

Iranian Quarterly Journal
of Breast Disease. 2022;
15(1):4-17.

Original Article

Evaluation of Factors Related to Short-Term and Long-Term Survival of Breast Cancer Patients by Mixture Cure Model

Fendereski A¹, Hajizadeh E^{1*}, Haghghat S^{2**}, Rasekhi A¹

¹ Department of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

² Department of Breast Diseases, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran

Receive: 2/12/2021
Accepted: 21/1/2022

*Corresponding Author:
hajizadeh@modares.ac.ir
**Co-correspond:
haghghat@acecr.ac.ir

Ethics Approval:
IR.MODARES.REC.1397.278

Abstract

Introduction: Breast cancer is the most common cancer among women. Today, with advancements in medical sciences, increasing the cure probability of patients as well as increasing survival time is an important goal of cancer treatment. Therefore, in this study, in addition to examining patients' survival, we investigated the cure probability of breast cancer patients and its prognostic factors using the semiparametric mixture cure model.

Methods: This is a retrospective cohort study of 1310 breast cancer patients admitted to Motamed Cancer Institute from 1995 to 2013 and followed up until 2018. The Kaplan-Meier curve and a semiparametric mixture cure model were fitted to data. In this model, patients were divided into two categories of cured and uncured, then the cure rate and the survival rate of uncured patients were calculated, and related factors were identified.

Results: Of the 1310 women with breast cancer in the study, 235 (18.1%) cases died and others were censored. Based on the Kaplan-Meier curve, the cure rate was 68%, and the last death case was observed about 12 years after diagnosis. Obesity, lymph node involvement, and mastectomy were identified as risk factors for patients' long-term survival, while larger tumor size, more advanced stage of the disease, and lack of chemotherapy were risk factors for short-term survival.

Conclusion: These findings indicate that many prognostic factors for breast cancer are not only important when choosing a treatment strategy in the short term, but they also play an important role in the long-term to identifying high-risk patients and those who still need further follow-up.

Keywords: Breast Cancer, Mixture Cure Model, Survival Analysis

Introduction

Breast cancer is the main cause of cancer mortality and morbidity among women worldwide(1). Nowadays due to cancer treatment progress, a fraction of patients is completely improved following treatment courses which called cured or long-term survivors and will have similar survival to the general population (2). In such cases, cure models can be used to analyze survival data(3). In cure models, the odds of cure or long-term survival and survival rate of uncured patients or short-term survival are determined. Moreover, factors related to patients' survival or cure probability can be calculated by this model. In this study, we investigate the cure fraction and survival rate of breast cancer patients and the related factors using the semiparametric mixture cure model.

Materials & Methods

In this current retrospective cohort study, we used data for 1310 female breast cancer patients admitted to Motamed Cancer

Institute between 1995 to 2013 and followed them up until 2018. The survival time was defined months from the diagnosis date to the death or the last confirmed date of patients' status. A proportional hazard mixture cure model was fitted to the data. In a mixture cure model, it is supposed that the population is a mixture of two groups: the cured, or long-term survivors, and the uncured, or short-term survivors. The odds of cure were indicated by the odds ratio (OR) and the risk of death was denoted by hazard ratio (HR).

Results

Of the 1310 cases, 235 (18.1%) had died. The median age of patients was 46 years and mean survival time was 224.37 ± 4.66 months. In addition, the 5-, 10-, and 15-year survival rates were calculated at 85%, 72%, and 68%, respectively. The Kaplan-Meier survival curve is shown in Figure 1. The survival plot is almost flat after about 141 months, and the cure fraction is about 68%.

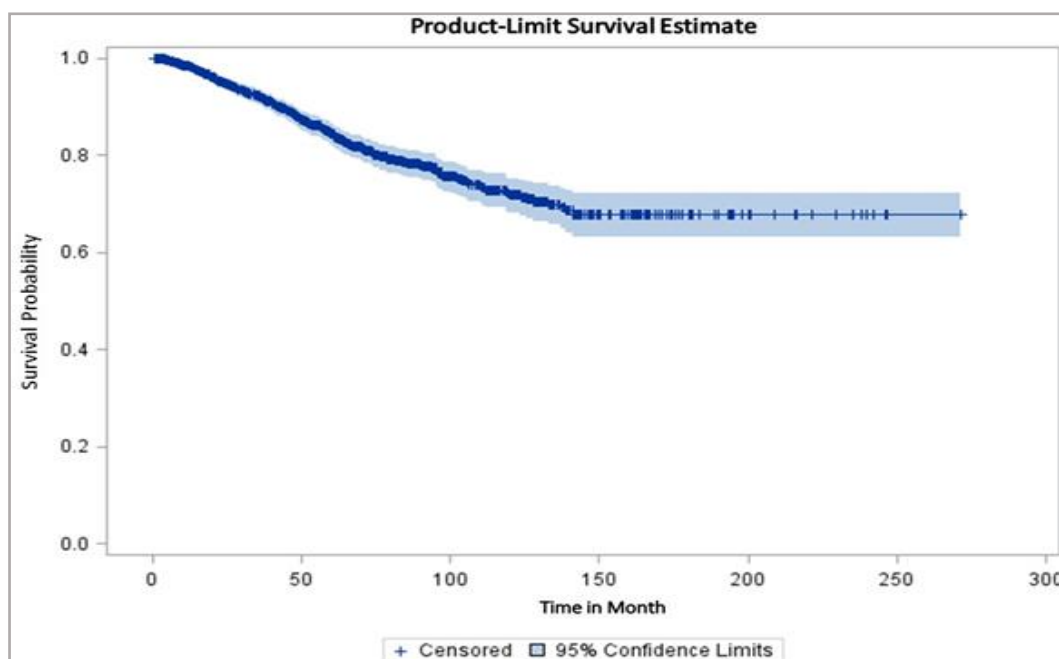


Figure 1: The Kaplan-Meier Survival Curve with 95% Confidence Limit for Breast Cancer Patients

According to the multivariate mixture cure model, chemotherapy, tumor size, and cancer stage were important factors in short-term survival, while BMI, lymph

node involvement, hormone therapy, and type of surgery were associated with the cure probability of patients in the long term (Table 1).

Table 1: Estimated Odds Ratio (OR) and Hazard Ratio (HR) Using the Cox Mixture Cure Model

Variables	HR (95% CI)	P value	OR (95% CI)	P value
BMI ≥ 30 vs <30	0.89 (0.63–1.25)	0.523	0.41 (0.29–0.59)	<0.001
Tumor size 2-5 cm vs <2 cm	2.13 (0.95–4.76)	0.064	1.06 (0.56–2.00)	0.866
Tumor size >5 cm vs <2 cm	3.20 (1.36–7.50)	0.007	0.96 (0.45–2.05)	0.922
Stage II vs I	1.97 (0.69–5.56)	0.203	2.05 (0.85–4.98)	0.112
Stage III vs I	3.20 (0.97–10.57)	0.056	1.70 (0.53–5.40)	0.367
Stage IV vs I	3.56 (1.06–11.96)	0.039	0.56 (0.15–2.02)	0.383
Lymph node involvement Yes vs No	1.45 (0.82–2.57)	0.193	0.51 (0.31–0.84)	0.007
Surgery BCS vs MRM	1.07 (0.72–1.59)	0.717	1.95 (1.37–2.77)	<0.001
Hormone therapy Yes vs No	0.85 (0.45–1.59)	0.622	2.55 (1.31–4.98)	0.005
Chemotherapy Yes vs No	0.19 (0.09–0.41)	<0.001	0.54 (0.25–1.17)	0.118

HR: hazard ratio; OR: odds ratio; MRM: modified radical mastectomy; BCS: breast-conserving surgery

Discussion

Our result showed that the median age of patients was 46.0 years, which was less than the median age in the East Asian countries (48–54 years) (4). The difference may be due to the younger age structure of the Iranian population or different disease patterns. In this study, obese patients were less likely to be cured. Patients with larger tumor size and higher stages of disease in the early years after diagnosis should be given more attention and might have higher risk of death. On the other hand, patients with lymph node involvement will have a lower probability of cure in the long term, which still requires more medical care. Chemotherapy had protective effect in the short term, while patients who had BCS and hormone therapy exhibited a better cure probability. In the study by

Hosseini et al (5), chemotherapy, hormone therapy, BCS, and radiotherapy were found to be associated with an increased odds of cure. Furthermore, in a multicenter study by Andersson et al (6), patients who had BCS showed a lower hazard of death than those who had MRM, a finding similar to our results.

Conclusion

In conclusion, the provision of nutrition counseling, maintaining a healthy weight, and shorter referral intervals need to be considered in the follow-up process. It is also recommended that the association of BCS and hormone therapy with increased cure probability be taken into consideration in the treatment protocol of patients according to the stage of the disease.

References

1. Miller KD, Goding Sauer A, Ortiz AP, Fedewa SA, Pinheiro PS, Tortolero- Luna G, et al. Cancer statistics for hispanics/latinos, 2018. *CA Cancer J Clin.* 2018; 68(6):425-45.
2. Haghghat S, Akbari M, Ghaffari S, Yavari P. Standardized breast cancer mortality rate compared to the general female population of Iran. *Asian Pac J Cancer Prev.* 2012; 13(11): 5525-8.
3. Schneider M. Dealing with Heterogeneity in Discrete Survival Analysis using the Cure Model. *epububuni-muenchende.* 2019.
4. Fan L, Goss PE, Strasser-Weippl K. Current status and future projections of breast cancer in Asia. *Breast care.* 2015; 10(6):372-8.
5. Hoseini M, Bahrampour A, Mirzaee M. Comparison of weibull and lognormal cure models with cox in the survival analysis of breast cancer patients in Rafsanjan. *J Res Health Sci.* 2017; (1):369.
6. Andersson Y, Bergkvist L, Frisell J, de Boniface J. Long-term breast cancer survival in relation to the metastatic tumor burden in axillary lymph nodes. *Breast Cancer Res Treat.* 2018; 171(2):359-69.