Survival Rate and Prognostic Factors in Turkish Women Patients with Breast Cancer

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Abstract

Background: The study aimed to estimate the overall and disease-free survival rates of breast cancer patients and the factors affecting these rates.

Methods: In this retrospective study, data were obtained from 686 patients diagnosed with breast cancer in Sivas Cumhuriyet University Faculty of Medicine Research and Application Hospital Oncology Center between 1988 and 2014. Total population sampling method was used. The survival rates at certain periods were determined by creating a Life Table. By using the Kaplan-Meier Analysis, the mean survival times and rates were determined, and whether the variables had an impact on survival was examined. By applying Cox regression analysis, the effect of prognostic factors that are significant on the survival time of breast cancer patients was examined.

Results: Overall mean survival time was found as 208.4±11.8 months. According to Kaplan-Meier analysis, 1, 5, 10 and 20-years overall survival rates were 96.6 ± 0.07%, 82.3 ± 1.7%, 64.4 ± 3.4% and 49%± 7.4%, respectively. According to Cox regression analysis results, variables that influence overall survival time were found as disease stage, multicentricity status, ECOG (performance status), presence of diabetes, CA15-3 value, neutrophil/lymphocyte ratio. Moreover, variables that had an impact on the disease-free survival time were found as tumor grade, multicentricity, and ECOG.

Conclusion: Many factors other than disease can prolong survival or accelerate death. Considering the findings of this study may be useful in planning the treatment of breast cancer patients have positive affect on overall survival rates.

Keywords: Breast cancer; Survival analysis; Cox regression; Life table; Kaplan-Meier

Introduction

Cancer is a public health issue and problem for both the world and our country with its burden of disease, lethality and increasing tendency. According to the World Cancer Database (GLOBOCAN) 2018 data, global cancer burden reached 18.1 million cases and 9.6 million cancer deaths. The International Agency for Research on Cancer (IARC) estimates that one in five men and one in six women worldwide will suffer cancer throughout their lives, and one in eight men and one in eleven women will die of cancer (1).
Breast cancer is the second most common cancer in the world, and it is the cancer that causes the most death among women. According to Globocan 2018 data, when the distribution of breast cancer cases in the world is analyzed, Asia comes first with 43.6% followed by Europe with 25%. In mortality rates, Asia comes first with 49.6% and Europe is second with 22%.

Although breast cancer is common, it is a type of cancer that generally shows a slow development rate. When the diagnosis is made early, successful treatment results can be obtained and the mortality rate can be reduced. For this reason, experts in all regions of the world are working on breast cancer (2-8). Because knowing every information and the factors that may affect the treatment processes positively or negatively regarding the course of breast cancer can help develop strategies for both improving the quality of life of patients and reducing the cost of treatment.

Mortality decreased in some western countries due to early diagnosis of the disease and improvement of treatment methods (2, 9), mortality is higher among developing countries due to low awareness and low level of early diagnosis (2, 10-12). The survival rate has been reported as 73% in developed countries and 53% in developing countries (2, 10, 11). “In 1993, the incidence of breast cancer was 24 per 100,000, and it increased to 50 per 100,000 in 2013; the number of new patients was 22,345 in Turkey in 2018” (13-15). Recently, the survival rate and prognostic factors of Iranian breast cancer patients were investigated (2).

In this study, the survival rates of breast cancer patients, which are very common in our geography, were investigated. For this purpose, Kaplan-Meier analysis was applied to the data obtained from breast cancer patients treated at Sivas Cumhuriyet University Faculty of Medicine Research and Application Hospital Oncology Center. Then 1, 5, 10 and 20 years survival rates were determined. Moreover, prognostic factors that affect the survival time of breast cancer patients were investigated using cox regression analysis.

Methods

In this retrospective study, data were obtained from 686 patients diagnosed with breast cancer in Sivas Cumhuriyet University Faculty of Medicine Research and Application Hospital Oncology Center between 1988 and 2014. The survival analysis was used to analyze and interpret the data obtained until the occurrence of any event of interest.

The time elapsed between a certain starting time and death (failure) of a living organism or an inanimate object is called the "survival time" or "failure time" (16). The survival analysis estimates how long an individual with a particular illness will survive after a diagnosis of the disease or how long it will take the disease to recur (relapse) after beginning the treatment.

The main feature that distinguishes survival analyzes from other analyzes is that the stopped, that is, censored data is included in the analysis. When the event of interest in a study is the lifetime of an individual or a case, it is sometimes not possible for them to be kept under observation until the end of the study. Individuals or cases who come out of the observation for various reasons are called paused or censored observation.

In the survival analysis, nonparametric and semi-parametric survival analyzes are used because the data structure is censored and the results obtained by parametric analysis methods may not be healthy.

The most well-known of these analyzes are:

- Life table analysis
- Kaplan-Meier Analysis
- Cox Regression Analysis

In these analysis methods, the results may differ as well as in the same direction.

The life table method can be used when the lifetime is grouped by intervals and the number of patients who die at each interval is measured (16). Main differences between the Kaplan-Meier method and the life table are that the follow-up period of the study is not divided into certain time intervals, that while the probability of death is calculated, the ones who left the study alive are
not included. Moreover, it can be studied with fewer observations in the Kaplan-Meier method (17). Cox regression (18) model used to measure the effects of explanatory variables on survival time, is an extremely flexible regression model that does not require any assumptions about the structure of survival data. In the basis of the model, there is a logic that the risk rate or survival times are taken as a dependent variable and these vary depending on some factors. In Cox regression model, the effects of explanatory variables on the dependent variable are multiplica-

tive. Refer to references (19,20) for more information.

**Results**

Incidents (death) occurred in 132 of the patients. The youngest patient’s age was 18 and the oldest 89 yr. The mean age was 52 and the median 51 yr.

**Statistical Analysis**

As seen in Table 1, 1, 5, 10, and 20-year overall survival rate was 97%, 78%, 63%, and 49%, respectively.

**Table 1: Overall life table of patients observed**

| Interval Start Time (Month) | Number of Patients Observed | Number of Censored Patients | Number of Risky Patients | Number of Patients Died | Termination Rate | Survival Rate | Cumulative Survival Rate |
|-----------------------------|-----------------------------|-----------------------------|--------------------------|------------------------|-----------------|---------------|--------------------------|
| 0                           | 686                         | 1                           | 685.5                    | 20                     | 0.03            | 0.97          | 0.97                     |
| 12                          | 665                         | 65                          | 632.5                    | 19                     | 0.03            | 0.97          | 0.94                     |
| 24                          | 581                         | 91                          | 535.5                    | 24                     | 0.04            | 0.96          | 0.90                     |
| 36                          | 466                         | 91                          | 420.5                    | 15                     | 0.04            | 0.96          | 0.87                     |
| 48                          | 360                         | 68                          | 326                      | 16                     | 0.05            | 0.95          | 0.82                     |
| 60                          | 276                         | 50                          | 251                      | 13                     | 0.05            | 0.95          | 0.78                     |
| 72                          | 213                         | 57                          | 184.5                    | 2                      | 0.01            | 0.99          | 0.77                     |
| 84                          | 154                         | 41                          | 133.5                    | 9                      | 0.07            | 0.93          | 0.72                     |
| 96                          | 104                         | 22                          | 93                       | 5                      | 0.05            | 0.95          | 0.68                     |
| 108                         | 77                          | 16                          | 69                       | 4                      | 0.06            | 0.94          | 0.64                     |
| 120                         | 57                          | 8                           | 53                       | 1                      | 0.02            | 0.98          | 0.63                     |
| 132                         | 48                          | 17                          | 39.5                     | 1                      | 0.03            | 0.97          | 0.61                     |
| 144                         | 30                          | 7                           | 26.5                     | 1                      | 0.04            | 0.96          | 0.59                     |
| 156                         | 22                          | 5                           | 19.5                     | 0                      | 0.0             | 1.00          | 0.59                     |
| 168                         | 17                          | 3                           | 15.5                     | 0                      | 0.0             | 1.00          | 0.59                     |
| 180                         | 14                          | 3                           | 12.5                     | 1                      | 0.08            | 0.92          | 0.54                     |
| 192                         | 10                          | 1                           | 9.5                      | 1                      | 0.11            | 0.89          | 0.49                     |
| 204                         | 8                           | 1                           | 7.5                      | 0                      | 0.0             | 1.00          | 0.49                     |
| 216                         | 7                           | 2                           | 6                        | 0                      | 0.0             | 1.00          | 0.49                     |
| 228                         | 5                           | 1                           | 4.5                      | 0                      | 0.0             | 1.00          | 0.49                     |
| 240                         | 4                           | 1                           | 3.5                      | 0                      | 0.0             | 1.00          | 0.49                     |
| 252                         | 3                           | 1                           | 2.5                      | 0                      | 0.0             | 1.00          | 0.49                     |
| 264                         | 2                           | 0                           | 2                        | 0                      | 0.0             | 1.00          | 0.49                     |
| 276                         | 2                           | 0                           | 2                        | 0                      | 0.0             | 1.00          | 0.49                     |
| 288                         | 2                           | 1                           | 1.5                      | 0                      | 0.0             | 1.00          | 0.49                     |
| 300                         | 1                           | 0                           | 1                        | 0                      | 0.0             | 1.00          | 0.49                     |
| 312                         | 1                           | 1                           | 0.5                      | 0                      | 0.0             | 1.00          | 0.49                     |
The disease-free survival time is the total time between the first relapse and the primary treatment of the disease. As seen in (Table 2), 1, 5, 10, and 20-year disease-free survival rate of the patients are 99%, 94%, 91%, and 68%, respectively.

### Table 2: Disease-free life table of the patients observed

| Interval Start Time (Month) | Number of Patients Observed | Censored Patients | Number of Risky Patients | Number of Patients Died | Termination Rate | Survival Rate | Cumulative Survival Rate |
|-----------------------------|-------------------------------|-------------------|--------------------------|------------------------|----------------|---------------|--------------------------|
| 0                           | 686                           | 70                | 651                      | 9                      | 0.01           | 0.99          | 0.99                     |
| 12                          | 607                           | 76                | 569                      | 7                      | 0.01           | 0.99          | 0.97                     |
| 24                          | 524                           | 103               | 472.5                    | 6                      | 0.01           | 0.99          | 0.96                     |
| 36                          | 415                           | 94                | 368                      | 5                      | 0.01           | 0.99          | 0.95                     |
| 48                          | 316                           | 77                | 277.5                    | 3                      | 0.01           | 0.99          | 0.94                     |
| 60                          | 236                           | 52                | 210                      | 0                      | 0.0            | 1.00          | 0.94                     |
| 72                          | 184                           | 56                | 156                      | 1                      | 0.01           | 0.99          | 0.93                     |
| 84                          | 127                           | 42                | 106                      | 1                      | 0.01           | 0.99          | 0.92                     |
| 96                          | 84                            | 20                | 74                       | 0                      | 0.0            | 1.00          | 0.92                     |
| 108                         | 64                            | 18                | 55                       | 1                      | 0.02           | 0.98          | 0.91                     |
| 120                         | 45                            | 7                 | 41.5                     | 0                      | 0.0            | 1.00          | 0.91                     |
| 132                         | 38                            | 16                | 30                       | 1                      | 0.03           | 0.97          | 0.88                     |
| 144                         | 21                            | 7                 | 17.5                     | 0                      | 0.0            | 1.00          | 0.88                     |
| 156                         | 14                            | 4                 | 12                       | 1                      | 0.08           | 0.92          | 0.80                     |
| 168                         | 9                             | 2                 | 8                        | 0                      | 0.0            | 1.00          | 0.80                     |
| 180                         | 7                             | 1                 | 6.5                      | 1                      | 0.15           | 0.85          | 0.68                     |
| 192                         | 5                             | 0                 | 5                        | 0                      | 0.0            | 1.00          | 0.68                     |
| 204                         | 5                             | 1                 | 4.5                      | 0                      | 0.0            | 1.00          | 0.68                     |
| 216                         | 4                             | 1                 | 3.5                      | 0                      | 0.0            | 1.00          | 0.68                     |
| 228                         | 3                             | 0                 | 3                        | 0                      | 0.0            | 1.00          | 0.68                     |
| 240                         | 3                             | 1                 | 2.5                      | 0                      | 0.0            | 1.00          | 0.68                     |
| 252                         | 2                             | 0                 | 2                        | 0                      | 0.0            | 1.00          | 0.68                     |
| 264                         | 2                             | 0                 | 2                        | 0                      | 0.0            | 1.00          | 0.68                     |
| 276                         | 2                             | 0                 | 2                        | 0                      | 0.0            | 1.00          | 0.68                     |
| 288                         | 2                             | 1                 | 1.5                      | 0                      | 0.0            | 1.00          | 0.68                     |
| 300                         | 1                             | 0                 | 1                        | 1                      | 1.00           | 0.0           | 0.0                      |

**Kaplan-Meier Analysis**

By using Kaplan-Meier analysis, both overall survival and disease-free survival rates were examined.

Overall mean survival time (months) ± Standard Error (SE) [95% Confidence Interval (CI)] was found as 208.4 months ± 11.8 months [185.3-231.4].

1, 5, 10, and 20-year overall survival rate was found as 96.6% ± 0.07%, 82.3% ± 1.7%, 64.4% ± 3.4%, and 49.5% ± 7.4%, respectively. The overall survival curve is given in Fig. 1.
The number of relapsed patients was 37. The number of censored data was 649 (94.6%). The mean disease-free survival time was found as 211 months ± 10.5 months [190.4-231.5]. 1, 5, 10, and 20-year disease-free survival rate was found as 98.6% ± 0.05%, 94% ± 1.1%, 90.6 ± 2.4%, and 69% ± 12.4%, respectively. The disease-free survival curve was given in Fig. 2.

With Kaplan-Meier analysis, factors affecting survival times were determined by looking at the results (P<0.05) of Log-rank tests for each variable. Factors affecting overall survival time were found as disease stage, patient's age, C-erb B-2 status, LUMB, tumor grade, tumor diameter, LVI1, multicentricity, ECOG, CEA value, CA15-3 value, neutrophil / lymphocyte ratio, neutrophil/Plt rate. Average, standard error and 95% confidence intervals of survival times for these factors are given in Table 3.

### Table 3: Averages of overall survival times by effective factors

| Variable          | Mean Estimate | Std. Error | 95% Confidence Interval |
|-------------------|---------------|------------|-------------------------|
|                   |               |            | Lower Limit              | Upper Limit              |
| Stage I           | 176.860       | 9.382      | 158.471                 | 195.249                 |
| Stage II          | 223.672       | 16.998     | 190.356                 | 256.987                 |
| Stage III         | 138.996       | 10.342     | 118.726                 | 159.266                 |
| Stage IV          | 41.417        | 8.140      | 25.463                  | 57.371                  |
| Stage unknow      | 206.778       | 49.791     | 109.187                 | 304.368                 |
| Stage insitu      | 133.923       | 8.721      | 116.830                 | 151.016                 |
| Overall           | 208.356       | 11.757     | 185.313                 | 231.400                 |
| Under 35          | 149.660       | 15.006     | 120.249                 | 179.071                 |
| 36-45             | 211.637       | 17.074     | 178.171                 | 245.102                 |
| 46-55             | 203.076       | 9.618      | 184.225                 | 221.927                 |
| 56-65             | 138.411       | 11.655     | 115.568                 | 161.255                 |
| 66-75             | 101.475       | 7.366      | 87.039                  | 115.912                 |
| Over 75           | 73.898        | 8.316      | 57.597                  | 90.198                  |
| Overall           | 208.356       | 11.757     | 185.313                 | 231.400                 |
| CerB2 negative    | 169.838       | 11.026     | 148.818                 | 190.356                 |
| CerB2 positive    | 187.267       | 8.140      | 168.726                 | 205.766                 |
| Overall           | 197.721       | 8.140      | 178.171                 | 217.271                 |
| LUMBA             | 225.554       | 21.897     | 182.636                 | 268.473                 |
| LUMBA (her2-)     | 165.981       | 17.074     | 148.818                 | 183.144                 |
| LUMBA (her2+)     | 99.464        | 9.618      | 89.107                  | 109.821                 |
| her2+             | 130.020       | 10.332     | 101.421                 | 158.621                 |
| Overall           | 203.076       | 8.140      | 170.852                 | 234.648                 |
| Tumor Grade 1.00  | 172.009       | 15.288     | 148.818                 | 208.865                 |
| Tumor Grade 2.00  | 188.845       | 15.288     | 158.880                 | 218.810                 |
Factors affecting the disease-free survival time were found as Ki-67 value, LUMB, grade, ECOG, diabetes, CEA value, CA15-3 value. Average, standard error and 95% confidence intervals of disease-free survival times for these factors are given in Table 4.

Table 4: Averages of disease-free survival times by effective factors

| Variable                        | Mean        | Std. Error | 95% Confidence Interval  |
|---------------------------------|-------------|------------|--------------------------|
| Ki67 value under 28             | 130.125     | 5.408      | 119.524 - 140.725        |
| Ki67 value over 28              | 217.639     | 17.905     | 182.546 - 252.732        |
| Overall                         | 209.989     | 13.443     | 183.640 - 236.338        |
| LUMBA                           | 299.721     | 3.787      | 292.300 - 307.143        |
| LUMBA (her2-)                   | 149.938     | 6.305      | 137.581 - 162.295        |
| LUMBA (her2+)                   | 114.436     | 3.712      | 107.161 - 121.710        |
| her2+                           | 173.443     | 6.760      | 159.606 - 187.281        |
| trible(-)                       | 166.057     | 7.060      | 152.808 - 187.306        |
| Overall                         | 248.878     | 24.061     | 201.719 - 296.037        |
| Tumor Grade 1.00                | 230.649     | 7.151      | 216.634 - 244.665        |
| Tumor Grade 2.00                | 211.244     | 31.566     | 149.374 - 273.114        |
| Tumor Grade 3.00                | 149.211     | 6.153      | 137.151 - 161.271        |
Cox Regresyon Analysis
In this section, by applying Cox regression analysis, the effect of 23 independent variables was measured in the death (survival times) of breast cancer patients. The results of Cox regression analysis conducted to determine the variables affecting overall survival are seen in Table 5. Accordingly, the variables that have an effect on the overall survival time were found as the stage of the disease, multicentricity status, ECOG (performance status), presence of diabetes, CA15-3 value, and neutrophil/lymphocyte ratio.

The death risk of patients in stage 4 was 60.433 times more than patients in stage 1 (P=0.008). No significant difference was observed in the second and third stages. Those who had multicentricity carry 3.063 times more death risk than who did not (P=0.043). While there was no significant difference in ECOG (performance status) 0, 1, 2, there was a significant difference in ECOG 3. Patients with diabetes were 4.93 (4.93=1/, 203) times more at risk than those without diabetes (P=0.047). CA15-3 value was another variable that affects survival time (P=0.0). Neutrophil/lymphocyte ratio was also another significant variable (P=0.015). The increase in this rate increased the survival time.

The results of Cox regression analysis conducted to determine the variables affecting disease-free survival are seen in Table 6.

### Table 5: Cox regression analysis results for overall survival

| Variable                      | β   | Std Error | Wald | d.f. | p     | Exp(β) | 95% Confidence Interval | 95% Confidence Interval |
|-------------------------------|-----|-----------|------|------|-------|--------|-------------------------|-------------------------|
| Age                           | 0.044 | 0.033     | 1.773 | 1    | 0.183 | 1.045  | 0.980-1.114             | 0.738-23.108             |
| Menopause condition           | 1.418 | 0.879     | 2.604 | 1    | 0.107 | 4.129  | 0.738-23.108             |                         |
| ER                            | -0.010 | 1.342     | 0.0   | 1    | 0.994 | 0.990  | 0.071-13.738             |                         |
| PR                            | 0.156 | 0.806     | 0.038 | 1    | 0.846 | 1.169  | 0.241-5.668              |                         |
| CerB2                         | -0.198 | 0.870     | 0.052 | 1    | 0.820 | 0.820  | 0.149-4.518              |                         |
| ki67                          | 0.012 | 0.011     | 1.221 | 1    | 0.269 | 1.012  | 0.991-1.033              |                         |
Table 6: Cox regression analysis for disease-free survival

| Variable          | β   | Std Error | Wald  | d.f. | p   | Exp(β) | 95% Confidence Interval |
|-------------------|-----|-----------|-------|------|-----|--------|-------------------------|
| Stage             |     |           |       |      |     |        |                         |
| Stage (1)         | 0.437 | 1.105     | 107.970 | 0.002 | 1 | 0.997 | 1.549 | 0.0 | 1.241E+092 |
| Stage (2)         | 4.367 | 1.325 | 107.711 | 0.002 | 1 | 0.968 | 78.844 | 0.0 | 3.761E+093 |
| Stage (3)         | 5.079 | 1.552 | 108.516 | 0.002 | 1 | 0.962 | 160.665 | 0.0 | 7.760E+093 |
| Stage (4)         | 12.967 | 1.531 | 109.516 | 0.002 | 1 | 0.906 | 427844.35 | 0.0 | 7.100E+098 |
| Histology         |     |           |       |      |     |        |                         |
| histology(1)      | -1.413 | 1.174     | 1.448 | 0.014 | 1 | 0.907 | 0.758 | 0.007 | 78.897 |
| histology(2)      | -0.277 | 2.370     | 0.896 | 0.014 | 1 | 0.907 | 0.758 | 0.007 | 78.897 |
| histology(3)      | -7.592 | 8.020 | 0.896 | 0.014 | 1 | 0.907 | 0.758 | 0.007 | 78.897 |
| Menopause         | 2.208 | 1.192 | 3.434 | 0.014 | 1 | 0.907 | 9.101 | 0.880 | 94.089 |

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Accordingly, variables that had an effect on disease-free survival time were found as tumor grade, multicentricity, ECOG (performance status), and ECOG (1).

In addition, patients with tumor grade 3 were at 10.75 (1/0.093) times more risk than patients who were 1. Patients with multicentricity were at 11.11 (11.11=1/0.090) times more risk than non-multicentric patients. Patients with ECOG 4 were at 200 (200=1/0.005) times more risk than patients with ECOG 2.

Discussion

In this retrospective study conducted in the Oncology Center of Sivas Cumhuriyet University Faculty of Medicine Research and Application Hospital in Turkey, 1, 5, 10, and 20-year overall survival rate was found as 96.6% ± 0.07%, 82.3% ± 1.7%, 64.4% ± 3.4%, and 49.5%± 7.4%, respectively. Variables that affect the overall survival time were found as disease stage, multicentricity status, ECOG (performance status), presence of diabetes, CA15-3 value, neutrophil / lymphocyte ratio. Moreover, variables that affect the disease-free survival time were found as tumor grade, multicentricity, and ECOG.

In a similar study among women with breast cancer in Iran (2), the survival rate decreased as the patient follow-up time increased. In addition, a significant relationship was observed between survival time and variables such as age, tumor size, lymph node number, stage, histological grade, estrogen receptor, progesterone receptor, and lymphovascular invasion. 1, 5, 10, 15, 20 and 25-year overall survival rate was found as 95%, 75%, 60%, 47%, 46% and 46%, respectively.
Moreover, in a retrospective cohort study of in-patient breast cancer cases in Indonesia (8), important factors associated with survival rate were found to be metastasis and comorbidity. In another study conducted in Egypt to determine the relationship between the survival time of women with breast cancer and sociodemographic and pathological factors (5), the median survival time was 83.8 ± 3.2. In addition, education level, bone metastasis, lung metastasis, tumor size and number of nodes were significantly correlated with survival. It is understood from these studies conducted in different countries, at different times and using different variables, the stage of the disease, the tumor size, the presence of another disease, and metastasis variables can be said to be common prognostic factors that affect the survival of breast cancer patients. Moreover, factors such as the level of awareness, screening programs, early diagnosis, access to treatment may lead to different survival rates according to countries.

Conclusion

The breast cancer was investigated, which is very common in our region. In addition, the prognostic factors were investigated affecting the survival rates and survival times of Turkish breast cancer patients. I hope that the findings from this study will not only contribute to the treatment processes of patients in this region, but will also contribute to the creation of general treatment strategies by comparing the results of similar studies conducted in different geographies of the world.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The author declares that there is no conflict of interest.

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