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Random Survival Forest Model for Predicting Survival in Non-Metastatic Breast Cancer

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ABSTRACT

Background & Objective: Breast cancer is one of the most commonly diagnosed cancers in women worldwide and remains a major public health concern in both developed and developing countries. This study aimed to identify key prognostic factors influencing survival in patients with non-metastatic breast cancer. A predictive model was developed using the Random Survival Forest (RSF) method to enhance survival estimation and support clinical decision-making.

Materials & Methods: In this retrospective cohort study, the medical records of 767 patients with non-metastatic breast cancer who were treated at the Mahdia Radiotherapy Center in Hamadan between 2006 and 2018 were reviewed. After excluding incomplete records, 442 patients remained for the final analysis. Demographic, clinical, and treatment-related data were extracted from the patients' medical history. Both the Cox proportional hazards (PH) regression (Cox regression) model and the RSF model were applied to identify significant predictors of survival.

Results: The mean age of the patients was 49.23 ± 10.85 years, and the mean survival time was 21.09 ± 2.27 months. One, three, and five-year survival rates were 98.8%, 97.5%, and 97.2%, respectively. Based on the RSF model, radiotherapy dose, recurrence, age, nodal stage (N), and overall stage were identified as the most influential predictors of survival. HER2 status, initial treatment approach, and surgical method were also included in the model. The RSF model achieved a C-index ranging from 0.63 to 0.73, outperforming the Cox regression model (C-index 0.54–0.66).

Conclusion: The RSF model effectively identified key predictors of survival in non-metastatic breast cancer and may serve as a valuable tool for personalized clinical decision-making. These findings demonstrate the potential value of machine learning-based models in oncology research and patient management.

Keywords: Non-metastatic Breast Cancer, Survival Analysis, Cox Proportional Hazards (PH), Regression (Cox regression), Random Survival Forest (RSF)

1. Introduction

Breast cancer is one of the most commonly diagnosed cancers in women worldwide and remains a major public health concern in both developed and developing countries. According to GLOBOCAN data published in 2022, breast cancer ranks as the fourth leading cause of cancer-related death globally and continues to increase rapidly in incidence, particularly in urban populations where lifestyle and environmental exposures are changing dramatically (1, 2). In Iran, the age of disease onset differs slightly from the global trend. While the average age at breast cancer diagnosis worldwide is 62 years, Iranian patients are typically diagnosed between the ages of 50 and 59 (3, 4). This discrepancy highlights potential ethnic, genetic, environmental and sociocultural variations that may influence disease presentation and outcomes.

Multiple risk factors are known to contribute to the development of breast cancer, including age, sex, race, history of breast disease, personal or family history of breast or ovarian cancer, hormonal and reproductive history, exposure to ionizing radiation, and other environmental or lifestyle factors (5). Prognosis is influenced by several variables including lymph node involvement, tumor size, hormone receptor status (estrogen and progesterone), tumor morphology, DNA content, age at diagnosis, and tumor cell proliferative capacity (6). Among these, the presence of distant metastases is the most critical determinant, as studies have shown that patients with metastatic disease tend to have significantly shorter survival and reduced quality of life across both physical and psychological domains (7-9). Despite global agreement on the primary prognostic factors, the extent to which each factor influences survival appears to vary significantly across populations with different racial, cultural, and geographic backgrounds.

Accurate prediction of survival in cancer patients is crucial for clinical decision-making, treatment planning, and patient counseling. In recent decades, numerous studies have aimed at identifying key determinants of breast cancer survival and developing reliable prediction models. In the context of Iranian patients, the need for localized predictive tools is critically important, given the evident demographic and clinical distinctions from western populations. Several studies have shown that survival probabilities decrease with advancing age and longer time since diagnosis (10). Conversely, patients diagnosed at early stages without lymph node involvement and who receiving timely and appropriate treatment tend to have significantly better outcomes (11). However, not all studies consistently confirm these findings, indicating the complexity of survival prediction in heterogeneous populations.

Prognostic models and survival prediction tools can provide clinicians with valuable support in tailoring personalized treatment plans while avoiding unnecessary, costly, or low-benefit interventions (12, 13). However, accumulating evidence suggests that clinicians frequently overestimate patient survival. Studies have shown that physicians, including oncologists, may overestimate survival expectations by as much as 60% (14-17), underscoring the need for objective, data-driven tools to assist with prognostic estimation. In response, researchers have developed various models and nomograms based on demographic, clinical, and treatment data extracted from hospital databases and cancer registries, primarily in western countries (18, 19). However, directly applying models to other populations is limited by population-level variability in risk profiles, clinical characteristics, and health system infrastructure.

Considering these limitations, it is essential to develop and validate population-specific survival models that reflect the unique features of the target community. This is especially relevant in Iran, where available datasets from cancer centers can serve as valuable resources for generating localized prediction tools. In recent years, advanced statistical and machine learning methods, such as Random Survival Forest (RSF), have demonstrated improved performance over traditional Cox proportional hazards (PH) regression (Cox regression) models in capturing complex interactions among prognostic variables (20, 21). These methods allow for more accurate estimation of survival probabilities, particularly in datasets with high-dimensional or nonlinear covariate relationships (22-24).

Therefore, the present study aims to identify the key prognostic factors influencing survival in breast cancer patients treated at a major cancer treatment center in Hamadan, Iran, over a period of more than 15 years. Using data from this regional patient population, we developed a prediction model using the RSF algorithm to estimate survival outcomes and identify the most influential factors. This effort is expected to advance personalized cancer care and enhance the precision of clinical decisions for Iranian breast cancer patients. Furthermore, the findings may provide comparative insights for researchers in other countries seeking to adapt or validate prediction models for culturally and demographically diverse populations.

2. Materials and Methods

2.1 Study Population

This retrospective cohort study included 767 breast cancer patients treated at Mahdia Radiotherapy Center between 2006 and 2018. Relevant data were extracted from the patients' records available in the center's database collected using a standardized checklist. These data included demographic characteristics, family history of breast cancer, disease characteristics including primary tumor size, breast location, surgical margin, TNM stage, molecular subtype, hormone receptors and HER2 status, grade, lymph node involvement, tumor pathology type, and presence of lymphovascular invasion [LVI]. Treatment details included the type of surgery, radiotherapy (number of sessions, total dose, and dose per session), and chemotherapy (type and number of sessions).

The inclusion criteria were patients with a definitive diagnosis of non-metastatic breast cancer based on pathology results, availability of required data and clear treatment outcomes. Incomplete medical records, inability to retrieve missing data, or lack of survival status information were the exclusion criteria. In the subsequent analysis, records with missing data were excluded to minimize potential errors, resulting in 442 patients included in the final analysis.

2.2 Statistical Analysis

After data collection and preprocessing, analyses were performed using SPSS (version 28) and R Studio (version 4.3.1). Univariate and multivariate Cox regression models were applied to identify significant prognostic factors. Subsequently, an RSF model was developed to predict the one- to five-year survival probabilities, and was validated for predictive performance and accuracy.

2.3 Cox regression model and RSF models

The classical method for identifying risk factors in time-to-event data is the Cox regression model, which was used as the initial step in the analysis. It is one of the most widely used methods for analyzing survival data. However, its primary assumption the proportional hazards assumption is crucial and may not always hold in real-world settings. Additionally, covariates may violate this assumption or exhibit multicollinearity **(20)**.

After initial analysis, an RSF model, based on a machine-learning approach was developed to determine factors related to survival. In this method, the importance of each variable was calculated by removing each variable and measuring the resulting change in prediction error. In this regard, 500 trees were used to predict survival. Figure 1 shows a schematic view of one of the 500 trees used in the RSF (a), and the model errors (b). As shown in the tree, the Estrogen receptor (ER) variable is in the highest branch. Then, at subsequent branches, the T variables and the disease stage are used for further splitting (branching is performed randomly). In the terminal nodes (shown in green) the survival prediction is provided. For example, the predicted survival for a person with T ≤ 4 is approximately 21 days (0.7 months).

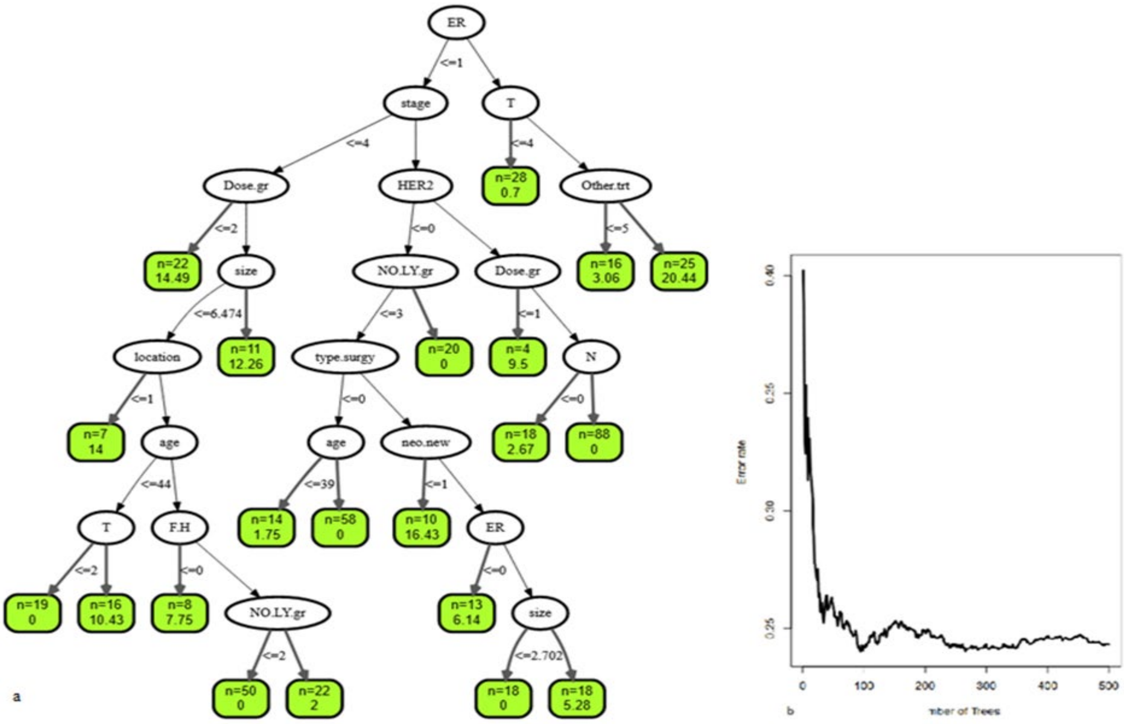


Figure 1. RSF model structure and performance. **(a)** Example of a decision tree illustrating splits based on estrogen receptor (ER), tumor stage (T), radiotherapy dose, overall stage, lymph node involvement, and surgery type. Terminal nodes (green) show patient numbers (n) and predicted survival times (months). **(b)** Out-of-bag (OOB) error rate across 500 trees, demonstrating model stability with increasing tree number. (**Prepared by Authors, 2025**).

3. Result

Based on the obtained results, the patients' mean age was 49.23 ± 10.85 years (range: 23–91 years); the mean initial tumor size was 3.39 ± 1.69 cm (range: 0.06–20 cm); and the mean number of involved lymph nodes was 3.35 ± 4.29 (range: 0–22). The mean follow-up time was 21.09 ± 2.27 months, with one, three, and five-year survival rates of 98.8%, 97.5%, and 97.2%, respectively.

The univariate Cox regression model showed a significant association between patient age and survival, indicating that each additional year of age was associated with a 3% increase in the hazard of death (HR = 1.029, P = 0.029). Survival was also significantly associated with disease stage, recurrence, N stage, type of surgery, and radiotherapy dose. However, in the multivariate Cox regression model, radiotherapy dose, disease recurrence, age, and N stage remained significantly associated with survival.

However, as previously discussed, traditional models such as the Cox regression model may be inadequate when the dataset includes a high proportion of censored observations, which is the case in this study. Moreover, in some studies, all covariates are measured at baseline and assumed to remain constant over time, even though their effects may change during the follow-up. This limitation necessitates the use of more flexible modeling approaches. In contrast, the RSF method is particularly well-suited for right-censored survival data, as it is a non-parametric technique that does not rely on assumptions such as proportional hazards. A key advantage of RSF is its strong ability to assess the relative importance of predictor variables in estimating survival outcomes **(21)**.

Based on the RSF model, the most important variables influencing survival time were radiotherapy dose, recurrence status, age, N stage, T stage, type of chemotherapy, type of surgery, tumor size, family history, estrogen receptor (ER) status, as well as the number of involved lymph nodes.

Figure 2 illustrates the RSF-based prediction of one-year survival probability across different variables. According to the results, patients who either did not receive radiotherapy or received a dose ≥ 5000 cGy had better one-year survival rates than those who received lower doses.

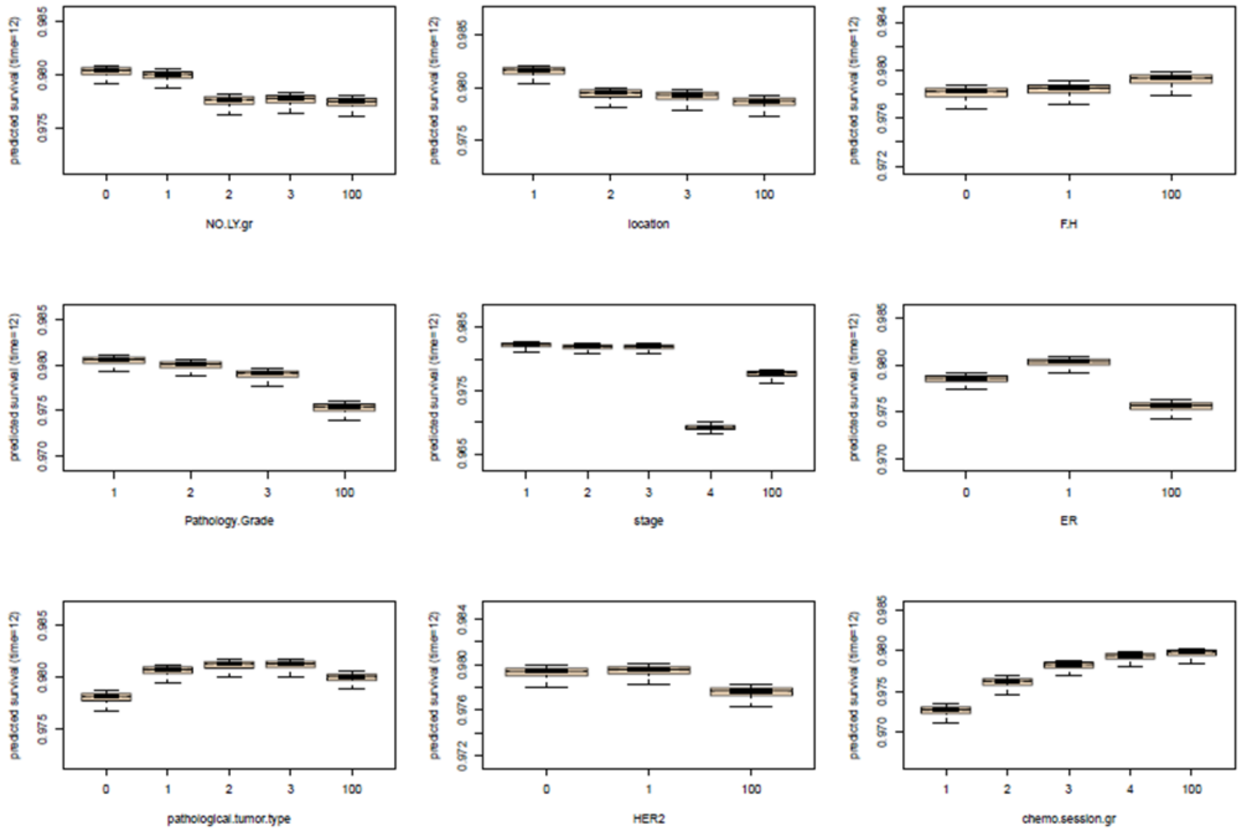
Additional RSF-based plots (similar to Figure 2) demonstrated that patients with stage IV disease had significantly lower one-year survival probabilities than those at earlier stages. Furthermore, patients with positive progesterone receptor (PR+) status exhibited higher one-year survival rates than those with negative PR status (PR–).

Figure 3 shows the predicted five-year survival probabilities across different variables, using the same RSF-based approach as described above.

Figure 4a illustrates the one-year survival probabilities for breast cancer patients according to age, disease recurrence, and radiotherapy dose. For example, a 45-year-old patient with recurrent disease who received a radiotherapy dose of 3000 cGy or less has an estimated one-year survival probability of approximately 0.97. Similarly, (Figure 4b) shows the predicted five-year survival probabilities using the same variables where the corresponding probability for the same patient profile is approximately 0.80.

Figure 5 presents the developed nomogram that predicts one-, three-, and five-year survival probabilities based on multiple variables. For instance, according to this model, a 65-year-old breast cancer patient with T stage=1, N stage=3, who underwent mastectomy as the initial surgical treatment, and received a radiotherapy dose of ≤ 3000 cGy, would have an estimated one-year survival probability of about 0.82, a three-year survival probability of approximately 0.42, and a five-year survival probability of around 0.17.

The concordance index (C-index) for the final multivariate Cox regression model ranged from 0.54 to 0.66, whereas for the RSF model, it ranged from 0.63 to 0.73.



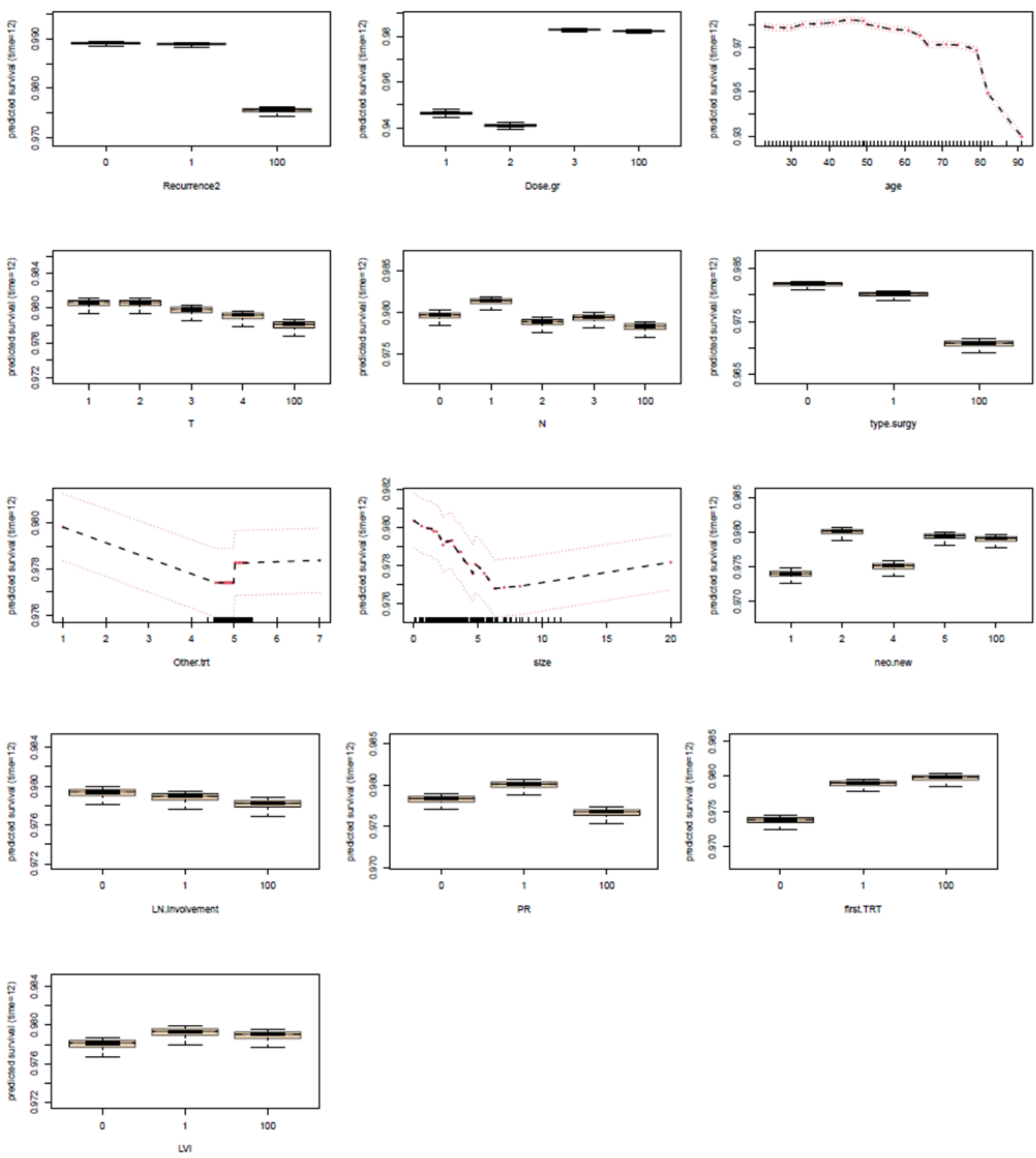


Figure 2. RSF-based prediction of one-year survival probabilities across clinical and treatment-related variables. (**Prepared by Authors, 2025**).

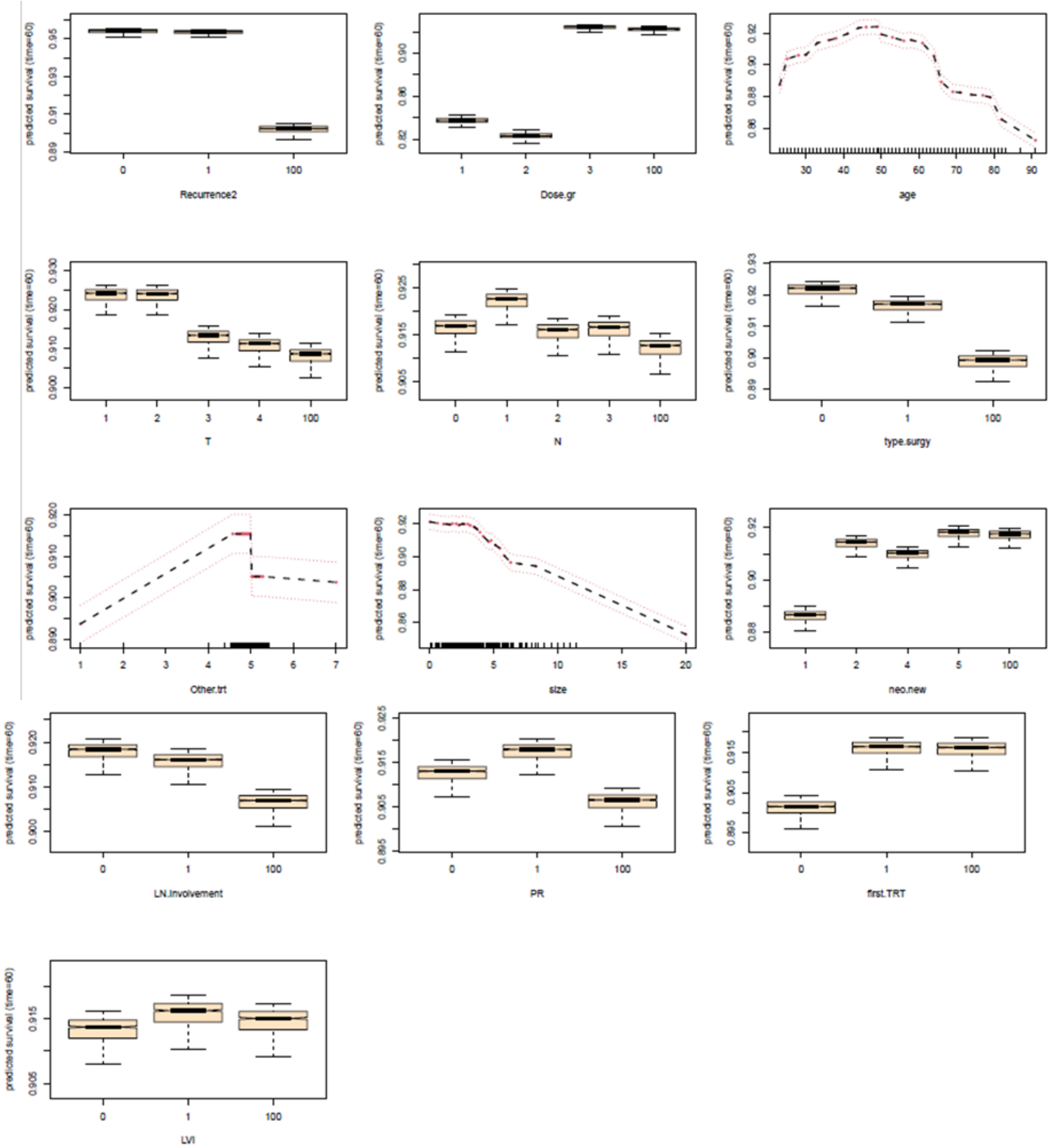


Figure 3. RSF-based prediction of five-year survival probabilities across clinical and treatment-related variables. (**Prepared by Authors, 2025**).

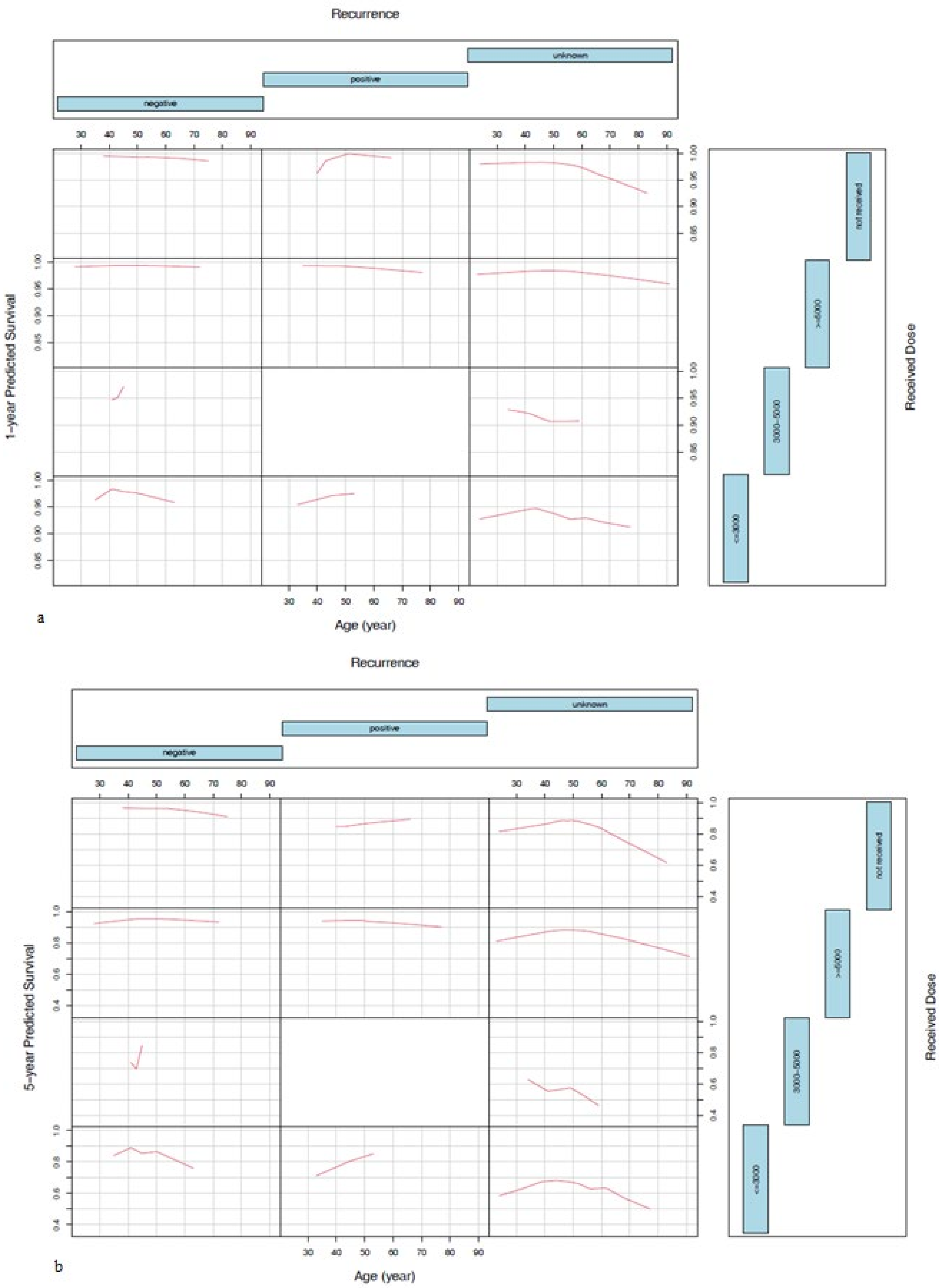


Figure 4. RSF-based prediction of survival probabilities according to patient age, disease recurrence, and radiotherapy dose. **(a)** One-year survival probabilities. **(b)** Five-year survival probabilities. (**Prepared by Authors, 2025**).

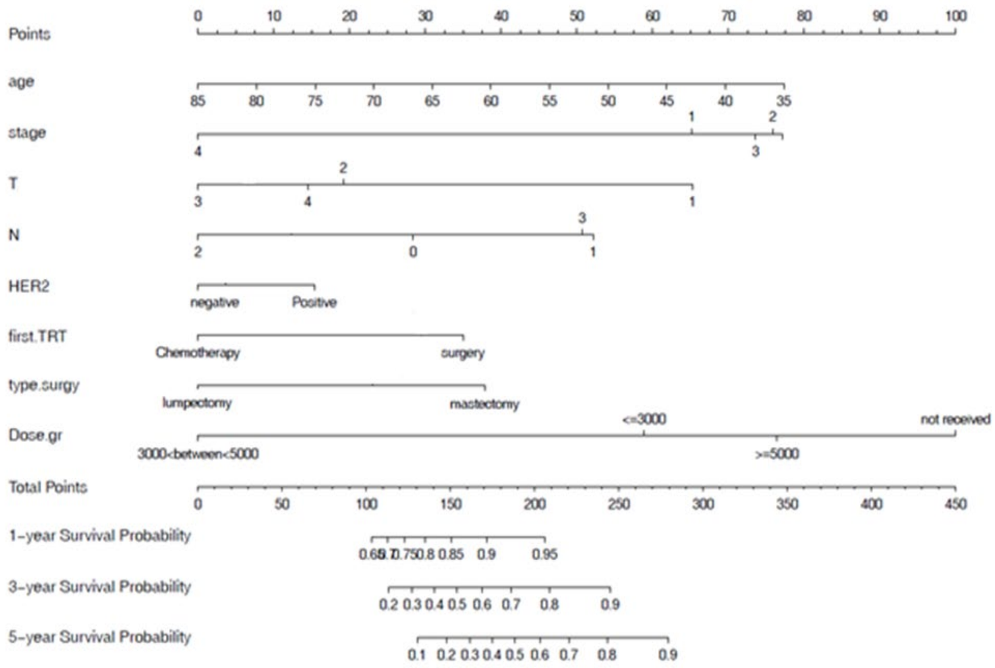


Figure 5. Nomogram predicting one-, three-, and five-year survival probabilities in breast cancer patients based on age, tumor and nodal stage, surgery type, and radiotherapy dose. (**Prepared by Authors, 2025**).

4. Discussions

This study analyzed the records of patients with non-metastatic breast cancer to develop a survival prediction model based on this information. In recent years, several studies have investigated risk factors influencing time to death in various diseases, showing that RSF outperforms the classical Cox regression model **(22-24)**. Moreover, risk factors may also vary across studies due to differences in patient characteristics across geographical regions. As this study aimed to identify significant prognostic factors affecting survival in Iranian breast cancer patients based on the data from the population of this region of Iran, the RSF model appeared to provide more accurate and reliable results.

The findings indicated that radiation dose, recurrence, and age were the most important determinants of survival. Other influential factors were stage, T, N, HER2 status, treatment type, and surgery, which were also included in the developed model. Notably, the RSF model indicated that patients who did not receive radiotherapy or received doses ≥ 5000 cGy had a higher one-year survival probabilities than those treated with lower doses. This counterintuitive finding is likely influenced by treatment selection bias and underlying clinical differences rather than a direct causal effect of radiotherapy dose. For instance, patients with earlier-stage disease may not have required radiotherapy, while those eligible for higher-dose regimens may have had better baseline performance status or fewer comorbidities. Conversely, patients receiving lower doses may have had more advanced disease, treatment interruptions, or comorbid conditions limiting tolerance. Therefore, these results should be interpreted with caution, and prospective validation is warranted.

The results of this study, based on data analysis using the Cox regression model and the RSF model, revealed a significant association between patient age and survival. Age emerged as the most influential parameter in the survival prediction nomogram. This finding is consistent with the nomograms proposed by Pan et al **(25)**, Sun et al **(26)**, and Paredes-Aracil et al **(27)**. Similarly, Meng et al **(28)** also identified age as a key predictor of survival. The next most influential parameters were disease stage, as well as T and N classifications, respectively. However, the order of importance of these variables differed from those of other studies. In the study by Pan et al **(25)**, the variables T stage and N stage were included after age; however, disease stage was not considered in their nomogram. Instead, ER and HER2 were regarded as important predictors in subsequent ranks for survival prediction **(25)**. HER2 was likewise included as a predictor in the nomogram developed in the present study.

In a study conducted by Akrami et al **(29)** in Shiraz the results of Cox multivariate analysis showed that tumor size, history of breast surgery, postoperative chemotherapy, radiotherapy, triple-negative status, and hypertension were the most important variables associated with overall survival of patients. The results of the present study showed that the radiotherapy dose, type of surgery, and type of primary treatment were factors affecting survival, consistent with Akrami's findings. However, treatment decisions such as the type and number of chemotherapy or radiotherapy sessions are determined by oncologists based on clinical factors such as stage, T, and N, which in turn influence survival.

Therefore, caution should be exercised when using these factors in developing predictive models.

Similarly, in a study conducted by Nourelahi et al (30) developed a logistic regression model to predict 60-month survival in breast cancer patients. This model, evaluated using 10-fold cross-validation, included parameters such as age at diagnosis, type of invasion, HER2 status, tumor size, lymph node involvement ratio, progesterone receptor status, and the total number of involved lymph nodes. The model showed that the presence of any type of invasion (e.g., vascular or lymphatic) was associated with a lower survival probability than other variables. This model was more similar to our study in terms of parameters affecting survival, including age, N, and HER2; however, unlike our model, it was based on mathematical relationships and did not include treatment-related factors (30).

As mentioned above, in a similar study in China, Meng et al (28) designed a nomogram to predict survival in non-metastatic breast cancer patients and calculated the overall survival probability of patients. Based on the results of LASSO regression, age, marital status, race, T status, N status, chemotherapy, surgery, and radiotherapy were identified as survival predictors in the nomogram. This model showed a satisfactory predictive performance over a 10-year period. Although variables such as age, T, and N overlapped with those in our model, marital status and race identified as important predictors in their study which were not assessed in ours (28).

A study conducted in China aimed to develop a nomogram to predict survival in patients with breast cancer employing univariate and multivariate logistic regression analyses to identify clinical and pathological factors. The results showed race, age at diagnosis, marital status, grade, stage T, stage N, breast cancer subtype, surgery, radiotherapy, and chemotherapy were significant predictors of survival (31). The factors affecting survival in this study were similar to those identified by Meng et al. and confirmed that the importance of certain parameters may vary across populations (28).

The results of Pan et al (25) also reported that race, age at diagnosis, breast cancer subtype, grade, stage N, stage M, radiotherapy, chemotherapy, and surgery were key prognostic factors for survival (25). Although the parameters used in this nomogram are largely similar to those of our nomogram, race emerged as one of the most significant predictors, a variable that not assessed in our study.

Paredes-Aracil et al (27) developed a scoring system in 2016 to predict 5 and 10-year breast cancer mortality, and the results showed that age, history of breast surgery, history of any type of cancer or breast cancer, menopausal status (premenopause or postmenopause), grade, estrogen receptor, progesterone receptor, c-erbB2, TNM stage, and multicentricity or multifocality were relevant factors for diagnosis and treatment.

Similarly, Sun et al (26) reported that age and race were identified as the most influential parameters, but tumor histology ranked third, a factor not considered in most reviewed studies (26). Other parameters such as radiotherapy doses were similar to those included in most studies and this work, but with different degrees of importance.

In a distinct study, Wang et al (32) correlated immune scores and clinical characteristics with patient prognosis to construct a nomogram for predicting survival in breast cancer patients. The Cox regression model was used. Patients were divided into three subgroups based on their immune profiles, each with a different immune score. The 3 and 5-year calibration curves demonstrated strong concordance between the nomogram predictions and actual observations (32). However, in the present and most reviewed studies, assessing immune scores was not feasible due to clinical constraints.

Colleoni et al (33) also conducted a study aimed at predicting disease-free survival in patients who did not achieve pathological complete remission after preoperative chemotherapy. A Cox regression model was used to generate a nomogram based on both categorical histological variables (PT, positive nodes, HER2, vascular invasion) and continuous histological variables (estrogen receptors and Ki-67 expression) at the time of surgery. Based on these findings, a nomogram with good predictive power for survival was designed; however, it is not feasible in a clinical setting due to limited access to the required parameters (33).

Bao et al (34) also employed a novel epigenetic signature-based approach to predict overall survival in breast cancer patients. Since epigenetic alterations in the genome of cancer cells including DNA methylation patterns may serve as key markers in the initiation and progression of breast cancer, DNA methylation and RNA-seq datasets from The Cancer Genome Atlas were analysed to construct a predictive nomogram that distinguishes between high-risk and low-risk cases. This model provides reliable survival predictions when genetic information is available; however, it is not applicable in most medical canters and for many patients.

5. Conclusion

This study confirms that demographic and early diagnostic parameters especially age remain among the most consistent predictors in breast cancer survival models. Race is often an important factor but is typically excluded from Iranian studies due to limited population diversity. Stage, grade, and lymph node involvement are commonly included, whereas tumor size and treatment types are inconsistently addressed due to data limitations. Although genetic and immunologic markers demonstrate predictive value, their clinical application is limited by cost and accessibility. Metastatic data were not included in this study but warrant further investigation.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

The study has been approved by the Hamadan University of Medical Sciences Ethical Committee (Ethical approval ID: IR.UMSHA.REC.1403.773).

6.3 Authors' Contributions

Publisher's Note: In accordance with the journal's publication policies, authors are required to provide information for this section. As no statement was provided, no information on the authors' contributions is available for this article.

6.4 Conflict of Interest

The authors have no conflict of interest.

6.5 Fund or Financial Support

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6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

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