

# High Bioscore predicts metastasis in breast cancer patients in Sanglah General Hospital, Denpasar, Bali, Indonesia

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## ABSTRACT

**Background:** Risk determination of breast cancer metastases is important for clinicians to be able to estimate the adequate therapy for the patients provide the basis for clinical reasoning and explanation of the possibility of metastasis to breast cancer patients who are in treatment. However, current prediction models have low accuracy and molecular determinants tend to have a high evaluation cost. Bioscore had emerged as a new reliable option in determining the risk of metastases in breast cancer, but it is not widely applied yet. Therefore, it is necessary to study its capability in determining risk of metastasis in the clinical setting in order to validate its future application.

**Objective:** To determine the bioscore scoring system as a risk determination for metastases in breast cancer at Sanglah Hospital, Denpasar.

**Methods:** This research was a nested case control study involving 32 subjects in two groups, namely metastatic and non-metastatic breast cancer groups. All patients are registered in the Cancer Registry Data at Sanglah Central General Hospital. The parameters in this study were age, stage, grading, hormonal status, HER2 status, menopausal status, metastatic status and bioscore values. Data were tabulated and statistically analyzed using SPSS 25.

**Results:** From all subjects, the average patient age of 51.50 ( $\pm 8.491$ ) years, ranging from 31 - 72 years old. The bioscore was significantly associated with all research variables. Risk analysis showed that breast cancer patients with a high bioscore (5-7) has a significantly higher risk of metastasis (OR: 21.00; 95% CI: 5.620 – 78.475) compared to those with low bioscore (1-4).

**Conclusion:** The bioscore scoring system may have a significant value in predicting metastasis in breast cancer patients. However, its application still needs further and more comprehensive studies to validate its application in breast cancer management.

**Keywords:** Bioscore, Breast Cancer, Metastasis, Risk Determinant.

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## INTRODUCTION

Breast cancer (KPD) is one of the most common cancers in women. It is estimated that 1.67 million new breast cancer cases are diagnosed worldwide each year, accounting for 25% of all cancers in women with a proportion of 240 among 100,000 female population.<sup>1</sup> Breast cancer is the second leading cause of death after lung cancer, which is 12.9%. The incidence of breast cancer in the United States is 27/100,000.<sup>1</sup> In Indonesia, although the proportion is not as much as the global data, breast cancer is the most common cancer treated in Indonesian hospitals, the incidence of breast cancer was reported at 39,381 cases and 20,052 cases of death in the same year. In developed countries

such as the United States and Canada, about 70% of new cases are diagnosed histopathologically in the early stages of PROM, while in developing countries such as Southeast Asia, most PROMs are diagnosed at stage III or IV.<sup>1,2</sup>

One of the main causes of death in breast cancer patients is metastasis. It is estimated that 20% to 30% of new female patients diagnosed with breast cancer are predicted to have metastases which cause a death rate of 400,000 to 500,000 per year worldwide.<sup>3</sup> The incidence of breast cancer metastases can occur through the blood (hematogenous), lymphatic vessels (lymphogenous) and/or direct extension through the chest wall (percontinuitatum). The time of onset is difficult to predict, but there are several factors that may influence

the risk of metastases such as tumor size and/or lymph node involvement, hormonal status, HER2 status, lymphovascular invasion, histopathological grade, and genetic profile.<sup>4</sup> Although metastatic breast cancer is considered incurable and has a poor prognosis, nowadays life expectancy is much longer, and the 5-year chance of survival has increased from 10% in 1970 to about 40% after 1995. The most common location Distant metastases in breast cancer are bone, liver, lung, brain, and contralateral breast. In breast cancer patients rarely found metastases in more than 1 location simultaneously. The more metastatic sites involved, the worse the patient's quality of life. Breast cancer management aims to reduce the rate of recurrence, spread or metastasis, prolong

the disease-free period, increase survival, and still provide a better quality of life.<sup>4</sup>

In a Surveillance, epidemiology and end results (SEER) study conducted by Omar Abdel-Rahman in 2018 on the M-Bioscore as a prognostic factor for breast cancer metastases, it was found that the M-Bioscore could predict the outcome of untreated metastatic breast cancer patients. A total of 6655 metastatic breast cancer patients were analyzed, it was found that 1911 cases (39%) had a bioscore of 5-7 (high risk) with factors associated with better cancer-specific survival in multivariate analysis were ER positive, distant nodal metastases. isolated, positive PR, lower nuclear level and positive HER 2 with a value ( $p < 0.01$ ).<sup>5</sup>

The use of Bioscore as a prognostic factor is also supported by research conducted by Ling Xu et al in 2018 where in their research the Bioscore validation test was carried out compared to the CPS-EG staging system. ) (Xu et al., 2018). A study from the MD Anderson Cancer Center, Houston, Texas, United States in 2017 reviewed a cohort of 3327 patients who received initial care at the MD Anderson Cancer Center from 2007 to 2013 determined the separation of values from the Bioscore which for high-risk patients with a bioscore of 5, 6 or 7 and low risk with a bioscore of 0 to 4.<sup>6</sup> By Juli Jamnasi, et al said in their research that T3-T4 status, positive pN status, and triple-negative subtype were statistically significant risk factors for breast cancer in distant metastases ( $p < 0.05$ ). In this study, it was found that from 678 non-metastatic patients the proportion of patients with triple negative was 85 patients (12%).<sup>7</sup>

The bioscore scoring system is still rarely used in daily practice, most likely due to the lack of research on this staging system. In Indonesia, until now there has been no research that examines this bioscore scoring system, for that it is very necessary to do research in Indonesia because cases of metastatic breast cancer are very common and need a staging system that is able to predict it.

Therefore, this study aimed to determine the bioscore scoring system as a risk factor for the incidence of metastases from breast cancer patients receiving treatment at Sanglah Hospital Denpasar from 2019-2020.

## METHODS

A Case control study was conducted from January - Augusts 31, 2020 at Department of Surgery, Faculty of Medicine, Universitas Udayana/Sanglah General Hospital. A minimum of 32 subjects in each group (Case and Control Groups) were required to ensure the validity of the result. The subjects were selected according to inclusion criteria such as women with breast cancer who had undergone mastectomy from January 2018 - December 2019 and had been confirmed by pathological as well as immunohistochemistry examination. Patients with incomplete medical records or had tumor in other organs were excluded. The bioscore were assessed using the combination of pathologic stage, ER status, Her2 type, and nuclear grade. The score was classified as low (Score 1-4) and High (Score 5-7). Other collected data were patient's age, stage, grade, metastatic status, and menopausal status. All data were compiled and analyzed using Spss.21 for windows. Chi-Square test were used to analyze the association between bioscore and metastasis as well as to determine the risk ratio (Odds Ratio) for bioscore classification toward metastasis.

## RESULTS

The baseline characteristics of the research subjects are presented in **Table 1**. Of the 64 study samples, the age distribution was divided into two groups, namely  $\geq 45$  years and  $< 45$  years. The study participant with the lowest age was 31 years and the highest age was 72 years with an average patient age of 51.50 ( $\pm 8.491$ ) years. In this study, patients aged  $\geq 45$  years 50 (78.1%) more than patients aged  $< 45$  years 14 (21.9%). **Table 1** shows that in the case group, patients aged  $\geq 45$  years (71.9%) were more than patients aged  $< 45$  years (28.1%).

Clinical staging was classified using TNM staging according to the American Joint Committee on Cancer Staging Manual 8th Edition (AJCC Staging system 8th edition). Of the 64 study subjects divided into 32 cases and 32 controls, the case group had the most samples having stage IIIB (68.8%) and the lowest is stage

IIA and IIIC with a percentage of 0% and 3.1%, respectively.

Based on tumor grading, from 64 study subjects that were divided into 32 cases and 32 controls, the case group found the most samples were grade 3, which was 21 (65.6%) and there were no samples with grade 1 in the case group. While in the control group the most samples were grade 3, which was 22 (68.8%) with grade 1 being 4 (12.5%).

Based on ER status, in the case group, the most samples were positive ER, which was 24 (75.0%) and negative ER was 8 (25.0%), while in the control group the most samples were also with positive ER, namely 25 (78.1%). ) and the rest with negative ER. Based on HER2 status, the most patients in the case group in this study were HER2 negative 20 (62.5%). While in the control group, most samples were also with a negative HER2 of 20 (62.5%).

Based on the menopausal status of the patients, this study was divided into 2 groups, namely pre-menopausal or non-menopausal patients and post-menopausal or post-menopausal patients. Of the 64 study subjects divided into 32 cases and 32 controls, 30 (46.9%) premenopausal patients and 34 (53.1%) menopausal patients were found. In the case group, the highest sample was the menopausal group, which was 19 (59.4%), while in the control group the most sample was the premenopausal group, which was 17 (53.1%).

The association between metastasis and bioscore is presented in **Table 2**. Case group was shown to have a high bioscore (5-7) (28/87.5%) compared to the control group (25.0%). Pearson Chi-Square statistical test shown a very significant result with  $p$  value  $< 0.001$  which means that there is a significant relationship between bioscore and the occurrence of breast cancer metastases in women at the Oncology Surgery Polyclinic of Sanglah Hospital Denpasar in 2018 with an OR value of 21,000 (95% CI: 5,620 - 78,475). It means women with breast cancer with a high bioscore (5-7) have a 21.00 times greater risk of metastases than women with breast cancer with a low bioscore (1-4).

**Table 1. The Baseline Characteristics of the Research Subjects**

| Variable                 | Metastatic<br>N = 32 | Non-metastatic<br>N = 32 | p value |
|--------------------------|----------------------|--------------------------|---------|
| <b>Age</b>               |                      |                          |         |
| < 45 years               | 9 (28.1%)            | 5 (15.6%)                | 0.226   |
| ≥ 45 years               | 23 (71.9%)           | 27 (84.4%)               |         |
| <b>Stage</b>             |                      |                          |         |
| IIA                      | 0 (0%)               | 6 (18.8%)                | 0.004   |
| IIB                      | 2 (6.3%)             | 9 (28.1%)                |         |
| IIIA                     | 7 (21.9%)            | 6 (18.8%)                |         |
| IIIB                     | 22 (68.8%)           | 11 (34.4%)               |         |
| IIIC                     | 1 (3.1%)             | 0 (37.5%)                |         |
| <b>Grade</b>             |                      |                          |         |
| Grade 1                  | 0 (0.0%)             | 4 (12.5%)                | 0.064   |
| Grade 2                  | 11 (34.4%)           | 6 (18.8%)                |         |
| Grade 3                  | 21 (65.6%)           | 22 (68.8%)               |         |
| <b>ER</b>                |                      |                          |         |
| Positive                 | 24 (75.0%)           | 25 (78.1%)               | 0.768   |
| Negative                 | 8 (25.0%)            | 7 (21.9%)                |         |
| <b>Menopausal status</b> |                      |                          |         |
| Premenopausal            | 13 (40.6%)           | 17 (53.1%)               | 0.316   |
| Menopausal               | 19 (59.4%)           | 15 (46.9%)               |         |
| <b>HER2</b>              |                      |                          |         |
| Positive                 | 12 (37.5%)           | 12 (37.5%)               | 1.000   |
| Negative                 | 20 (62.5%)           | 20 (62.5%)               |         |

**Table 2. The association between bioscore and the incidence of metastases**

| Variable        | Metastatic<br>N = 32 | Non-metastatic<br>N = 32 | OR     | 95% CI  | p value |
|-----------------|----------------------|--------------------------|--------|---------|---------|
| <b>Bioscore</b> |                      |                          |        |         |         |
| High (5-7)      | 28 (87.5%)           | 8 (25.0%)                | 21.000 | 5.620 - | <0.001  |
| Low (1-4)       | 4 (12.5%)            | 24 (75.0%)               |        | 78.475  |         |

## DISCUSSION

Breast cancer is one of the most common cancers in women. It is estimated that 1.67 million new breast cancer cases are diagnosed worldwide each year, accounting for 25% of all cancers in women with a proportion of 240 among 100,000 female population. Breast cancer is also the second leading cause of death after lung cancer, which is 12.9%.<sup>1</sup>

In Indonesia, breast cancer is the most common cancer treated in Indonesian hospitals. The incidence of breast cancer was reported at 39,381 cases and 20,052 cases of death in the same year. In developed countries such as the United States and Canada, about 70% of new

cases are diagnosed histopathologically in the early stages of breast cancer, while in developing countries such as Southeast Asia, most breast cancers are diagnosed at stage III or IV.<sup>1,2</sup>

The most important prognostic factors in patients with breast cancer are age, stage, hormonal status, HER2 status, grading, and menopausal status. Using these data, a new scoring system, bioscore, is developed by American Joint Committee on Cancer (AJCC) which is based on tumor biology. It has a great role in determining treatment outcomes and has a significant impact on the prognosis of breast cancer patients.<sup>6</sup>

The population characteristics of this study was not very different from previous

studies on metastatic breast cancer. Research conducted by Abdel Rahman et al found that metastatic breast cancer patients tend to occur in women with an older age group where in his study 92.7% of metastatic breast patients had an age > 40 years.<sup>5</sup> Jamnasi et al in their research also found that metastases tend to occur in women in the older age group with the mean age of patients at 52 years.<sup>7</sup> A study from the MD Anderson Cancer Center, Houston, Texas, United States in 2005 to 2012 retrospectively reviewed 2377 breast cancer patients and found that the average patient age was 50 years (age range: 21-87 years).<sup>6</sup>

Epidemiologically, the prevalence of metastatic breast cancer varies. Some studies showed that the prevalence of lung metastases in breast cancer patients was 9.75% of the total number of breast cancer patients. However, breast cancer prevalence was higher in the age group above 40 years (79.26%) compared to those under 40 years old.<sup>8</sup> That finding is in accordance with our study where it was found that in the metastasis occurred more often in patients aged 45 years (71.9%) than patients aged < 45 years (28.1%).

The clinical stage was classified using TNM staging according to the American Joint Committee on Cancer Staging Manual 8th Edition (AJCC Staging system 8th edition). From this study, the most sample group of cases had stage IIIB (68.8%) and the lowest were stages IIA and IIIC with percentages of 0% and 3.1%. Case group had more advanced stage IIIB (68.8%) compared to the control group (34.4%). This finding is in accordance with a cohort study conducted at MD Anderson where the higher the staging, the higher the value bioscore tends to be.<sup>6</sup> The result of this study is also supported by Jamnasi et al who found that T3-T4 and positive pN status were significantly correlated with the incidence of metastases in the metastatic group compared metastases-free group ( $p < 0.05$ ).<sup>7</sup>

Based on ER status, the most samples in the case group were ER positive, which was 24 (75.0%) while the control group had the most samples with positive ER, i.e. 25 (78.1%). Based on HER2 status, most patients in the case and control group in this study were HER2 negative.

Similar finding was shown by Jamnasi et al which the triple-negative subtype was significantly correlated with the incidence of metastases in the metastatic group compared to the metastatic-free group ( $p < 0.05$ ).<sup>7</sup> In addition, multivariable analysis of two studies involving HER2-positive patients revealed a significant positive relationship between stage III/recurrence and risk of BCBM (OR: 2.05,  $p = 0.020$ ; RR: 9.39,  $p = 0.0032$ ).<sup>9,10</sup> Although HER2-positive status is considered a more aggressive marker of disease in the adjuvant and metastatic setting, the MD-Anderson study data suggest a better prospect for patients with HER2-positive disease. One important context for this finding is that the majority of HER2-positive patients in both analyzes were mostly treated by anti-HER2 therapy.<sup>5,11</sup> In a study conducted at MD Anderson, TNBC patients (ER-, PR-, HER2-) who presented with a small initial stage (II) had an estimated 5-year DSS of 98% (CPS + EG) and 97% (Neo-Bioscore). The results differed in patients with advanced stage (IIIC) which has the 5-year DSS values at 87% (CPS + EG) and 86% (Neo-Bioscore).<sup>6</sup>

This study is also supported by Hung et al who reported a significant relationship between advanced stage (III) and the occurrence of brain metastases in breast cancer which were analyzed multivariately (effect estimate range: 4.836 - 67.07).<sup>12</sup> Azim et al reported that tumor size (T2-3 vs T1) was positively associated with a significantly shorter time to brain metastases in univariate analysis. This is also in accordance with the study by Foulkes et al who found that TNBC with advanced clinical stages tended to metastasize to visceral organs, especially the lung (40%) and brain (30%).<sup>13</sup>

Based on tumor grading, it was found that in the case group the most samples were grade 3 while there are no samples with grade 1 in the case group. Meanwhile in the control group, the highest sample was grade 3. This finding is also similar to previous studies which found a higher frequency at high grades among breast cancer patients. The study by Dent et al found that patients with metastatic breast cancer tended to have a higher histological grade compared to non-metastatic patients (66% vs. 28.3%,  $P < 0.001$ ).<sup>14</sup>

Based on the value Bioscore patient's in this study, it was reported that there are 28 (43.8%) patients with a low bioscore and 36 (56.8%) with a high bioscore. There are more patients who had a high bioscore (5-7 in the case group (metastatic) (87.5%) compared to the control group (nonmetastatic) (25.0%). In a cohort study conducted at MD Anderson, a separate score was determined for high-risk patients with a bioscore of 5, 6 or 7 and a bioscore of 1 to 4 low risk patients.<sup>6</sup> In that study was also found a lower bioscore was associated with a better DSS.<sup>6</sup>

In the research of Abdel Rahman et al, a bioscore that combines biologic factors that are routinely assessed including clinical staging and status of estrogen receptor (ER), progesterone receptor (PR), and HER2 has found that lower bioscores are associated with better (disease-specific survival) DSS. Current ASCO guidelines recommend the application of biomarkers, in particular ER and HER2, to guide adjuvant therapy decisions. Bioscore describes this clinical management of breast cancer to provide accurate prognostic information for patients treated with regimens that target the basic biology of their breast cancer.<sup>6</sup> In the study of Abdel Rahman et al, a model for patients with metastatic breast cancer "M-bioscore" was proposed for the first time and validated from the surveillance, epidemiology and end results (SEER) cohort database. This prognostic scoring system (ER, PR, grade, HER2 and metastatic site) is quite accessible, the M-bioscore seems to be an easily affordable model for patients with breast cancer.<sup>5</sup>

In this study, it was found that a high bioscore had a strong correlation as a risk factor for the occurrence of metastases in women with breast cancer and it is hoped that these results can as a basis for explanation and education to patients about the possibility of metastasis in breast cancer patients who undergoing treatment. It can also be used to assess the effectiveness of chemotherapy, both neoadjuvant or adjuvants.

## CONCLUSION

High bioscore (Score 5-7) is a potential risk factor for metastasis in breast cancer. However, this finding need to be validated

by controlling other confounding factors so the potential biases can be averted.

## CONFLICT OF INTEREST

All authors declared that there is no conflict of interest regarding the publication of this article

## ETHICS APPROVAL

This study had been approved by the ethics committee of Faculty of Medicine Universitas Udayana with Ethical Clearance number 1200/UN.14.2.2.VII.14/LT/2020

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## AUTHOR CONTRIBUTION

All authors contributed equally in constructing and reviewing this manuscripts

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