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Survival Analysis of Young Breast Cancer Patients Based on The Number of Red Cell Width Distribution (RDW) at Prof Dr. I.G.N.G Ngoerah Hospital Denpasar

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ABSTRACT

Background: Breast cancer is the most common type of cancer among adolescents and young adults diagnosed in the age range of 15-39 years old and approximately 30% of cancers among women belong to the adolescent and young adult age groups. The prognosis of breast cancer occurring in young women tends to be worse than in old age. Red cell distribution width (RDW) is a routinely examined parameter, and its endpoint is a prognostic marker in solid tumors. Recently, RDW has been increasingly recognized as having an important role in carcinogenesis, tumor progression, and prognosis. ***Objective:*** This study aims to identify the number of RDWs that affect the survival of young breast cancer patients and other factors at Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar. ***Methods:*** This study used a retrospective cohort design by taking medical records and Cancer Registry data from young breast cancer patients treated at RSUP Prof. Dr. I.G.N.G Ngoerah Denpasar from January 1st, 2017, to January 1st, 2022. Variables studied included the number of RDW pre-treatment, tumor size, lymph node status, metastasis, tumor stage, tumor grading, lymphovascular invasion (LVI), tumor-infiltrating lymphocyte (TIL), and subtype. ***Result:*** A total of 160 patients were included in this study. The majority of patients are aged 15-40 years. Median survival for young breast cancer patients is 57 months with low RDW pre-treatment (95% CI 55.08-59.27) and 46 months with high RDW (95% CI 41.53-50.74). Factors associated with the survival of breast cancer patients, age, the tumor stage, and the difference in 5-year survival between Stages I-II, III, and IV 87.0% vs 88.2% vs 42.1% ($p<0.05$). Tumor grading, LVI, TIL, subtype, and Histopathology type found no significant effect on patient survival. ***Conclusion:*** This study suggests that RDW can be a potential early indicator in assessing the prognosis of young breast cancer, especially in identifying patients at risk of shorter survival, given that breast cancer at a young age tends to be more aggressive and has a more variable therapeutic response compared to older patients, cheap and easily accessible hematological parameters such as RDW can help in devising more targeted patient management strategies.

Keywords: prognostic factors; young breast cancer; RDW; survival analysis.

INTRODUCTION

Breast cancer is the most common type of cancer among adolescents and young adults diagnosed in the age range of 15-39 years and approximately 30% of cancers among women belong to the adolescent and young adult age groups (Elizabeth J Cathcart-Rake et al, 2021). Adolescents and young adults are said to be more likely to have a worse prognosis than older women with breast cancer. Even among early-stage breast cancer survivors, adolescent and young adult women are 39% more likely to die compared to older women (Elizabeth J Cathcart-Rake et al, 2021).

Adolescent and young adult breast cancer is often familial, and about half of adolescent and young adult women with breast cancer under the age of 30 have germline mutations in BRCA1, BRCA2, or TP53 (Elizabeth J Cathcart-Rake et al, 2021). Hormonal factors that increase breast cancer risk among adolescent and young adult women include early onset of menstruation, oral contraceptives, anovulatory infertility, and late parity occurring over the age of 30 (Kotsopoulos J, Lubinski J, Moller P, et al, 2014).

The prognosis of breast cancer occurring in young women tends to be worse than in old age. Red cell distribution width (RDW) is a routinely examined parameter and is of late a prognostic marker in solid tumors. This study aimed to assess the predictive value of RDW for prognosis in young women with breast cancer.

It is now widely recognized that chronic inflammation in cases of widely identified tumors plays an important role in the initiation, development, and progression of cancer. Red cell distribution width is a measurement of erythrocyte variability and size and is routinely performed as part of a complete blood cell examination. As one of the easily measured indicators as a marker of systemic inflammatory response, RDW has been reported in many pathophysiological conditions including cardiovascular disease, and generally increases progressive inflammation.

Recently, RDW has been increasingly recognized to have important roles in carcinogenesis, tumor progression, and prognosis. In addition, previous studies suggest that RDW may be a potential biomarker of breast cancer activity. However, there have been no reports on the prognostic value of RDW in young women with breast cancer. Therefore, this study aimed to investigate the relationship between RDW, disease-free survival (DFS), and overall survival (OS) in young women with breast cancer.

METHODS

This study used a retrospective cohort design by taking medical records and Cancer Registry data from young breast cancer patients treated at Prof. Dr. I.G.N.G Ngoerah Hospital Denpasar. This study uses a survival analysis design to compare the survival of young breast cancer patients based on the number of red blood cell distribution (RDW) before therapy. Red Cell Width Distribution is classified into >13.75% and ≤13.75%.

The population of this study was all young breast cancer patients diagnosed at Prof. I.G.N.G Ngoerah Hospital from January 2017 to January 2022. The sample of this study was selected using consecutive *sampling,* with a total sample size of 160 people who met the inclusion criteria.

The inclusion criteria in this study are 1) Female patients over 15 years old and under 40 years old, 2) Patients with young breast cancer and red blood cell distribution (RDW) screening before treatment. The exclusion criteria in this study are incomplete medical record data.

RESULT

Description of the Research Subjects

The age of the samples in this study were all patients aged 15-40 years with the oldest age diagnosed with breast cancer being 40 years old. Most of the samples had a high RDW count before therapy (>13.75%) as much as 50.6% and the rest (49.3%) had a low RDW count before therapy (≤13.75%).

There was a significant difference in the proportion of survival based on the Breast Cancer Stage variable ($p<0.05$). There was a difference in 5-year survival between Stages I-II, III, and IV (87.0% vs 88.2% vs 42.1%). There was no difference in 5-year survival based on the histopathology group, LVI, TIL, subtype ($p>0.05$). The majority of patients who were still alive at 5 years post-diagnosis were of Histopathology No Special Type (79.0%), Luminal B Subtype (73.8%), LVI negative (79.5%), TIL positive (77.1%), and low stage (88.2%).

TABLE 1: Characteristics of the research sample.

Characteristics	5-year survival			P-value
	Total (N=160)	Alive (N=123)	Died (N=37)	
Histopathology type				
No Specific Type	124 (77,5%)	98 (79,0%)	26 (21,0%)	0,227[a]
Lobular Type	30 (18,75%)	20 (66,7%)	10 (33,3%)	
Mucinous Type	3 (1,875%)	3 (100%)	0 (0,0 %)	
Medullary Type	0 (0,0%)	0 (0,0%)	0 (0,0 %)	
Tubular Type	1 (0,62%)	1 (100%)	0 (0,0 %)	
Signet Ring Type	1 (0,62%)	1 (100%)	0 (0,0 %)	
Papillary Type	1 (0,62%)	0 (0,0%)	1 (100%)	
Subtype				
Luminal A	13 (8,12%)	13 (100%)	0 (0,0%)	0,323[a]
Luminal B	80 (50,00%)	59 (73,8%)	21 (26,3%)	
Luminal, HER-2	14 (8,75%)	10 (71,4%)	4 (28,6%)	
HER-2 Type	24 (15,00%)	19 (79,2%)	5 (20,8%)	
TNBC	29 (18,12%)	22 (75,9%)	7 (24,1%)	
LVI				
Negative	112 (70,00%)	89 (79,5%)	23 (20,5%)	0,235[b]
Positive	48 (30,00%)	34 (70,8%)	14 (29,2%)	
TIL				
Negative	51 (31,87%)	39 (76,5%)	12 (23,5%)	0,934[a]
Positive	109 (68,12%)	84 (77,1%)	25 (22,9%)	
Stage				
Stage I-II	46 (28,75%)	40 (87,0%)	6 (13,0%)	0,000[a]
Stage III	76 (47,50%)	67 (88,2%)	9 (11,8%)	
Stage IV	38 (23,75%)	16 (42,1%)	22 (57,9%)	

Differences in Survival Proportion Based on the Number of RDW (Red Cell Width Distribution)

The results showed that there was a significant difference in the proportion of 5-year survival based on the amount of RDW (p=0.000). Patients with pre-therapy RDW ≤13.75% who were still alive at 5 years were significantly higher than patients with pre-therapy RDW >13.75%.

TABLE 2: The Difference in Survival Proportion Based on the Number of RDWs.

Number of RDW	5-year survival			P-value
	Total (N=160)	Alive (N=123)	Died (N=37)	
≤13,75%	79 (49,37%)	70 (88,6%)	9 (11,4%)	0,001
>13,75%	81 (50,62%)	53 (65,4%)	28 (34,6%)	

Analysis of 5-Year Survival of Young Breast Cancer Patients

Observation for 60 months showed that 123 samples were still alive at the end of observation with an overall survival (OS) of 76.9%. The mean survival time in the group of patients with low RDW before therapy was 57 months (IK95% 55.08-59.27) while the mean survival time in the group of patients with high RDW before therapy was 46 months (IK95% 41.53-50.74).

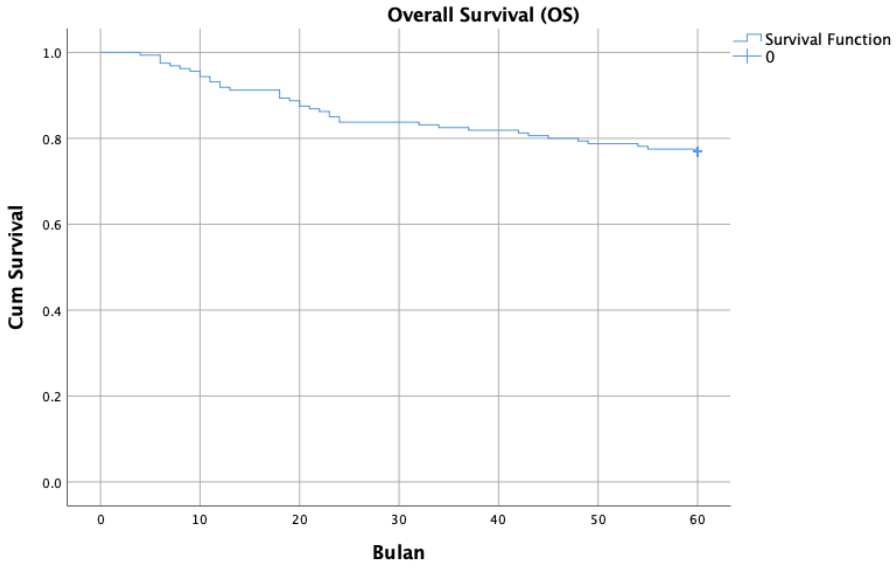

FIGURE 1: Kaplan-Meier 5-year Overall Survival Curve.

OS distribution was assessed using the Kaplan-Meier method with a comparison between groups using the log-rank test. Young breast cancer patients with pre-treatment RDW ≤13.75% had a 5-year survival rate of 88.6%, while young breast cancer patients with pre-treatment RDW >13.75% had a 5-year survival rate of 65.4%. This difference was statistically significant (p=0.000).

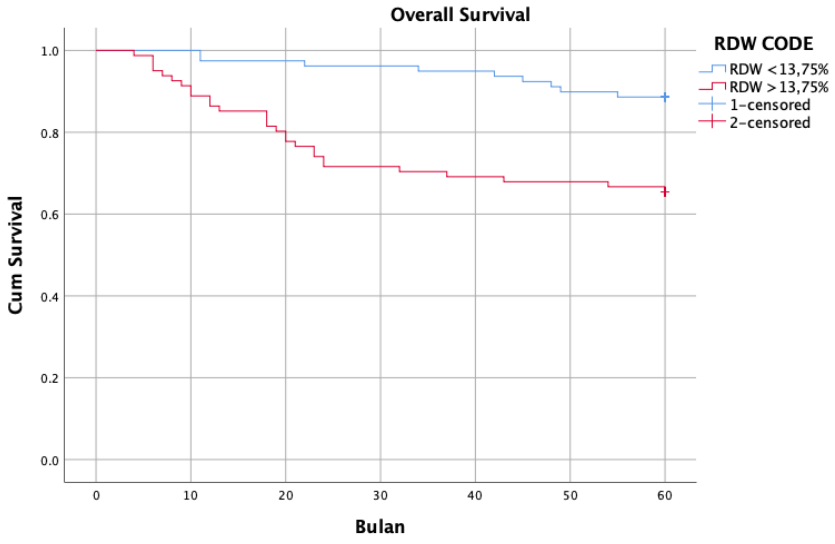

FIGURE 2: Kaplan Meier Survival Curve Based on Number of RDWs.

Multivariate Analysis

Multivariate analysis showed that the number of RDW was a significant independent predictor of 5-year survival ($p < 0.05$). Young breast cancer patients with a pre-treatment RDW count ≤13.75% had a 2.277 times greater chance of being alive within 5 years post-diagnosis than patients with a pre-treatment RDW count >13.75%. In addition to RDW count, breast cancer stage was also a significant independent predictor of 5-year survival ($p<0.05$).

TABLE 3: Multivariate analysis with Cox-regression test of factors associated with 5-year survival of young breast cancer patients.

Variable	HR	CI 95%	P-value
RDW (≤13,57%)	**2,227**	**1,032-5,025**	**0,042**
Stage (III)	0,865	0,307-2,437	0,784
Stage (IV)	**4,664**	1,823-11,93	**0,001**

DISCUSSION

Observation for 60 months (5 years) showed that 123 samples were still alive at the end of observation with a 5-year overall survival (OS) of 76.9%. The mean survival time in the group of patients with low RDW before therapy was 57 months (IK95% 55.08-59.27) while the mean survival time in the group of patients with high RDW before therapy was 46 months (IK95% 41.53-50.74%). The median OS could not be determined in this study because it coincided with the end of follow-up, which was 60 months.

The 5-year survival observed in this study was lower compared to previous studies. The overall survival in 5 years reported was higher than our study, at 89.0% but the 10-year OS was reported to be lower at 76.00%. Research in Taiwan on very young breast cancer patients showed that the overall survival (OS) in 5 years was 79.50% (Chen, et al, 2021). Penelitian sebelumnya menemukan bahwa RDW tinggi secara signifikan dikaitkan dengan ukuran tumor yang lebih besar (P = 0,002), metastasis kelenjar getah bening positif (P=0,011), dan stadium lanjut (P=0,004) (Huang, Du-Ping et al, 2016).

This study suggests that young women with breast cancer are more likely to experience more aggressive disease and have worse outcomes compared to older women. Inflammation in the biomolecular microenvironment of a tumor promotes tumor growth, invasion, angiogenesis, and ultimately metastasis. Elevated inflammatory markers such as CRs, neutrophil to lymphocyte ratio (N/L), and IL-6, have been associated with poorer survival among breast cancer patients. In addition, inflammation can cause abnormalities in red blood cell maturation by disrupting the red blood cell membrane, resulting in increased RDW. As an easy-to-perform marker of systemic inflammatory response, RDW has recently been shown to negatively impact clinical outcomes in breast cancer patients (Huang, et al, 2016).

In the study by Shin, Lee, Han, et al. the mechanism underlying the relationship between RDW and survival or disease activity is unclear. However, high RDW is thought to be caused by chronic inflammation, age-related diseases, and oxidative stress, leading to altered erythropoiesis. As malignant tumors may expand the inflammatory response in the process of progression and increase circulating levels, RDW may be a potential biomarker of cancer growth and metastatic activity. These things are in accordance with the findings in our study, there is not too much difference compared to supporting studies.

Red Cell Width Distribution is the distribution of red blood cells as a widely used laboratory parameter to measure the degree of erythrocyte anisocytosis, reflecting the variability of circulating erythrocyte size. Its main clinical application to date has been limited to the evaluation of suspected iron deficiency anemia (Forhecz, et al, 2009). However, increased RDW has been reported in many pathologic conditions. Increased RDW is closely associated with ischemic heart disease, acute and chronic heart failure, atherosclerosis, vascular occlusive disease, hypertension, active inflammatory status, bowel disease, rheumatoid arthritis, and, in general, conditions leading to progressive inflammatory status. The molecular basis of the association is attributed to the ability of RDW to be a factor in increased levels of circulating cytokines, such as IL-6, TNF-a, and hepcidin (de Gonzalo, et al, 2012).

This study used a cut-off point of 13.75% to classify the amount of RDW into high (>13.75%) and low (≤13.75%). Half of the sample had a high RDW count, 50.6%. Young breast cancer patients with low RDW (≤13.75%) had a 5-year survival rate of 88.6%, while young breast cancer patients with RDW >13.75% had a 5-year survival rate of 65.4%. This difference was statistically significant (p=0.000). Multivariate analysis also showed that the amount of RDW was a significant independent predictor of 5-year survival (HR=2.227; IK95%=1.032-5.025; p=0.042). The selection of the cut-off of 13.75% considered the study by Jun-Ming, et al, 2023, which stated that young breast cancer patients with high RDW counts were associated with worse OS and DFS. Therefore, RDW is a simple predictive factor for the prognosis of patients with breast cancer. The previous study showed prognosis results, where after pooling all data, it was found that the high RDW group was associated with worse OS (HR = 2.12, 95% CI = 1.47 to 3.08, $P < 0.01$) and poor DFS values (HR = 1.77, 95% CI = 1.32 to 2.37, $P < 0.01$).

In addition to the number of RDW, breast cancer stage, especially higher stage, was also a significant independent predictor of 5-year survival in this study ($p<0.001$). Previous research also mentioned that younger breast cancer patients with the higher stage (Stage III-IV) were predictors of 5-year survival ($p<0.00001$, HR 1.77) (Jun-Ming, et al, 2023).

CONCLUSIONS

Overall, this study suggests that RDW may be a potential early indicator in assessing the prognosis of young breast cancer, especially in identifying patients at risk of shorter survival, given that breast cancer at a young age tends to be more aggressive and has a more variable therapeutic response compared to older patients, cheap and easily accessible hematological parameters such as RDW may help in devising more targeted patient management strategies.

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