

Analysis of Disease-Free Survival and Overall Survival of HER2 Positive Subtype Breast Cancer Patients at Prof. Dr. I.G.N.G. Ngoerah Denpasar Hospital

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ABSTRACT

Aim: This study aim to assess the characteristics of the patients, as well as the 3-year and 5-year overall survival and disease free survival of HER2+ breast cancer patients treated at Prof. Dr. I.G.N.G. Ngoerah Hospital Denpasar **Methods:** This retrospective cohort study assessed survival rates and prognostic factors among HER2+ breast cancer patients treated at Prof. Dr. I.G.N.G. Ngoerah Hospital Denpasar from January 2017 to December 2022. The study used medical records to examine variables such as age, tumor characteristics, metastasis patterns, histology, treatments, and survival outcomes over 3- and 5-year periods. **Results:** The 3-year survival rate was 77.7% and the 5-year survival rate was 74.3%, with median survival times of 31 months (95%CI 30.7-32.86) and 49 months (95%CI 47.85-52.089), respectively. Disease-free survival rates indicated median durations of 33 months (95%CI 32.949-34.545) at 3 years and 54 months (95% CI 53.063-56.357) at 5 years. **Conclusion:** This study enhances understanding of HER2+ breast cancer prognosis, emphasizing the critical roles of lymph node status, metastatic burden, and treatment strategies in determining patient outcomes.

Keywords: breast cancer, HER2, survival, prognosis.

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INTRODUCTION

Breast cancer is a global problem, accounting for about a quarter of all cancer cases in women, and is ranked as the fifth leading cause of cancer death. These cancers are categorized into four molecular subtypes: Luminal A, Luminal B, HER2+, and Triple Negative. HER2+ represents approximately 20% of all breast cancer subtypes and is considered the subtype with the worst prognosis until the discovery of HER2 therapies. The incidence of breast cancer is higher in developing countries than in developed countries. Indonesia had a total of 65,858 new cases diagnosed in 2020.¹

Overall, breast cancer has a good outcome, especially when diagnosed at an early stage. Level of Overall Survival (OS) among patients differs based on molecular subtype and stage.²⁻⁴ Factors affecting OS of HER2+ breast cancer patients include age, tumor size, lymph invasion, number of metastases, type of histology, grade, therapy, ER/PR hormone receptors, and age >75 years. There is an increase in the risk of death in all breast cancer subtypes.^{5,6}

The OS at four years among women with HR+/HER2- is estimated at 92.5%, followed by HR+/HER2+ at 90.3%, HR-/HER2+ at 82.7%, and HR-/HER2- at 77.0%. It is well known that HER2 overexpression is

associated with higher disease recurrence and mortality rates. HER2+ breast cancer also has a higher risk of brain metastasis.⁷

The predictors of OS in breast cancer based on previous studies are still debatable. Moreover, there was no OS and disease-free survival (DFS) data for breast cancer patients in Bali. Therefore, we are interested in determining the DFS and OS of HER2 subtype breast cancer patients at Prof. dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali.

METHOD

A retrospective cohort was conducted to determine 3 and 5-year DFS and OS HER2+ subtype breast cancer patients at Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar. All HER2+ subtype breast cancer patients who received treatment from January 2017 to December 2022 were included. Patients with kidney, cardiac, immunological, neurological, or other systemic diseases diagnosed prior to breast cancer diagnosis were excluded from the study. Age, tumor size, lymph invasion, number of metastatic organs, type of histology, TIL, LVI, histopathological degree,

and type of therapy data were collected from medical records. Data was analyzed using SPSS version 26. Kaplan-Meier curve analyzed DFS and OS values. All hypothesis tests were carried out in both directions with a significance value of $p < 0.05$.

RESULT

There were 300 patients included in this study. The characteristics of the subjects can be seen in **Table 1**. Two hundred and sixty one (87%) were ≥ 40 years old. The majority of the study subjects had T3 size (70%), N1 (51.7%), and no metastasis (69.7%). Generally, the patients received chemotherapy and surgery (51%). Only 10.3% received chemotherapy, surgery, and anti-HER2. Of the 184 patients who underwent surgery, the majority had grade III histopathology (45.7%), histopathological types other than IDC and ILC (91.3%), LVI negative (69.6%), and TIL positive (71.7%). In the 3-year follow-up, there were 67 patients (22.3%) who died, and 35 patients had relapse (11.7%). At the 5-year follow-up, 77 patients (25.7%) died and 40 patients (13.3%) had relapsed.

Table 1. Characteristics of the Research Subject

Characteristics	Number (%) N=300
Age, n (%)	
<40 years	39 (13.0)
≥ 40 years	261 (87.0)
Tumor Size, n (%)	
T1	9 (3.0)
T2	81 (27.0)
T3	210 (70.0)
Spread of Lymphnodes, n (%)	
N0	60 (20.0)
N1	155 (51.7)
N2	68 (22.7)
N3	17 (5.7)
Number of Target Organs, n (%)	
None	209 (69.7)
1 Organ	76 (25.3)
≥ 2 Organs	15 (5.0)

Characteristics	Number (%) N=300
Histopathology Type, n=184 (%)	
Invasive ductal carcinoma (IDC)	1 (0.5)
Invasive lobular carcinoma (ILC)	15 (8.2)
Others	168 (91.3)
Degree of Histopathology, n=184 (%)	
Grade I	17 (5.7)
Grade II	83 (45.1)
Grade III	84 (45.7)
Lymphovascular Invasion (LVI), n=184 (%)	
Negative	128 (69.6)
Positive	56 (30.4)
Tumor-Infiltrating Lymphocyte (TIL), n=184(%)	
Negative	52 (28.3)
Positive	132 (71.7)
Treatment, n (%)	
Chemotherapy only	56 (18.7)
Chemotherapy and Anti-HER2	60 (20.0)
Chemotherapy and Surgery	153 (51.0)
Chemotherapy, Anti-HER2, and Surgery	31 (10.3)

The mean DFS in patients with HER2+ subtype breast cancer at 3-year intervals was 33 months (95%CI=32.949-34.545) and at 5-year intervals was 54 months (95%CI=53.063-56.357) (Table 2). The mean OS of HER2 subtype breast cancer patients at the 3-year interval was 31 months (95%CI 30.7-32.86) while at the 5-year interval was 49 months (95%CI 47.85-52.089) (Table 3). The Kaplan-Meier DFS and OS curves can be seen in Figure 1 and Figure 2, respectively.

Table 2. Disease-Free Survival at 3- and 5-Years

Duration	Disease-free	Relapse	Mean	95% Confidence Interval
3 years	265 (88.3)	35 (11.7)	33.7	32.90-34.54
5 years	260 (86.7)	40 (13.3)	54.7	53.06-56.36

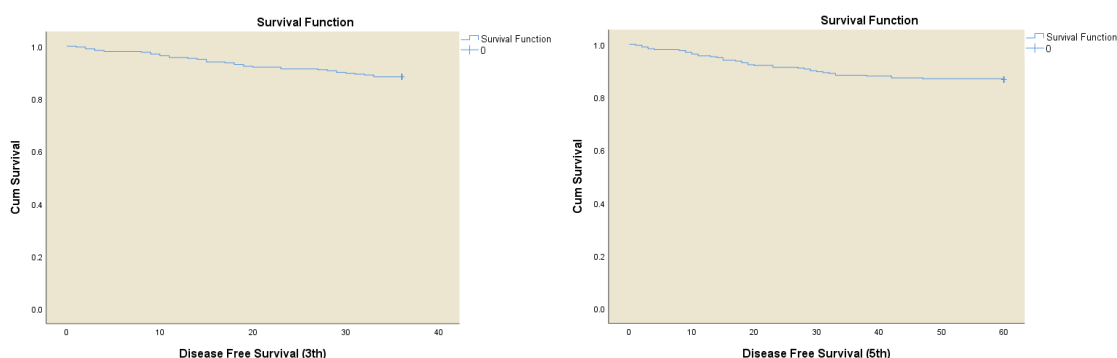
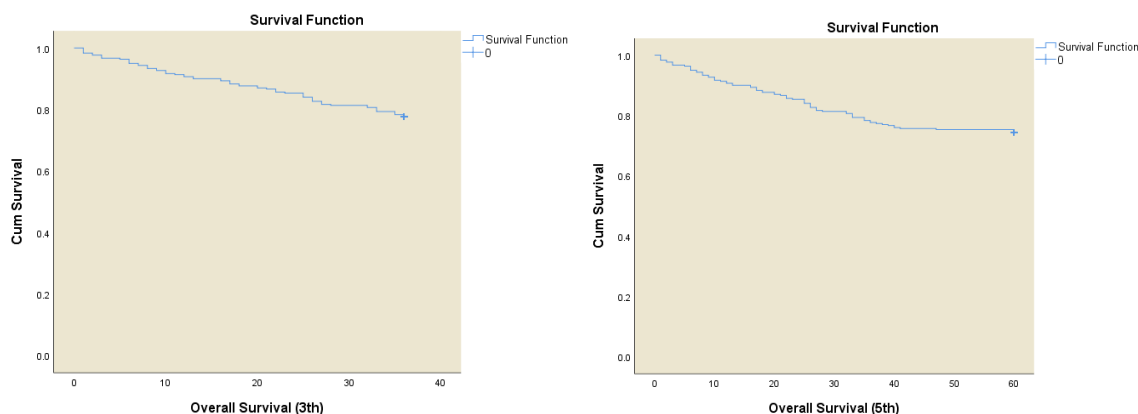


Figure 1. Kaplan-Meier Curve for Disease-Free Survival

Table 3. Overall Survival at 3- and 5-Years

Duration	Live	Die	Mean	95% Confidence Interval
3 years	233 (77.7)	67 (22.3)	31.79	30.7-32.86
5 years	223 (74.3)	77 (25.7)	49.97	47.85-52.09

**Figure 2.** Kaplan-Meier Curve for Overall Survival

DISCUSSION

HER2+ subtype breast cancer patients in this study were dominated by patients ≥ 40 years old (87%). The findings are similar to studies conducted in Ethiopia, Japan, and Norway, where patients over 40 years old dominated more than 50% of the subjects.^{3,8,9} The same findings were found in Surveillance, Epidemiology, and End Results (SEER) studies.^{5,6}

As many as 70% of the patients in this study had a tumor size of more than 5 cm. In contrast to the findings in other studies where most research subjects had a tumor size of ≤ 2 cm.³ Another study conducted in Sweden also showed that the majority of patients in the study had a tumor size of < 21 mm.⁴

Studies in HER2+ breast cancer patients showed that the majority of patients had lymph invasion to the unfixed ipsilateral axilla (51.7%) or N1, the remaining 22.7% had spread to the corrected ipsilateral axilla or N2, 5.7% to the ipsilateral infraclavicular or N3, and 20% had no spread or N0. This finding is the same as a study conducted in Japan where

The majority of subjects in the study experienced the spread of N1-N3 lymphnodes.³

HER2-positive breast cancer patients in this study generally did not metastasize far or to the target organ (69.7%). Only 5% of patients experienced metastasis in ≥ 2 organs, and 25.3% had metastases to 1 target organ. The proportions found in our study are almost identical to those conducted in Ethiopia.⁸

All HER2+ subtype breast cancer patients in this study underwent minimal treatment with chemotherapy. Only 10.3% of the total patients in this study underwent chemotherapy, surgery, and anti-HER2 treatment. The findings in our study are similar to previous studies in which most patients underwent chemotherapy therapy.¹⁰ The patients in the study conducted in Ethiopia also underwent chemotherapy for the most part.⁸

The majority of HER2+ subtype breast cancer patients who underwent surgery, namely 184 patients, had histopathological types other than invasive ductal carcinoma

(IDC) and invasive lobular carcinoma (ILC) (91.3%). In addition, it was found that as many as 84 patients undergoing surgical therapy had grade III, 128 patients had negative Lymphovascular invasion (LVI), and 132 patients were positive for Tumor-infiltrating Lymphocyte (TIL). The findings of IDC and ILC patients were also found by Tesfay et al., where in the study, the majority of patients who underwent surgery had a type of ductal carcinoma in situ. The findings of most patients with grade III were also found in studies conducted in Arabia and Sweden.^{4,11} Most patients with LVI negative found in our study were similar to those conducted in France.¹² Research examining the status of TIL shows that patients with TIL > 10% are more common in HER2-positive patients.¹³

This study's survival rate of 3 and 5 years was 77.7% and 74.3%, respectively. The overall survival probability at the three-year and five-year intervals was 0.7767 and 0.7433, respectively. The average overall survival at the interval of three years of this study is 31 months, while the average duration of overall survival at an interval of five years is 49 months. This result is lower than the study conducted in Japan, where it was found 3-year overall survival in the study by 97%.³ In addition, a study by Elobaid et al. in the United Arab Emirates also has a Survival higher, namely 2-year overall survival breast cancer patients by 97% and 5-year overall survival by 89%.¹¹ However, the results of our study were higher than those conducted in Ethiopia, where 2-year overall survival and 5-year overall survival were 54.24% and 25.8%, respectively.⁸

Based on cohort data in France, the number of 5-year overall survival HER2+ type breast cancer is higher compared to luminal type and triple-negative breast cancer (TNBC). The findings in the study are associated with the increasing findings of anti-

HER2 therapies that are considered to have high effectiveness.¹⁴ Different findings were found in Ukraine and Brazil, where the HER2+ type has Overall Survival smaller than the luminal type.^{15,16}

Subtype breast cancer Human Epidermal Receptor Positive (HER2+) was reported to have a lower risk of death compared to the subtype triple-negative breast cancer (TNBC) in a study in Bandung, with a 5-year survival rate of 61.6% and an average overall survival was 34 months.¹⁷ Other research conducted in Makassar also showed that the average Overall Survival HER2+ is higher than TNBC, which is 28 months compared to 27 months.¹⁸ The 5-year survival rate in this study is still higher than the study by the two studies, probably because the study included breast cancer patients of all subtypes. In contrast, this study only included the HER2+ subtype. Therefore, the number of HER2+ subtype breast cancer patients in our study was higher than in the two studies, which affected the percentage of overall survival.

In this study, 3- and 5-year DFS were 88.3% and 86.7%, respectively with the mean DFS for 33 months and 54 months, respectively. The findings in our study follow the study conducted in the UK, where it was found that 4-year disease-free survival in HER2+ subtype breast cancer patients by 89%.¹⁹ The study conducted in Padang found that the proportion of cancer patients who did not experience recurrence was 80% of the total study patients.²⁰ Average 3-year disease-free survival in our study is also higher than the average in Makassar, which is 22 months.¹⁸

This study has described the overall survival rate and disease-free survival rate in patients with HER2+ subtype breast cancer at I.G.N.G. Ngoerah Denpasar analyzed for 3 and 5 years. However, this study has some limitations, including the use of anti-HER2 therapy, which is only intended for patients

with metastases of the target organ, and the difficulty of contacting patients to complete data in several patient registers.

CONCLUSION

The values of the 3-year overall survival rate and 5-year overall survival rate in HER2+ subtype breast cancer in this study were 77.7% and 74.3%, respectively, with an average of 31 months (95% CI 30,717-32,863) and 49 months (95% CI 47,852-52,088). This study's average 3-year and 5-year disease-free survival were 33 months (95%CI 32,949-34,545) and 54 months (95%CI 53,063-56,357), respectively. Further research suggests adding other variables that can affect patient survival, such as comorbid diseases suffered and causes of death.

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DISCLOSURE

The author stated that there was no conflict of interest in any form in the preparation of this research article.

REFERENCES

1. Globocan. Breast. The Global Cancer Observatory. World Heal Organ. 2020
2. Lyu X, Luo B. Prognostic factors and survival prediction in HER2-positive breast cancer with bone metastases: A retrospective cohort study. *Cancer Med.* 2021;10(22):8114–26.
3. Fujita N, Enomoto Y, Inakami K, Yanagisawa T, Iguchi C, Aono T, *et al.* Prognostic Factors in HER2-Positive Primary Breast Cancer Patients Treated Using Neoadjuvant Chemotherapy Plus Trastuzumab. *Oncol.* 2020; 98(1):35–41.
4. Ellegård S, Engvall K, Asowed M, Hallbeck AL, Elander N, Stål O. Long-term follow-up of early-stage HER2-positive breast cancer patients treated with trastuzumab: A population-based real-world multicenter cohort study. *Front Oncol.* 2022;12:861324.
5. Kim HJ, Kim S, Freedman RA, Partridge AH. The impact of young age at diagnosis (age <40 years) on prognosis varies by breast cancer subtype: A U.S. SEER database analysis. *Breast.* 2022;61:77–83.
6. Cai S, Zuo W, Lu X, Gou Z, Zhou Y, Liu P, *et al.* The Prognostic Impact of Age at Diagnosis Upon Breast Cancer of Different Immunohistochemical Subtypes: A Surveillance, Epidemiology, and End Results (SEER) Population-Based Analysis. *Front Oncol.* 2020;10:1–10.
7. Patel A, Unni N, Peng Y. The changing paradigm for the treatment of HER2-positive breast cancer. *Cancers (Basel).* 2020;12(8):2081.
8. Tiruneh M, Tesfaw A, Tesfa D. Survival and Predictors of Mortality among Breast Cancer Patients in Northwest Ethiopia: A Retrospective Cohort Study. *Cancer Manag Res.* 2021;13:9225–34.
9. Johansson ALV, Trewin CB, Fredriksson I, Reinertsen KV, Russnes H, Ursin G. In modern times, how important are breast cancer stage, grade and receptor subtype for survival: a population-based cohort study. *Breast Cancer Res.* 2021;23(1):1-10.
10. Weiss A, Menen RS, Lin HY, Shen Y, Rosso KJ, Shaitelman S, *et al.* Factors associated with improved outcomes for metastatic inflammatory breast cancer patients. *Breast Cancer Res Treat.* 2018; 169(3):615–23.
11. Elobaid Y, Aamir M, Grivna M, Suliman A, Attoub S, Mousa H, *et al.* Breast cancer survival and its prognostic factors

- in the United Arab Emirates: A retrospective study. *PLoS One*. 2021; 16:1–10.
12. Houvenaeghel G, Cohen M, Classe JM, Reyat F, Mazouni C, Chopin N, *et al*. Lymphovascular invasion has a significant prognostic impact in patients with early breast cancer, results from a large, national, multicenter, retrospective cohort study. *ESMO Open*. 2021;6(6):100316.
 13. Sun T, Wang T, Li X, Wang H, Mao Y. Tumor-infiltrating lymphocytes provides recent survival information for early-stage HER2-low-positive breast cancer: a large cohort retrospective study. *Front Oncol*. 2023;13:1–9.
 14. Grinda T, Antoine A, Jacot W, Blaye C, Cottu PH, Diéras V, *et al*. Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort. *ESMO Open*. 2021; 6(3):100114.
 15. Movchan OV, Bagmut IY, Shipko AF, Smolanka II, Sheremet MI, Kolisnyk IL, *et al*. HER2/positive and HER2/low in inflammatory breast cancer recurrence. *J Med Life*. 2022;15(12):1573–8.
 16. Marczyk VR, Rosa DD, Maia AL, Goemann IM. Overall Survival for HER2-Positive Breast Cancer Patients in the HER2-Targeted Era: Evidence From a Population-Based Study. *Clin Breast Cancer*. 2022;22(5):418–23.
 17. Arnetha TS, Hernowo BS, Adha MJ, Rezano A. Relationship between Molecular Subtypes and Overall Survival of Breast Cancer in Bandung. *Biomed Pharmacol J*. 2020;13(3):1543–8.
 18. Wijayanto A, Pieter JSLA, Prihantono P, Syamsu SA, Thaufix NS, Abdi A. Survivability Rates Based on Molecular Subtype, Stage and Metastasis of 36 months cohort in Breast Cancer Patients. *Nusant Med Sci J*. 2022;7(1):29–38.
 19. Earl HM, Hiller L, Vallier AL, Loi S, McAdam K, Hughes-Davies L, *et al*. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomized phase 3 non-inferiority trial. *Lancet*. 2019; 393(10191):2599–612.
 20. Ayuza M, Harahap WA, Rustam R, Nindrea RD. Factors Affecting Disease Free Survival and Overall Survival in Young Breast Cancer Patients in Padang City in 2008 - 2018. *J Andalas' Health*. 2020; 9(1S):65–73.