increase breast cancer survival rates in Indonesia. This study aimed to determine the role of the Nottingham Prognostic Index in determining the survival of breast cancer patients, especially in Triple Negative Breast Cancer at Prof. dr. IGNG Ngoerah Hospital. **Methods:** This research is an observational study with a cross-sectional design, taking data from the Bali Cancer Registry. Data analysis was performed using SPSS and Stata programs. The inclusion criteria were complete data such as age, menstrual status, parity, use of hormonal contraception, tumor size, lymph nodes, and histopathological grading. **Results:** The results of the study showed that an NPI cut-off of ≥ 5.2 had a 5-year overall survival of 18.18%, while < 5.2 had a survival of 94%. The Nottingham Prognostic Index plays a role in determining the survival of Triple Negative Breast Cancer patients at RSUP Prof. Dr. I.G.N.G Ngoerah, with a cut-off value of ≥ 5.2 , obtained a kappa accuracy of 0.868, which means it is very good in determining 5-year overall survival. Tumor size > 3 cm was found to have a 5-year overall survival of 37.37% with a risk of death of 5.86 (95% CI 2.85-12.05; $p < 0.001$). Lymph nodes with positive nodes were found to have a 5-year overall survival of 27.27% with a risk of death of 7.5 times (95% CI 2.16-25.94; $p < 0.001$). Stage III-IV was found to have a 5-year overall survival of 47% with a risk of death of 2.45 times (CI 1.32-4.55; $p = 0.001$). A high histopathological grade was found to have a 5-year overall survival of 49.50% with a risk of death of 2.99 times (95% CI 1.52-5.88; $p = 0.001$). **Conclusions:** This study concludes that the Nottingham Prognostic Index can determine the survival of breast cancer patients, especially in Triple Negative Breast Cancer at Prof. Hospital Dr. IGNG Ngoerah.

Keywords: Nottingham Prognostic Index; breast cancer; TNBC; overall survival; prognosis.

INTRODUCTION

Breast cancer is a significant public health concern globally and is the second leading cause of cancer-related mortality, following lung cancer. The increasing incidence of breast cancer necessitates rapid assessments to determine mortality rates, which are crucial for improving community healthcare services. One promising tool for this purpose is the Nottingham Prognostic Index (NPI), which aids in predicting patient outcomes based on

various prognostic factors. Previous studies have demonstrated the utility of the NPI in various populations, indicating its potential for broader application in different healthcare settings.

According to data from Globocan 2020, breast cancer has become the most prevalent cancer worldwide, with 2,261,419 new cases reported in 2020, resulting in 684,996 deaths. In Asia, breast cancer accounts for 45.4% of new cases and 50.5%

of cancer-related deaths, highlighting the urgent need for effective screening and treatment strategies.[1] The American Cancer Society/ASCO 2020 estimates that one in eight women in the United States is diagnosed with breast cancer. Based on the latest Breast Cancer Facts and Figures 2020, the relative survival rates in the United States for women with breast cancer are 91% in the first five years, 84% after ten years, and 80% after fifteen years post-diagnosis. The overall survival rate for the first five years of breast cancer is recorded at 99% for localized tumors, 84% for those with regional spread, and 23% for tumors that have metastasised.[2]

In Indonesia, breast cancer cases, 58,256 cases and a mortality rate of 22,692 cases compared to other Southeast Asian countries.[3] Globocan 2020 reports that breast cancer is the most common new case in Indonesia, with a total of 65,858 cases and a mortality rate of 15.3% per 100,000 cases. The incidence of breast cancer in Bali was noted to reach 0.6% in 2013.[4] The high morbidity and mortality rates associated with breast cancer underscore the importance of accurate prognostic assessments to inform treatment decisions and improve patient outcomes, particularly for the Triple Negative Breast Cancer (TNBC) subtype.[5]

TNBC is characterised by the absence of oestrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). Approximately 15-20% of breast cancer patients are classified as having TNBC, which is known for its aggressive behaviour and poor prognosis, with a mortality rate of 40% within five years of diagnosis.[5] The SEER (Surveillance, Epidemiology, and End Results Program) reported that from 2014 to 2018, TNBC accounted for 13.1% per 100,000 women of new breast cancer cases in the United States, with a five-year survival rate for breast cancer with the TNBC subtype is the lowest, with 91.2% for localized cancer, 65% for regional metastasis, and 12.2% for distant metastasis. The survival rate pattern for the TNBC subtype shows the poorest survival compared to other subtypes, at 76.9%.[6] A study by [7] reported that TNBC patients have a higher risk of metastasis and recurrence compared to non-TNBC patients. Approximately 38% of TNBC patients die within five years compared to 19% for non-TNBC. The recurrence rate is 43% for TNBC, compared to 25% for non-TNBC.

The NPI is a widely accepted prognostic tool that reflects the behaviour of breast cancer, including metastasis, growth rate, and genetic instability. It has been validated in various studies and can accurately predict survival patterns based on stratification following the primary diagnosis of breast cancer.[8,9] Despite its widespread use, there is a lack of research on the application of NPI in Indonesia, particularly concerning TNBC patients. A study by [10] demonstrated that the NPI could effectively stratify TNBC patients in European cohorts, but similar validation in Asian populations remains limited.

This study aims to investigate the Nottingham Prognostic Index's effectiveness in determining the survival rate of TNBC patients at RSUP Prof. dr. I.G.N.G Ngoerah. By understanding the prognostic factors associated with TNBC in this population, we hope to contribute to the body of knowledge that can inform clinical practice and guide future research in breast cancer management. This research is particularly relevant given the disparities in survival outcomes observed in different populations and the need for tailored prognostic tools that consider local epidemiological factors.

METHOD

This study is an observational research with a cross-sectional design, utilizing data collected from the Cancer Registry of Bali. The research was conducted at RSUP Prof. dr. I.G.N.G Ngoerah in Denpasar, Bali, chosen for its status as the main referral hospital in the region, which provides a diverse population of breast cancer patients suitable for the study. Data collection occurred over a two-month period, from February 2023 to March 2023, involving all breast cancer patients at the hospital.

The target population included all breast cancer patients at RSUP Prof. dr. I.G.N.G Ngoerah, with the accessible population consisting of confirmed cases of TNBC based on histopathological examination. The sample was derived from this accessible population, including subjects who met the inclusion criteria and were not excluded based on specific criteria. Inclusion criteria included patients with breast cancer registered in the Bali Cancer Registry, confirmed through histopathological and immunohistochemical examinations, and aged between 20 and 70 years. Exclusion criteria included a history of other malignancies besides breast cancer and mortality due to other diseases. The required sample size for survival analysis was calculated based on the area under the curve (AUC) for the NPI in survival prognosis from previous research, which indicated a minimum of 54 samples for each group (survivors and non-survivors).

The variables in this study included the Nottingham Prognostic Index, which is used to determine breast cancer prognosis based on tumor size, lymph node involvement, and histological grade. Other variables included tumor size, lymph node status, tumor grade, overall survival, and confounding factors such as age, parity, menstrual status, and hormonal contraceptive use. The study was conducted after obtaining ethical approval from the local ethics committee. Samples meeting the inclusion criteria and willing to participate were included, with clinical and histopathological data collected from patient records in the Cancer Registry.

The primary parameter was survival, defined as the time from diagnosis to death, and all statistical analyses were performed using SPSS software. Data processing involved summarising statistics through stages including editing, coding, entry, cleaning, and saving.

Editing checked the accuracy and completeness of the data while coding involved correcting and manually coding the data before computer processing. Data were entered into Microsoft Excel, and in the cleaning stage, all data were rechecked to avoid entry errors. Confirmed accurate data were saved and prepared for analysis. Univariate analysis was performed to determine the frequency distribution of all research variables, with numeric variables expressed as mean and standard deviation, and categorical variables expressed as frequency and percentage. Bivariate analysis was conducted using SPSS, with normality testing performed using the Kolmogorov-Smirnov test. The relationship between tumor size, lymph node status, and tumor grade with patient survival was analysed using the Chi-square test. After calculating the NPI, expected and observed outcomes were computed, and statistical calculations regarding agreement were performed using the Kappa test. If appropriate, Cox regression analysis was conducted to determine the hazard ratio with a 95% confidence interval. For validation, the cut-off point was determined using the Receiver Operating Characteristic (ROC) curve and Youden Index, with diagnostic tests performed to determine sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (LR), and accuracy.

RESULTS

In this study, 162 subjects were obtained according to the inclusion criteria. The characteristics of the subject data are presented in Table 1. The results indicated that the average age of patients with Triple Negative Breast Cancer was 52.00 ± 11.61 years, with the majority being multiparous, comprising 125 individuals (77.2%), and an average parity of 2.19 ± 1.2 . The menstrual status showed no significant difference, with premenopausal patients numbering 80 (49.4%) and postmenopausal patients 82 (50.6%). The history of hormonal contraceptive use also showed no significant difference, with 83 individuals (49.4%) using it and 82 individuals (50.6%) not using it. The average tumor size was found to be 5.14 ± 2.76 cm, with the majority being >3 cm, accounting for 86 individuals (53.1%). Lymph node involvement was positive in 132 individuals (81.5%), with the most common stage being IIIB, comprising 52 individuals (32.1%). The most prevalent histopathological grading was III, with 96 individuals (59.3%). The overall five-year survival rate showed that 99 individuals (61.1%) were alive, while 63 (38.9%) had died, with an average NPI of 4.66 ± 1.30 . The NPI was low in 28 individuals (17.3%), moderate in 85 individuals (52.5%), and high in 49 individuals (30.2%).

TABLE 1: The Characteristics of the Research Data.

Variable	Mean \pm SD	Percentage (%)
Age (years)		
- Minimum	26	
- Maximum	77	
- Mean	52.00 ± 11.61	
Parity		
	2.19 ± 1.2	
- Nulliparous		18 (11.1)
- Primiparous		19 (11.7)
- Multiparous		125 (77.2)
Menstrual Status		
- Premenopausal		80 (49.4)
- Postmenopausal		82 (50.6)
History of hormonal contraceptive use		
- Yes		83 (49.4)
- No		82 (50.6)
Tumor Size		
	5.14 ± 2.76	
- ≤ 3 cm		76 (46.9)
- > 3 cm		86 (53.1)
Lymph Nodes		
- Negative nodes		30 (18.5)
- Positive nodes		132 (81.5)
Stage		
- I		5 (3.1)
- IIA		17 (10.5)
- IIB		25 (15.4)
- IIIA		27 (16.7)
- IIIB		52 (32.1)
- IIIC		6 (3.7)
- IV		30 (18.5)

Variable	Mean ± SD	Percentage (%)
Histopathological Grading		
- I		16 (9.9)
- II		50 (30.9)
- III		96 (59.3)
Overall five-year survival		
- Alive		99 (61.1)
- Dead		63 (38.9)
NPI	4.66±1.30	
- Low		28 (17.3)
- Moderate		85 (52.5)

The results of the analysis of the relationship between tumor size, lymph node status, and tumor grade with overall five-year survival are presented in Table 5.2. The findings indicated that a tumor size >3 cm had an overall five-year survival rate of 37.37%, with a mortality risk of 5.86 (95% CI 2.85-12.05; p<0.001) compared to a size ≤3 cm, which had an overall five-year survival rate of 62.62%. Lymph nodes with positive nodules had an overall five-year survival rate of 27.27%, with a mortality risk of 7.5 times (95% CI 2.16-25.94; p<0.001)

compared to negative nodules, which had an overall five-year survival rate of 72.72%. High histopathological grading was associated with an overall five-year survival rate of 49.50%, with a mortality risk of 2.99 times (95% CI 1.52-5.88; p=0.001) compared to low histopathological grading, which had an overall five-year survival rate of 50.50%. The risk of death was found to increase by 2.45 times (95% CI 1.32-4.55; p=0.001) in stage III-IV compared to stage I-II.

TABLE 2: Relationship Between Tumor Size, Lymph Node Status, and Tumor Grade with Overall Five-Year Survival in Patients with Triple Negative Breast Cancer.

Chemotherapy Response	Overall Five-Year Survival		RR	95% CI	p-value
	Dead n=63 (%)	Alive n=99 (%)			
Tumor Size			5,86	2,85-12,05	<0,001
- >3 cm	49 (77,78)	37 (37,37)			
- ≤3 cm	14 (22,22)	62 (62,62)			
Lymph Nodes			7,50	2,16-25,94	<0,001
- Positive nodes	60 (95,23)	27 (27,27)			
- Negative nodes	3 (4,76)	72 (72,72)			
Histopathological Grading			2,99	1,52-5,98	0,001
- High (III)	47 (74,60)	49 (49,50)			
- Low (I-II)	16 (25,39)	50 (50,50)			
Stage			2,45	1,32-4,55	0,001
- III-IV	54 (47,00)	61 (53,00)			
- I-II	9 (19,10%)	38 (80,9)			

The relationship between overall five-year survival and NPI results is illustrated in the Kaplan-Meier curve shown in Figure 1. The association between average survival duration based on NPI category values is displayed in Table 3. The findings of this study indicated that the low NPI category had an overall five-year survival rate of 92.9% with an average survival of 53.42±3.94 months (95% CI 45.69-61.16). The moderate NPI category had an

overall five-year survival rate of 83.5% with an average survival of 46.52±2.51 months (95% CI 41.59-1.455). The high NPI category had an overall five-year survival rate of 4.1%, with 47 individuals (95.9%) and an average survival of only 25.23±1.97 months (95% CI 21.37-9.103) or approximately 2 years. The overall average survival was 36.45±1.73 months (95% CI 33.05-9.863) or (3 years) with an overall five-year survival rate of 61.61%.

Table 3: Relationship Between NPI and Overall Five-Year Survival in Patients with Triple Negative Breast Cancer.

NPI Category	Overall Survival		Average Survival (months)	95% CI
	Dead	Alive		
Low	2 (7,1)	26 (92,9%)	53.42±3.94	45.69-61.16
Moderate	14 (16,5)	71 (83,5%)	46.52±2.51	41.59-1.455
High	47 (95,9)	2 (4,1%)	25.23±1.97	21.37-9.103
Overall	63 (38,9)	99 (61,1)	36.45±1.73	33.05-9.863

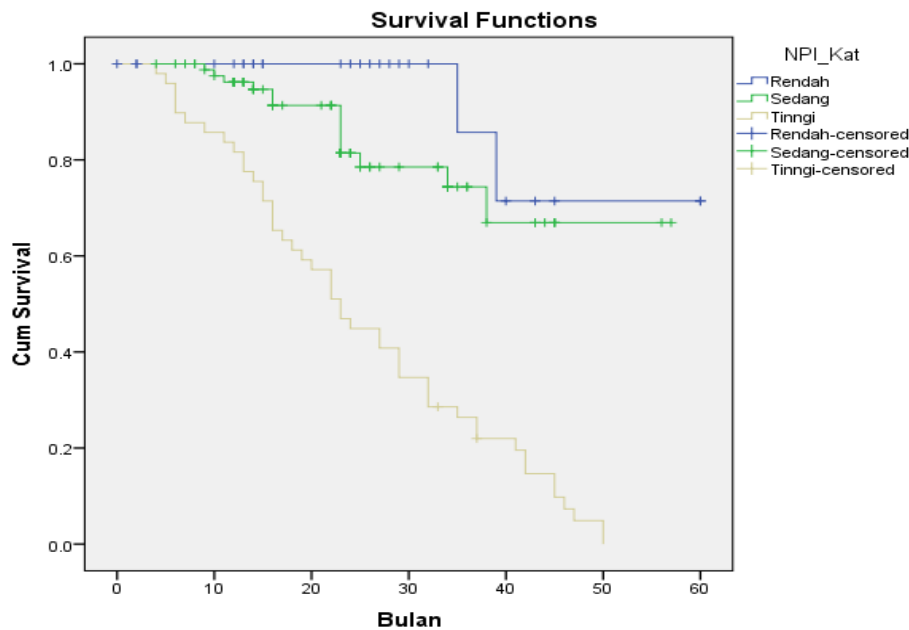


FIGURE 1: Kaplan-Meier Curve Based on NPI Degree.

A bivariate analysis was conducted using Cox regression on tumor size, lymph node status, tumor grade, and NPI results. The analysis yielded significance values based on Cox regression and hazard ratios interpreted by Exp(B). The results are presented in Table 4.

The results in Table 4 indicate that tumor size, lymph node status, and histopathological grading in patients with Triple Negative Breast Cancer were not significantly associated with five-year survival, whereas the NPI results were significantly associated with $p < 0.001$, indicating that a high NPI had a mortality risk of 3.8 times (95% CI 1.8-7.7).

TABLE 4: Cox Regression Analysis of Tumor Size, Lymph Node Status, Histopathological Grading, and NPI Results on Overall Five-Year Survival in Patients with Triple Negative Breast Cancer.

Variable	B	Exp(B)/HR	95% CI	p-value
Tumor Size	-0,172	0,842	0,515-1,376	0,492
Lymph Node Status	0,408	1,505	0,904-2,504	0,116
Histopathological Grading	0,297	1,346	0,817-2,216	0,243
Stage	-0,436	0,647	0,389-1,074	0,092
NPI	-1,054	0,349	0,229-0,531	<0,001

The results from the data analysis in Table 4 indicate that the NPI can be used as a marker for survival; thus, validation will determine the cut-off point using the ROC and Youden Index.

The assessment results of the ROC curve are shown in Figure 2. The determination of the cut-point values is presented in Table 5.

TABLE 5: Results of Sensitivity and Specificity Analysis of NPI with Overall Five-Year Survival.

Cut-point	Sensitivity (%)	Specificity (%)	Accuracy (%)	Youden Index	LR (+)	LR (-)
≥4.8	93.65	81.82	86.42	81.75	5.1508	0.0776
≥5	93.65	87.88	90.12	87.81	7.7262	0.0722
≥5.2	85.71	94.95	91.36	94.80	16.9714	0.1505
≥5.4	82.54	97.98	91.98	97.80	40.8571	0.2106
≥5.6	79.37	97.98	90.74	97.77	39.2857	0.4490

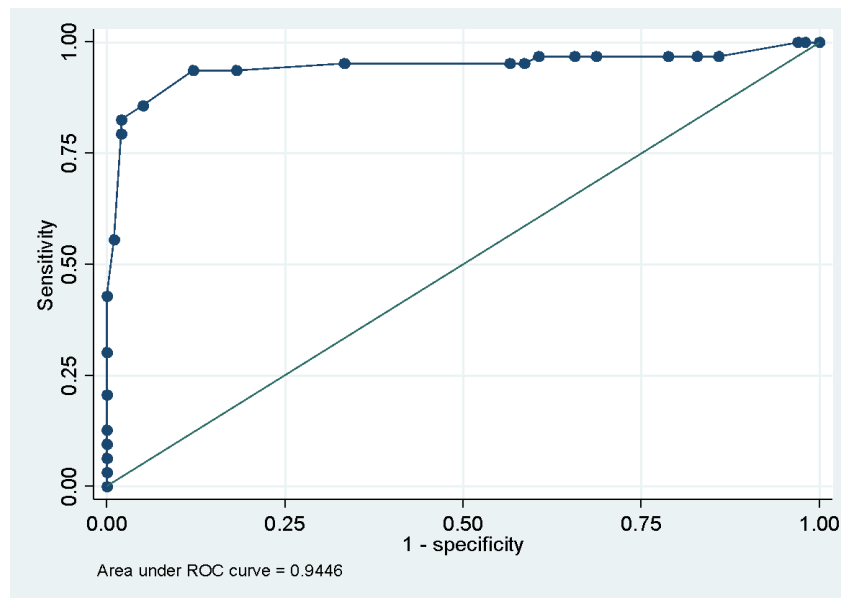


FIGURE 2: Receiver Operating Characteristic Curve.

The ROC analysis yielded an AUC of 94.46% (89.92%-98.99%) with a Youden index of 94.80, resulting in a cut-off of ≥5.2, sensitivity of 85.71%, specificity of 94.36%, accuracy of 91.36%, positive likelihood ratio (LR+) of 16.97, and negative likelihood ratio (LR-) of 0.15.

Subsequently, the results from the cut-off of ≥5.2 will be applied to the NPI results of this study, as shown in Table 6. The kappa value obtained was 0.868, indicating that the NPI score with a cut-off of ≥5.2 is very good in determining accuracy regarding overall five-year survival.

TABLE 6: Relationship Between NPI and Overall Five-Year Survival.

Survival	Nottingham Prognostic Index		Kappa Value
	Score ≥5.2 n=59	Score <5.2 n=103	
Dead	54 (81.81)	9 (8.77)	0,868
Alive	5 (18.18)	94 (91.26)	
Mean ±SD	5.78-0.90	3.96-0.97	

DISCUSSION

The results of this study found that there were 162 patients with TNBC, with an average age of 52.00±11.61 years. This finding is similar to that of [11], who reported an average age of 53±13.7 years, with the majority being aged ≥50 years. In Indonesia, a study by [12] found that among 228 TNBC subjects, the most common age was 50 years. A study by [13] reported 322 TNBC patients with an average age of 57.5 years, with the majority being ≥35 years, specifically 277 patients (86.02%). Similar results were found by [10], who reported an average age of 59±13 years, with a median of 64 and

an age range of 28-92 years, and by [7], who reported an average age of 57±13 years. Conversely, younger ages were reported in studies by [14], with a median age of 48 years (20-89 years), and [8], with an average age of 46.5±13.7 years. Age was found not to influence prognosis.

Among the known risk factors, age has the strongest influence on the incidence of breast cancer, with half of all new cases occurring in women aged between 50 and 69 years.[1] However, age is not associated with breast cancer prognosis. In this study, no significant effect of age on overall five-year survival

in TNBC was found, consistent with the findings of [14–16], as the majority of ages reported were in the range of 40-60 years. Overall survival was found to be significant in those aged over 65 years, while no significant relationship was found for those aged <45 years with TNBC regarding overall five-year survival.[14] The development of TNBC predominantly occurs in younger individuals, specifically those <50 years. [17]

Regarding parity status, the majority were multiparous, comprising 125 individuals (77.2%), with an average parity of 2.19 ± 1.2 . The incidence of multiparity in Finland from 1508 breast cancer cases showed that 90.2% were multiparous, with a statistically significant risk of developing breast cancer at 2.76 times (95% CI 0.80-4.56, $p = 0.001$). This is similar to the risk of breast cancer in multiparous women in India, where 90.5% were multiparous with a risk of 2.90. In Indonesia, data from the Ministry of Health (KEMENKES) in 2020 indicated that out of 65,858 breast cancer cases, 89.78% were multiparous.[1,18,19] High parity status was found to be associated with TNBC incidence, with a risk of 1.08 (95% CI: 0.8-2.6, $P=0.04$).[17]

In terms of menstrual status, the results showed no significant difference, with premenopausal patients numbering 80 (49.4%) and postmenopausal patients 82 (50.6%). Different results were reported by Kwon et al. (2017), who found that the majority were premenopausal, comprising 138 individuals (60.3%), while postmenopausal patients numbered 91 (39.7%), and this menstrual status was not associated with overall survival. The highest prevalence of TNBC was found in premenopausal women, with a proportion of 39%, particularly among African women, with a threefold higher ratio compared to other ethnicities.[20] The incidence of breast cancer was found to increase in postmenopausal patients due to high circulating oestrogen levels, leading to hormonal imbalance. [21]

Regarding the history of hormonal contraceptive use, no significant difference was found, with 83 individuals (49.4%) using it and 82 individuals (50.6%) not using it. A study by [17] found that oral contraceptives used for ≥ 1 year were associated with an increased risk of TNBC ($p=0.008$), with a relative risk of TNBC of 4.2 for those aged ≤ 40 years who used oral contraceptives for ≥ 1 year (95% CI 1.9-9.3).

The average tumor size was found to be 5.14 ± 2.76 cm, with the majority being >3 cm, accounting for 86 individuals (53.1%). These findings are consistent with those of [8], who reported an average size of 5.5 ± 3.9 cm, and [11], who reported an average tumor size of 4.5 ± 2.8 cm, with the majority being ≤ 5 cm (46 patients, 51.7%) and >5 cm (43 patients, 48.3%). A study by [7] reported that the majority of tumors were >2 cm, accounting for 58 individuals (67.4%).

In the study by [14], the majority of tumors were classified as T2-4, comprising 142 patients (60.9%), while T1 was found in 91 subjects (39.1%). In contrast [22], reported that the majority were T1, with 67 individuals (53.1%).

Lymph nodes were found to be positive in 132 individuals (81.5%). This finding is similar to that of [8], who reported positive nodes in 52 individuals (94.5%) with TNBC. Conversely [14], found that the majority had negative lymph nodes, comprising 147 patients (63.1%), while [22] reported the highest number of negative lymph nodes at 75 individuals (59.6%), and [7] found the majority to be negative at 44 individuals (52.4%).

The study found that the majority of patients were in stages III and IV, consistent with the findings of [23], which reported that 26 (56.5%) subjects were in these stages. In the RSUD Haji Adam Malik Medan, TNBC patients were found to be in stage IIIA (15 subjects, 25%) and stage IIIB (45 subjects, 75%).[24] This study's results are also similar to those of [25], where 70% were found to be in advanced stages III and IV. This is attributed to the heterogeneous nature of Triple Negative Breast Cancer, which exhibits various gene expression patterns and mutations. Compared to other breast cancer subtypes, this subtype is characterised by aggressive behaviour and a mortality rate of 40% within five years of diagnosis, with 46% of patients experiencing distant metastasis.[5]

The most common histopathological grading was III, with 96 individuals (59.3%). This is consistent with [11], who reported the highest number of patients with histopathological grading III at 59 individuals (62.1%), compared to low histopathological grades I and II, which accounted for 36 individuals (37.9%). In contrast [22], found that the majority were in histopathological grading II, with 51 individuals (40.5%), grading I at 47 individuals (37.3%), and grading III at 27 individuals (21.4%). A study by [8] also reported the highest number in histopathological grading II, with 44 individuals (51.8%), grading I at 6 individuals (7.1%), and grading III at 25 individuals (29.4%). A study by [7] similarly found the highest number in histopathological grading II, with 33 individuals (49.3%), grading I at 10 individuals (14.9%), and grading III at 24 individuals (35.8%).

The overall five-year survival rate was found to be 61.1%. This is similar to [11], who reported an overall five-year survival rate of 69% for patients with TNBC, with an average survival of 28 months. In contrast [14], reported an overall five-year survival rate of 81.4% among 233 TNBC subjects, with a median survival of 67.8 months. A study by [22] also reported a higher overall five-year survival rate of 85% compared to this study.

The average NPI was 4.66 ± 1.30 , with the most common NPI being moderate, comprising 85 individuals (52.5%), and a high NPI in 49 individuals (30.2%).

These results are consistent with those of [10], who reported low NPI in 99 individuals (24.4%), moderate in 188 (46.4%), and high in 118 (29.2%). Tumor size >3 cm was found to have a mortality risk of 5.86 (95% CI 2.85-12.05; $p < 0.001$) and an overall five-year survival rate of 37.37%, compared to sizes ≤ 3 cm. Similar significant findings were reported by [11] ($p < 0.001$), who found a mortality risk of 20.5 times for tumors >5 cm, and by [7], who reported a mortality risk of 3.29 (95% CI 1.82-2.46; $p = 0.001$) with a survival rate of 38%. In contrast [14], reported that tumors classified as T2-4 had an overall survival rate of 86.5%.

Lymph nodes with positive nodules were found to have a mortality risk of 7.5 times (95% CI 2.16-25.94; $p < 0.001$) and an overall five-year survival rate of 27.27%, compared to negative nodules. Similar results were found by [7], who reported a mortality risk of 2.8 (95% CI 1.26-6.25; $p = 0.012$) with an overall survival rate of 50%. In contrast [14], found that N2-3 had an overall five-year survival rate of 59.2%, which was lower than N0-1, which had an overall five-year survival rate of 92.9%.

The results for stages III-IV showed an increased mortality risk of 2.45 times (95% CI 1.32-4.55; $p = 0.001$) compared to stages I-II. In stages III-IV, a five-year survival rate of 77% was observed among TNBC patients. The high mortality rate in TNBC may be attributed to mutations in BRCA, increased immunomodulatory (IM) factors, decreased immune response, changes in DNA structure, increased cytokine-receptor interactions, T cell receptor signalling pathways, B cell receptor signalling pathways, chemokine signalling pathways, and NF-kappa-B signalling pathways, which accelerate cellular changes and metastasis.[26]

High histopathological grading (III) was found to have a mortality risk of 2.99 times (95% CI 1.52-5.88; $p = 0.001$) with an overall five-year survival rate of 49.50% compared to low histopathological grading. Similar results were found by [11], who reported a $p < 0.001$ with a mortality risk of 52.3 times for high histopathological grading (III), and by [7], who reported a mortality risk of 52.3 times for high histopathological grading (III) with a survival rate of 43%. In contrast, [14] reported an overall five-year survival rate of 89.6%, which was higher than the low histopathological grading I/II, which had a survival rate of 80.2%. This difference may be due to the subjects in this study being predominantly aged 40-50 years. Younger ages were found to have a better prognosis compared to those aged >50 years.

A study by [14], stated that overall five-year survival in TNBC patients is influenced by age-related factors, with a statistically significant correlation ($p = 0.002$) and the presence of LVI+ yielding an HR of 3.9 (95% CI (1.56-7.28) $p = 0.001$). Patients aged <35 years had an overall five-year survival rate of 83.3%. In this study, the results indicated that a high categorical NPI had a mortality risk of 3.8 times (95% CI 1.8-7.7), with an average survival of 36.45 ± 1.73 months

(95% CI 33.05-9.863) or approximately 3 years, and an overall five-year survival rate of 61.61%. A study by [27] showed a poor prognosis, with only 13% survival over 15 years for those with a high NPI. The moderate NPI group had a 15-year survival rate of 42%, while the low NPI group had an 80% survival rate. In this study, the low NPI category had an overall five-year survival rate of 92.9%, with an average survival of 53.42 ± 3.94 months (95% CI 45.69-61.16). The moderate NPI category had an overall five-year survival rate of 83.5%, with an average survival of 46.52 ± 2.51 months (95% CI 41.59-1.455). The high NPI category had an overall five-year survival rate of 4.1%, with 47 individuals (95.9%) and an average survival of only 25.23 ± 1.97 months (95% CI 21.37-9.103) or approximately 2 years.

The results of this study showed that the NPI cut-off of ≥ 5.2 was found in 59 patients, while < 5.2 was found in 103 patients, with the ≥ 5.2 scores having an overall five-year survival rate of 18.18%, while < 5.2 had an overall five-year survival rate of 94%. A higher cut-off was reported by [16], who found that an NPI of ≥ 5.4 had an overall five-year survival rate of 55.6% and an HR of 2.598 (95% CI 1.423-4.744). A study by [8], reported that an NPI of ≥ 5.4 was found in 36 individuals with an overall five-year survival rate of 50%. For an NPI of 3.4-5.4, 28 individuals had an overall five-year survival rate of 70%, while for an NPI of 2.4-3.4, 10 individuals had an overall five-year survival rate of 85%. An NPI of < 2.4 was found in 1 individual with an overall five-year survival rate of 93%.

In the study by [14], the NPI cut-off of ≤ 4.6 was found in 120 subjects (58.8%) and > 4.6 in 84 (41.2%), with an overall five-year survival rate of 96.3%. A modified NPI cut-off of ≤ 6.5 was found in 136 individuals (66.3%), with an overall five-year survival rate of 95.1%, while > 6.5 had 69 (33.7%) with an overall five-year survival rate of 77.3%.

This study has demonstrated the accuracy of the Nottingham Prognostic Index in determining the survival of patients with Triple Negative Breast Cancer at RSUP Prof. dr. I.G.N.G Ngoerah, with a cut-off value of ≥ 5.2 yielding a kappa accuracy of 0.868, indicating very good performance in determining overall five-year survival. However, the limitations of this study stem from the reliance on existing medical records, which resulted in data limitations. In addition to age, parity status, menstrual status, and hormonal contraceptive use, the researchers did not assess other risk factors that could influence TNBC, such as early menarche, young age at first pregnancy, short breastfeeding duration, medications that suppress lactation, high Body Mass Index, high waist-to-hip ratio, and metabolic syndrome. Furthermore, the follow-up of patients to validate the NPI assessment was not conducted, which suggests a recommendation for future research to include initial patient follow-up and consider the therapies administered, which could also impact overall five-year survival outcomes in TNBC patients.

CONCLUSIONS

This study concludes that the Nottingham Prognostic Index is an effective tool for determining the survival of breast cancer patients, particularly those with Triple Negative Breast Cancer, at Prof. Hospital Dr. IGNG Ngoerah. The findings underscore the importance of utilizing the NPI in clinical practice to guide treatment decisions and improve patient management in this challenging subtype of breast cancer.

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