

Article

Study of Ordinal Regression Method for Supporting Factors Investigation in Stages Condition of Breast Cancer Patients in Dr. Soetomo Surabaya Hospital, Indonesia

Article Info

Article history :

Received July 27, 2021
Revised September 9, 2021
Accepted September 10, 2021
Published September 30, 2021

Keywords :

Ordinal logistic regression
breast cancer, breast
cancer stages

Thania Muhammad^{1*}, Destri Susilaningrum², Vidi Vianney C.M.Tanggo³

¹Department of Business Statistics (FV), Institut Teknologi Sepuluh Nopember, Indonesia

²Department of Business Statistics (FV), Institut Teknologi Sepuluh Nopember, Indonesia

³Surgery Department, Faculty of Medicine Airlangga University, Dr. Soetomo Surabaya Hospital, Indonesia

Abstract. Dr. Soetomo Surabaya Hospital in 2019 received 167,000 cancer patients, and the highest was breast cancer. The increase in the stage of breast cancer is caused by the size of the tumor and how widely the cancer cells have spread to other organs. The purpose of this study was to apply the ordinal logistic regression method in the case of factors that support the condition of breast cancer stage in Dr. Soetomo Surabaya Hospital. The result of this study is that the factors that support the condition of breast cancer stages are grade and family history of breast cancer with a classification accuracy rate of 84.3%. Breast cancer patients at Dr. Soetomo Surabaya Hospital with grade 3 is likely to support staging conditions from locally advanced to advanced by 0.06 times compared to grade 1 patients. Patients with grade 2 is likely to support staging conditions from locally advanced to advanced by 0.17 times compared to grade 1 patients. Patients who have a history of breast cancer in their family will have a risk of developing breast cancer with locally advanced stages to advanced stages 3.84 times than in patients with no family history of breast cancer.

This is an open access article under the [CC-BY](https://creativecommons.org/licenses/by/4.0/) license.



This is an open access article distributed under the Creative Commons 4.0 Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. ©2021 by author.

Corresponding Author :

Thania Muhammad
Department of Business Statistics, Faculty of Vocational Studies (FV),
Institut Teknologi Sepuluh Nopember, Surabaya, Indonesia
Email : thaniabwdn@gmail.com

1. Introduction

Breast cancer also known as *Carcinoma Mammariae (Ca Mammariae)* is a malignant tumor that grows in breast tissue. These tumors can grow in the mammary glands, fatty tissue, or in the connective tissue of the breast. This cancer can grow if there is an abnormal growth of breast cells. Breast cancer can spread or move to surrounding tissues, spread to lymph nodes, enter blood vessels to other organs and cause malfunction which can lead to death. Survival depends on regional distribution of [1-9].

The increase in the stage of breast cancer is caused by the size of the tumor and how widely the cancer cells have spread to other organs in the body. Breast cancer based on the stage level can be classified into 3 categorizes. Stage I – III A as early stage of breast cancer, Stage III B – III C locally advanced, Stage IV advanced breast cancer[10-12]. These stages have different characteristics of tumor size and distant spread so that the stage of breast cancer is obtained. The incidence of breast cancer in Dr. Soetomo Surabaya Hospital from time to time is increasing and most breast cancer patients only come for treatment after diagnosed with advanced stage[13].

Therefore, this study was conducted to determine the factors that support the condition of breast cancer stage in patients at Dr. Soetomo Surabaya Hospital and its risk opportunities. The method used is ordinal logistic regression with the response variable in the form of stages of breast cancer which consists of early stage, local advanced stage and advanced stage.

2. Experimental Section

2.1. Method

The method that used in this research is ordinal logistic regression. Ordinal logistic regression analysis is one of the statistical methods used to analyze the relationship between response variables and predictor variables[14]. The response variable in ordinal logistic regression uses an ordinal scale [15-16]. The following is the general equation of ordinal logistic regression.

$$P(Y \leq m | x) = \frac{\exp\left(\alpha_m + \sum_{k=1}^p \beta_k x_k\right)}{1 + \exp\left(\alpha_m + \sum_{k=1}^p \beta_k x_k\right)} \quad (1)$$

Where, β_k for each $k = 1, 2, \dots, p$.

Simultaneous testing is a test carried out to check the significance of the parameters β to the overall response variable [6]. Testing the significance of the parameters simultaneously using the Likelihood Ratio Test which can be seen as follows.

Hypothesis:

$$H_0 : \beta_k = 0$$

$$H_1 : \text{There is at least 1 } \beta_k \neq 0, k = 1, 2, \dots, p$$

Test Statistics :

$$G = -2 \ln \left[\frac{\binom{n_1}{n} \binom{n_2}{n} \binom{n_3}{n}}{\prod_{r=1}^n [\pi_1(x_r)^{y_{1r}} \pi_2(x_r)^{y_{2r}} \pi_3(x_r)^{y_{3r}}]} \right] \quad (2)$$

Where,

$$n_1 = \sum_{r=1}^n y_{1r}, n_2 = \sum_{r=1}^n y_{2r}, n_3 = \sum_{r=1}^n y_{3r}, \text{ dan } n = n_1 + n_2 + n_3$$

Rejection Area : Reject H_0 if $G > \chi^2_{(11,0.05)}$ atau $\chi^2_{hitung} > \chi^2_{(11,0.05)}$ or $P_{\text{value}} < \alpha$.

Partial testing was conducted to determine the significance of the parameters on the individual response variables. Testing the significance of the parameters using the Wald test with the following hypothesis [6].

Hypothesis:

$$H_0 : \beta_k = 0$$

$$H_1 : \beta_k \neq 0, k = 1, 2, \dots, p$$

Test Statistics:

$$W_k = \frac{\hat{\beta}_k}{SE(\hat{\beta}_k)} \sim N(0,1) \tag{3}$$

The rejection Area: Reject H_0 if $|W_k| > Z_{\alpha/2}$ or $P_{value} < \alpha$

The evaluation was needed to evaluate the opportunities of the errors made by a classification function, its measured by APER (Apparent Error Rate) the value of the proportion of samples that are incorrectly classified by the classification function [7]. the value of classification accuracy given through the following table.

Table 1. Calculation of Classification Accuracy

<i>Actual Membership</i>	<i>Predicted Membership</i>		
	<i>y = 1</i>	<i>y = 2</i>	<i>y = 3</i>
<i>y = 1</i>	n_{11}	n_{12}	n_{13}
<i>y = 2</i>	n_{21}	n_{22}	n_{23}
<i>y = 3</i>	n_{31}	n_{32}	n_{33}

With :

n_{11} = Yi's sum of y = 1 is appropriately classified as y = 1

n_{12} = Yi's sum of y = 1 is appropriately classified as y = 2

n_{13} = Yi's sum of y = 1 is appropriately classified as y = 3

n_{21} = Yi's sum of y = 2 is appropriately classified as y = 1

n_{22} = Yi's sum of y = 2 is appropriately classified as y = 2

n_{23} = Yi's sum of y = 2 is appropriately classified as y = 3

n_{31} = Yi's sum of y = 3 is appropriately classified as y = 1

n_{32} = Yi's sum of y = 3 is appropriately classified as y = 2

n_{33} = Yi's sum of y = 3 is appropriately classified as y = 3

$$APER(\%) = \frac{n_{12} + n_{13} + n_{21} + n_{23} + n_{31} + n_{32}}{n_{11} + n_{12} + n_{13} + n_{21} + \dots + n_{32} + n_{33}} \times 100\% \tag{3}$$

2.2 Data Source and Research Variable

The source of the data used in this studyresearch is secondary data taken from the medical records of patients suffering breast cancer at Dr. Soetomo Surabaya Hospital in 2019 there were 217 patients. The variables used in this research described in Table 2.

Tabel 2. Research Variable

Indicator	Variable	Categorical	Data Scale
Y	Breast Cancer Stages	1= advanced stage 2= Locally advanced stage 3= Early stage	Ordinal
X1	Grade	1= Grade 3 2= Grade 2 3= Grade 1	Ordinal
X2	Age	-	Ratio
X3	Obesity History	1= Obesity 2= No obesity	Nominal
X4	Comfort Level	1= Pain 2= No Pain	Nominal
X5	Patient Psychology	1= Anxiety / Depression 2= Surrender	Nominal
X6	Experiencing Anemia	1= Yes 2= No	Nominal
X7	Actions taken on the patient	1= Operation (MRM, BCS) 2= Chemotherapy	Nominal
X8	Family History of Suffering from Breast Cancer	1= Yes 2= No	Nominal
X9	Distant Metastasis Occurs	1= Yes 2= No	Nominal

The operational definition of each variable is as follows.

Breast Cancer Stage

Early Stage Breast Cancer: Stage I and III A

Locally Advanced Stage Breast Cancer: Stage III B – IIIC

Advanced Stage Breast Cancer: Stage IV [11].

Grade Breast cancer

Using the WHO criteria, namely the Nottingham Grading system (also called Elston-Ellis modification of the Scarff-Bloom Richardson grading system). This rating scale looks at 3 different cell images and is classified each score from 1-3. The classifications are:

Table 3. Breast Cancer Grade

Grade	Score	Information
Grade I	Score 3-5	Low grade with well differentiated cancer (well differentiated) where the cancer cells do not grow quickly and do not appear to spread.
Grade II	Score 6-7	Cancer with moderate differentiation (moderately/intermediate differentiated) which has a picture between grades 1 and 3.
Grade III	Score 8-9	Cancer that is poorly differentiated (poorly differentiated or undifferentiated) in which cancer cells grow rapidly and are more likely to spread.

Another benefit of determining the grading is to determine the response to therapy that will be given. At a poor degree of differentiation, where cell growth and spread is considered to be more rapid or aggressive, additional therapy is needed besides definitive, namely by administering chemoradiation [13]. The relationship between stage and grade of breast cancer is that the stage in breast cancer

serves to describe the condition of the cancer, namely the location and spread of cancer cells and how far it affects other body organs[9].

Comfort Level

Pain is a common complaint after treatment of breast cancer patients, even years after treatment [17]. Cancer pain is often found in patients who first come for treatment [18].

Patient Psychology

Reactions in some people with cancer vary widely, such as shock, fear, anxiety, feelings of grief, anger, sadness, and even withdrawal. Anxiety is a mental condition filled with worry and fear of what might happen, both related to limited problems and strange things [19].

Anemia

Anemia in cancer patients can cause fatigue and decreased quality of life and increased mortality. In general, the presence of anemia in cancer patients can increase mortality by up to 65%. Patients are said to be anemic if they have hemoglobin < 12 g/dL [20].

Family History of Suffering from Breast Cancer

Family history of inherited breast cancer is a risk factor for breast cancer. Family history of breast cancer will increase the development of breast cancer at a young age [21].

Treatment

Breast cancer treatment consists of surgery, radiation therapy, chemotherapy and hormone blocking drugs [22].

Metastases

Cancer cells have the ability to infiltrate the surrounding tissues and spread (metastasize) through blood vessels and lymph vessels. Metastases are cancer cells that have spread beyond the organs or tissues from where the cancer first appeared. Spread of cancer cells to other parts of the body is affected by many things, such as the type of cancer, the severity or cancer stage, and the location of the cancer originating [23].

4. Result and Discussion

Characteristics the Stage of Breast Cancer Patients

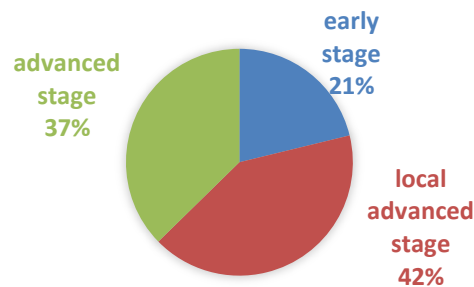


Figure 1. Pie Chart Breast Cancer Stage

Figure 1. Described that the majority of breast cancer patients in DR Soetomo Surabaya Hospital

diagnosed as locally advanced breast cancer, with 42% of them diagnosed with locally advanced breast cancer, 37% of patients were diagnosed with advanced breast cancer and the remaining were diagnosed as early-stage breast cancer.

The grade variable is categorized into three. Grade 1, grade 2, and grade 3. The following is a contingency table between grade and breast cancer stage conditions.

Table 4. Grade of Breast Cancer

Y	X1 (%)			Total
	Grade 3	Grade 2	Grade 1	
Advanced Stage	26.3	10.1	0.9	37.3
Local Advanced Stage	2.6	17.5	1.4	41.5
Early Stage	6.5	9.7	5.1	21.2
Total	55.3	37.3	7.4	100.0

The highest number of patients classified based on the grade and condition of the stage of breast cancer were patients who had grade 3 and suffered from advanced stage breast cancer, which was 26.3% or 57 patients. While the least number of patients is patients who have grade 1 and suffer from breast cancer with advanced stage conditions, which is 0.9% or as many as 2 patients.

Characteristics Patient's Age of Breast Cancer

The patient's age variable was categorized into three. The first category is the age of the patient 27-43 years. While the second category is the age of patients who are less than 44-57 years. The third is the patient's age > 57 years. The following is a contingency table between age variables and breast cancer stage conditions.

Table 5. Patient Age

Y	X2 (%)			Total (%)
	27-43	44-57	>57	
Advanced Stage	9.7	18.9	8.8	37.3
Local Advanced Stage	10.1	19.4	12.0	41.5
Early Stage	6.5	11.5	3.2	21.2
Total	26.3	49.8	24.0	100.0

The largest number of patients classified by age and staging of breast cancer were patients aged 44 – 57 years and suffering from breast cancer with locally advanced conditions, namely 19.4% or 42 patients. While the least number of patients is patients aged > 57 years and suffering from breast cancer with an early stage condition, which is 3.2% or as many as 7 patients.

Characteristics History of Anemia

Variable history of anemia was categorized into two. Anemia and not anemia. Table 7 shows the contingency between these variables and the stage of breast cancer.

Table 6. Anemia

Y	X6 (%)		Total (%)
	Anemia	No Anemia	
Advanced Stage	9.7	27.6	37.3
Local Advanced Stage	5.1	36.4	41.5
Early Stage	2.3	18.9	21.2
Total	17.1	82.9	100.0

The highest number of patients classified based on a history of anemia and breast cancer stage conditions were patients who did not have anemia and had breast cancer with locally advanced stage conditions, namely 36.4% of 217 breast cancer patients. While the least number of patients are patients with anemia and breast cancer with an early stage condition, which is 2.3% of 217 breast cancer patients.

Characteristics Family History of Breast Cancer

Variable family history of breast cancer is categorized into two. Table 7 shows the contingency between these variables and the stage of breast cancer.

Table 7. Family History

Y	X8 (%)		Total (%)
	Yes	No	
Advanced Stage	8.3	29.0	8.3
Local Advanced Stage	3.2	38.2	3.2
Early Stage	3.2	18.0	3.2
Total	14.7	85.3	14.7

The highest number of patients classified based on family history of breast cancer and breast cancer stage conditions were patients who did not have a family history of breast cancer and had breast cancer with locally advanced conditions, namely 38.2% of 217 breast cancer patients. While the least number of patients are patients who do not have a history of breast cancer in their family and suffer from breast cancer with early stage and local advanced stage conditions, which is 3.2% of 217 breast cancer patients

Characteristics of Metastases

Condition variables related to metastases were categorized into two. That is distant metastases and no distant metastases. Table 9 shows the contingency between the variables of the occurrence of distant metastases and the condition of the stage of breast cancer.

Table 8. Metastases

Y	X8 (%)		Total (%)
	Yes	No	
Advanced Stage	37.3	0.0	37.3
Local Advanced Stage	0.0	41.5	41.5
Early Stage	0.0	21.2	21.2
Total	37.3	62.7	100.0

The highest number is patient classified as not having distant metastases with local advanced breast cancer stage conditions were 41.5% of 217 breast cancer patients. In the table above, it can be seen that there are no patients classified as having distant metastases at an early stage or locally advanced stage, as well as in patients with classification not having distant metastases in advanced stages.

Ordinal Logistic Regression Supporting Factors in Stages Conditions of Breast Cancer

Parameter estimation is the first step in ordinal logistic regression analysis. The initial parameter estimation results were obtained from all predictor variables that were thought to support the condition of breast cancer stage in patients at Dr. Soetomo Surabaya Hospital is shown in Table 18. The initial model formed is as follows.

$$LogitP(Y \leq 1 | x_r) = - 20.302 - 2.717X1(1) - 1.780 X1(2) - 0.941 X2(1) - 0.212 X2(2) + 0.757 X3(1) - 0.806 X4(1) - 0.369 X5(1) - 0.520 X6 (1) + 0.081 X7(1) + 1,384 X8(1) - 35,835 X9(1)$$

$$LogitP(Y \leq 2 | x_r) = - 1.592 - 2.717X1(1) - 1.780 X1(2) - 0.941 X2(1) - 0.212 X2(2) + 0.757 X3(1) - 0.806 X4(1) - 0.369 X5(1) - 0.520 X6 (1) + 0.081 X7(1) + 1,384 X8(1) - 35,835 X9(1)$$

After the initial parameter estimation has been carried out, simultaneous testing is used to determine whether the factors that are thought to influence the stage of breast cancer have a significant effect on the condition of the stage of breast cancer by testing together. The hypothesis used in the simultaneous test of ordinal logistic regression analysis is as follows.

Table 9. Simultaneous Test

χ^2	df	P-value	$\chi^2_{0.05, 11}$	Decision
434,668	11	0,000	19,675	Reject H_0

Table 9. shows that with significances level $\alpha = 0.05$ its reject H_0 because the P-value $< \alpha$. So there are at least one of the factors that support the stage of breast cancer. The result of partial test of parameters given by Table 10.

Table 10. Partial Test

Variable	Estimate	Wald	df	P-value	$\chi^2_{0.05, df}$	Decision
$Y = 1$	-20,302	0,002	1	0,968	3,841	-
$Y = 2$	-1,592	3,578	1	0,059	3,841	-
$X_{1(1)}$	-2,717	12,341	1	0,000	3,841	Reject H_0
$X_{1(2)}$	-1,780	5,768	1	0,016	3,841	Reject H_0
$X_{2(1)}$	-0,941	2,396	1	0,122	3,841	Failed to Reject H_0
$X_{2(2)}$	-0,212	0,200	1	0,655	3,841	Failed to Reject H_0
$X_{3(1)}$	0,757	2,878	1	0,090	3,841	Failed to Reject H_0
$X_{4(1)}$	-0,806	3,299	1	0,069	3,841	Failed to Reject H_0
$X_{5(1)}$	-0,369	0,687	1	0,407	3,841	Failed to Reject H_0
$X_{6(1)}$	-0,520	0,523	1	0,407	3,841	Failed to Reject H_0
$X_{7(1)}$	0,081	0,033	1	0,855	3,841	Failed to Reject H_0
$X_{8(1)}$	1,348	4,377	1	0,036	3,841	Reject H_0
$X_{9(1)}$	-35,835	0,001	1	0,970	3,841	Failed to Reject H_0

Table 10. shows that there are only 2 (two) variables had a significant effect in supporting the stage of breast cancer were the grade factor (X_1) and family history of breast cancer (X_8).

Odds Ratio

Odds ratio used to facilitate the interpretation of the model of the significant variables. The odds ratio of this study is as follows.

Table 11. Odds Ratio

Variable	Estimate	Odds Ratio	Variable	Estimate	Odds Ratio
X1(1)	-2,717	0.06	X5(1)	-0.369	0.69
X1(2)	-1,780	0.17	X6(1)	-0.520	0.59
X2(1)	-0.941	0.39	X7(1)	0.081	1.08
X2(2)	-0.212	0.80	X8(1)	1.348	3.84
X3(1)	0.757	2.13	X9(1)	-35,835	2.73
X4(1)	-0.806	0.44			

Table 11. shows that breast cancer patients at Dr. Soetomo Surabaya Hospital with: Grade 3 is likely to be at risk of developing breast cancer at a local advanced stage to an advanced stage 0.06 times compared to grade 1 patients. Grade 2 is likely to be at risk of suffering from breast cancer at a local advanced stage to an advanced stage 0.17 times compared to grade 1 patients. Age > 57 years, has a possible risk of developing locally advanced breast cancer to an advanced stage of 0.39 times than patients who have an age range of 27-43 years. Age range of 44-57 years, has a possible risk of suffering from locally advanced breast cancer to an advanced stage of 0.80 times than patients who have an age range of 27-43 years.

History of obesity have a 2.13 times risk of developing breast cancer at a local advanced stage to an advanced stage compared to patients who do not have a history of obesity. Feel pain disorders tend to have the risk of suffering from breast cancer with local advanced stage to advanced stage 0.44 times compared to those who do not feel pain. Who has a psychological condition of anxiety/ depression tends to have a risk of suffering from breast cancer with a local advanced stage to an advanced stage 0.69 times compared to patients who have a psychological condition of surrender or in the sense of being able to accept the situation.

With anemia condition will have the risk of suffering from breast cancer with local advanced stage to advanced stage 0.59 times than patients who do not have anemia. Who underwent surgical treatment tended to have a risk of developing breast cancer at a local advanced stage to an advanced stage 1.08 times compared to patients undergoing chemotherapy. Who has a history of breast cancer in his family will have a risk of developing breast cancer with a local advanced stage to an advanced stage 3.89 times than patients who do not have a family history of breast cancer. Those detected with metastases in their cancer will have a higher risk of suffering from breast cancer with local advanced to advanced stages 2.73 times than in patients breast cancer undetected metastases in the cancer.

4. Conclusion

The factors that support the condition of the stage of breast cancer in patients at Dr. Soetomo Surabaya Hospital is grade and family history of breast cancer. Breast cancer patients at Dr. Hospital. Soetomo Surabaya with grade 3 is likely to support staging conditions from locally advanced to advanced by 0.06 times compared to grade 1 patients. Patient with grade 2 are likely support staging conditions from local advanced to advanced by 0.17 times compared to grade 1 patients. Patients who have a history of breast cancer in their family will have a risk of developing breast cancer with local advanced to advanced stages 3.84 times than patients without family history of breast cancer.

5. Acknowledgement

Acknowledgement to the Department of Business Statistics, The Directorate of Research and Community Service (DPRM) ITS, for funding this research.

References

- [1] Hu, C., Hart, S. N., Gnanaolivu, R., Huang, H., Lee, K. Y., Na, J., ... & Couch, F. J. (2021). A population-based study of genes previously implicated in breast cancer. *New England Journal of Medicine*, 384(5), 440-451.
- [2] Maller, O., Drain, A. P., Barrett, A. S., Borgquist, S., Ruffell, B., Zakharevich, I., ... & Weaver, V. M. (2021). Tumour-associated macrophages drive stromal cell-dependent collagen crosslinking and stiffening to promote breast cancer aggression. *Nature materials*, 20(4), 548-559.
- [3] Gong, Y., Ji, P., Yang, Y. S., Xie, S., Yu, T. J., Xiao, Y., ... & Shao, Z. M. (2021). Metabolic-pathway-based subtyping of triple-negative breast cancer reveals potential therapeutic targets. *Cell Metabolism*, 33(1), 51-64.
- [4] Gathani, T., Clayton, G., MacInnes, E., & Horgan, K. (2021). The COVID-19 pandemic and impact on breast cancer diagnoses: what happened in England in the first half of 2020. *British Journal of Cancer*, 124(4), 710-712.
- [5] Farvid, M. S., Spence, N. D., Rosner, B. A., Willett, W. C., Eliassen, A. H., & Holmes, M. D. (2021). Post-diagnostic coffee and tea consumption and breast cancer survival. *British journal of cancer*, 124(11), 1873-1881.
- [6] Noordhoek, I., Treuner, K., Putter, H., Zhang, Y., Wong, J., Kranenbarg, E. M. K., ... & Liefers, G. J. (2021). Breast cancer index predicts extended endocrine benefit to individualize selection of patients with HR+ early-stage breast cancer for 10 years of endocrine therapy. *Clinical Cancer Research*, 27(1), 311-319.
- [7] McKinney, S. M., Sieniek, M., Godbole, V., Godwin, J., Antropova, N., Ashrafian, H., ... & Shetty, S. (2020). International evaluation of an AI system for breast cancer screening. *Nature*, 577(7788), 89-94.

- [8] Coles, C. E., Aristei, C., Bliss, J., Boersma, L., Brunt, A. M., Chatterjee, S., ... & Rivera, S. (2020). International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. *Clinical Oncology (Royal College of Radiologists (Great Britain))*, 32(5), 279.
- [9] Balasubramaniam, SM (2013). Risk Factors of Female Breast Carcinoma A Case Control Study at Puducherry. *Indian J Cacer*, 50(1):65-70.
- [10] Unger-Saldaña, K., Miranda, A., Zarco-Espinosa, G., Mainero-Ratchelous, F., Bargalló-Rocha, E., & Miguel Lázaro-León, J. (2015). Health system delay and its effect on clinical stage of breast cancer: Multicenter study. *Cancer*, 121(13), 2198-2206.
- [11] Ye, Y., Pei, L., Wu, C., & Liu, S. (2019). Protective effect of traditional Chinese medicine formula RP on lung microenvironment in pre-metastasis stage of breast cancer. *Integrative cancer therapies*, 18, 1534735419876341.
- [12] Bobrowska-Korczak, B., Gałtarek, P., Skrajnowska, D., Bielecki, W., Wyrebiak, R., Kowalczyk, T., ... & Kałużna-Czaplińska, J. (2020). Effect of zinc supplementation on the serum metabolites profile at the early stage of breast cancer in rats. *Nutrients*, 12(11), 3457.
- [13] Ramanto, K. N., Agustriawan, D., Parikesit, A. A., Nurdiansyah, R., & Nasution, M. Z. (2019, June). Correlation and Meta-Analysis of HER2 in Each Stage of Breast Cancer. In *IOP Conference Series: Materials Science and Engineering* (Vol. 546, No. 6, p. 062024). IOP Publishing.
- [14] Ataman, M. G., & Sariyer, G. (2021). Predicting waiting and treatment times in emergency departments using ordinal logistic regression models. *The American Journal of Emergency Medicine*, 46, 45-50.
- [15] Xu, K., Zhou, M., Yang, D., Ling, Y., Liu, K., Bai, T., ... & Li, J. (2020). Application of ordinal logistic regression analysis to identify the determinants of illness severity of COVID-19 in China. *Epidemiology & Infection*, 148.
- [16] Mebetu, D., Atsedeweyn, A., & Abathun, D. (2021). Ordinal logistic regression analysis of hypertension data and identifying factors that influence the incidence of hypertension in Gondar University Teaching Hospital, North-west Ethiopia. *Journal of Public Health and Epidemiology*, 13(3), 176-183.
- [17] Bennett, TM, and Purushotham, AD (2009). Understanding breast cancer related lymphoedema surgeon, Medline 2, 120–4.
- [18] Gartner, R., Jensen, MB, Nielsen, J., Ewertz, M., Kroman, N., and Kehlet, H. (2009). Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA*, 302:1985–1992
- [19] Gavic, L., Cigic, L., Biocina Lukenda, D., Gruden, V., & Gruden Pokupec, J. S. (2014). The role of anxiety, depression, and psychological stress on the clinical status of recurrent aphthous stomatitis and oral lichen planus. *Journal of Oral Pathology & Medicine*, 43(6), 410-417.
- [20] Lai, K., Huang, G., Su, L., & He, Y. (2017). The prevalence of thalassemia in mainland China: evidence from epidemiological surveys. *Scientific reports*, 7(1), 1-11.
- [21] Vanni, G., Materazzo, M., Pellicciaro, M., Ingallinella, S., Rho, M., Santori, F., ... & Buonomo, O. C. (2020). Breast cancer and COVID-19: the effect of fear on patients' decision-making process. *in vivo*, 34(3 suppl), 1651-1659.
- [22] Kabel, A. M., & Baali, F. H. (2015). Breast cancer: insights into risk factors, pathogenesis, diagnosis and management. *Journal of Cancer Research and Treatment*, 3(2), 28-33.
- [23] Benzarti, M., Delbrouck, C., Neises, L., Kiweler, N., & Meiser, J. (2020). Metabolic potential of cancer cells in context of the metastatic cascade. *Cells*, 9(9), 2035