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Mapping significant clinical factors to relapse-free survival prognosis in breast cancer patients

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ABSTRACT

This study explores the role of clinical factors in influencing relapse-free survival (RFS) in breast cancer patients through comprehensive survival analysis (SA). The data were derived from a large cohort of breast cancer patients, encompassing clinical variables such as age at diagnosis, tumor size, number of positive lymph nodes, tumor grade, histological subtype, and receipt of chemotherapy and radiotherapy. Analytical methods included Kaplan-Meier plots, log-rank tests, Cox proportional hazards modeling, and feature ranking based on univariate and multivariate log-rank and Cox tests. The results show that patients who received chemotherapy demonstrated a shorter median RFS compared to those who did not (102.7 vs. 145.0 months, p = 0.03), likely due to high-risk patients being selected for chemotherapy. Meanwhile, radiotherapy was associated with improved prognosis (hazard ratio (HR) < 1 in Cox model, $p < 10^{-5}$), in line with meta-analyses showing reduced breast cancer mortality post-radiotherapy. The contribution maps the key clinical determinants of RFS in breast cancer and highlights the practicality of performing SA.

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1. INTRODUCTION

Breast cancer remains one of the most prevalent oncological diseases among women globally [1], [2], contributing substantially to morbidity and mortality rates. Despite advancements in diagnostic and therapeutic modalities, the risk of relapse continues to pose a significant clinical challenge. Relapse-free survival (RFS) [3], defined as the time from initial treatment to the recurrence of disease, is a crucial endpoint for evaluating treatment efficacy and tumor characteristics. Previous studies have demonstrated that traditional clinical factors such as tumor grade, tumor size, and lymph node involvement play a significant role in determining RFS. Kawase *et al.* [4] found that higher-grade tumors and positive nodal status were independently associated with shorter RFS, even after multivariate analysis. Large cohort studies have consistently shown that increases in tumor size and nodal spread signal a worsening prognosis [5]. In addition to that, biological markers such as hormone receptor status and histological subtypes [6]–[8] are known to present differing prognoses [9]. Where hormone receptor status [10] refers to whether a tumor's cells express receptors for the female sex hormones—estrogen (ER) [11] and progesterone (PR) [12]—which drive cell growth and differentiation in hormone-sensitive tissues.

Adjuvant interventions [13], including chemotherapy [14] and radiotherapy [15], play a significant role in improving RFS outcomes in cancer patients. These treatments, administered after the primary

intervention such as surgery, are designed to eliminate residual disease and reduce the likelihood of recurrence, thereby extending the duration of remission and improving long-term survival rates. Among the various chemotherapy regimens, anthracycline-based [16] adjuvant therapy has been extensively studied and widely adopted in clinical practice, particularly in the management of breast cancer. Evidence from large-scale clinical trials and meta-analyses indicates that this class of drugs can significantly reduce breast cancer mortality. The extent of the benefit, however, can vary based on several patient-related factors, including age and tumor characteristics. Specifically, anthracycline-based regimens have been associated [17], [18], with a 20% to 38% reduction in mortality, demonstrating a substantial improvement in prognosis when used as part of a comprehensive treatment strategy.

Radiotherapy [19], particularly after surgical resection of the primary tumor, is another critical component of adjuvant treatment. Its primary objective is to eradicate any microscopic residual tumor cells at the site of surgery, which are often responsible for local recurrence. Numerous studies have shown that postsurgical radiotherapy not only lowers the risk of local recurrence but also contributes to a meaningful decrease in long-term mortality. For patients undergoing breast-conserving surgery, the addition of radiotherapy has become a standard of care due to its proven ability to enhance local control and survival outcomes.

The integration of these adjuvant modalities into treatment protocols has led to notable improvements in RFS curves in various types of cancer, especially early stage breast cancer. The benefits are particularly evident in the subgroups of patients with high-risk pathological characteristics, where the risk of recurrence without adjuvant therapy would otherwise be substantial. Importantly, the effectiveness of adjuvant therapy must be balanced against potential toxicities and patient comorbidities, which can influence treatment tolerance and results. This study contributes by enhancing the analytical capability to investigate the relationship between various clinical variables and RFS in breast cancer patients. By applying survival analysis (SA) model, it offers deeper insights into how specific clinical factors influence patient outcomes, potentially guiding more effective treatment and follow-up strategies.

2. METHOD

2.1. Data collection

Dataset for this study was from the molecular taxonomy of breast cancer international consortium (METABRIC) [20]–[22]. METABRIC analyzed genomic and transcriptomic data from approximately 2,000 primary breast tumors, integrating this information with long-term clinical outcomes. This comprehensive approach enabled the identification of ten distinct molecular subtypes of breast cancer, each characterized by unique genomic drivers and associated with specific clinical prognoses. The METABRIC dataset available via cBioPortal and the European genome-phenome archive.

Key features in the dataset include age at diagnosis, which serves as an important demographic factor known to influence disease progression and treatment response. Tumor size, measured in millimeters, and the number of positive lymph nodes are included as indicators of cancer stage and spread—both strong prognostic markers for SA. Tumor grade, classified from I to III, reflects the level of abnormality of the cancer cells, with higher grades typically associated with more aggressive disease.

Histological subtypes [23], such as ductal, lobular, tubular, and mucinous carcinomas, is also recorded to account for biological heterogeneity within breast cancer cases. These subtypes differ in clinical behavior and may respond differently to therapy. Additionally, treatment variables such as the administration of chemotherapy (yes/no) and the receipt of radiotherapy (yes/no) are included. These variables are particularly relevant as they are known to influence RFS outcomes by reducing the risk of recurrence.

2.2. Data preprocessing

The data preprocessing in this study was conducted using the Orange3 platform and comprised several essential steps. The METABRIC dataset, which includes 1,904 breast cancer patients and over 24,000 clinical and genetic features, served as the primary data source. Categorical variables such as tumor grade, chemotherapy, and radiotherapy were converted into numerical format using the "First value as base" method to facilitate statistical analysis. Numerical features including tumor size, age at diagnosis, and lymph nodes examined positive were normalized to a [0, 1] range and subsequently discretized into three intervals using the equal frequency discretization method for Kaplan-Meier analysis. Relevant features were selected, consisting of six clinical predictors and RFS time as the target variable. Missing values were imputed using the average or most frequent method to ensure a complete and analyzable dataset. Finally, the data were

transformed into a survival format by defining RFS time as the time variable and survival event as the censoring indicator.

2.3. Survival analysis

This work implement SA that is a statistical approach used to analyze and interpret time-to-event data, commonly applied in clinical and epidemiological studies. It focuses on estimating the probability of an event occurring over time while accounting for censored observations. Key components include the survival function, hazard function, and models such as Kaplan-Meier estimator and Cox proportional hazards regression. These methods allows us to identify factors influencing survival time and assess differences between groups. The SA is essential in longitudinal studies where the timing of events is critical and traditional statistical methods may be inadequate.

The analysis workflow was structured as follows: the dataset was first loaded and then the non-clinical columns were excluded to reduce noise. The initial step involved univariate analysis via the Kaplan–Meier plot, where users can partition the dataset by categorical variables and visualize survival curves along with median RFS for each subgroup. Subsequently, two parallel analytical procedures were executed: rank survival features [24] was used to rank clinical variables based on univariate Cox tests or multivariate log-rank tests and Cox proportional hazards [25] was applied to model simultaneous effects of multiple clinical variables on RFS.

The Cox model was implemented using all independent variables concurrently (multivariate analysis) to estimate the hazard ratio (HR) for each covariate. In addition, feature ranking was conducted using both the Cox log-likelihood ratio test (univariate) and the multivariate log-rank test. These rankings generated a prioritized list of statistically significant features contributing to RFS outcomes. The interpretation of the results was conducted using both p-values and effect sizes to ensure a comprehensive understanding of the statistical significance and practical relevance of the findings. p-values were utilized to determine whether the observed associations or differences were statistically significant, typically evaluated against a predefined threshold (e.g., $p < 0.05$). However, recognizing that statistical significance alone does not imply meaningful impact, effect sizes were also calculated to quantify the magnitude of the observed effects. This dual approach enabled a more nuanced interpretation, balancing statistical rigor with the real-world implications of the results across the variables examined.

3. RESULTS AND DISCUSSION

This section presents the results of the SA conducted using the METABRIC dataset through the Orange3 data mining platform. The analysis aimed to identify clinical variables significantly associated with RFS in patients with breast cancer. A total of 1,904 patient records were processed, and six clinical variables were investigated: tumor grade, lymph nodes examined positive, chemotherapy, radiotherapy, age at diagnosis, and tumor size.

3.1. Kaplan–Meier survival estimates

Kaplan–Meier survival curves were generated to examine the RFS probability across stratified groups for each clinical variable. Each curve represents the survival function over time, and the differences between groups were statistically tested using the log-rank test. These curves provide visual and statistical insights into the heterogeneity of clinical outcomes based on key patient characteristics and therapeutic interventions.

Figure 1 shows Kaplan–Meier curves of RFS stratified by tumor size. Patients with the smallest primary tumors (< 19.5 mm, blue curve) exhibit substantially higher survival than those with intermediate or large tumors. In particular, the blue curve (small tumors) has a median RFS of 199.1 months, whereas the green curve (tumors ≥ 26.5 mm) has a median of only 86.6 months. The confidence bands (shaded regions) indicate minimal overlap between the extreme groups. For example, by 150 months only about 30% of the large-tumor group remain relapse-free, compared to roughly 60% of the small-tumor group. The log-rank test yields $p < 0.005$, confirming that these differences are highly significant. Notably, all curves decline from near 100% survival at time zero, but the large-tumor curve drops much more steeply during early follow-up, indicating earlier relapses in that group. Throughout the follow-up, the separation persists: at 100 months roughly 50% of the small-tumor patients remain event-free, whereas the majority of patients with large tumors have already relapsed. These observations demonstrate that increasing tumor size is strongly associated with higher hazard of relapse in this cohort. Tumor size thus emerges as a powerful prognostic factor, since even

the moderate-sized group (red curve) lies between the extremes in both median survival (148.1 months) and curve trajectory.

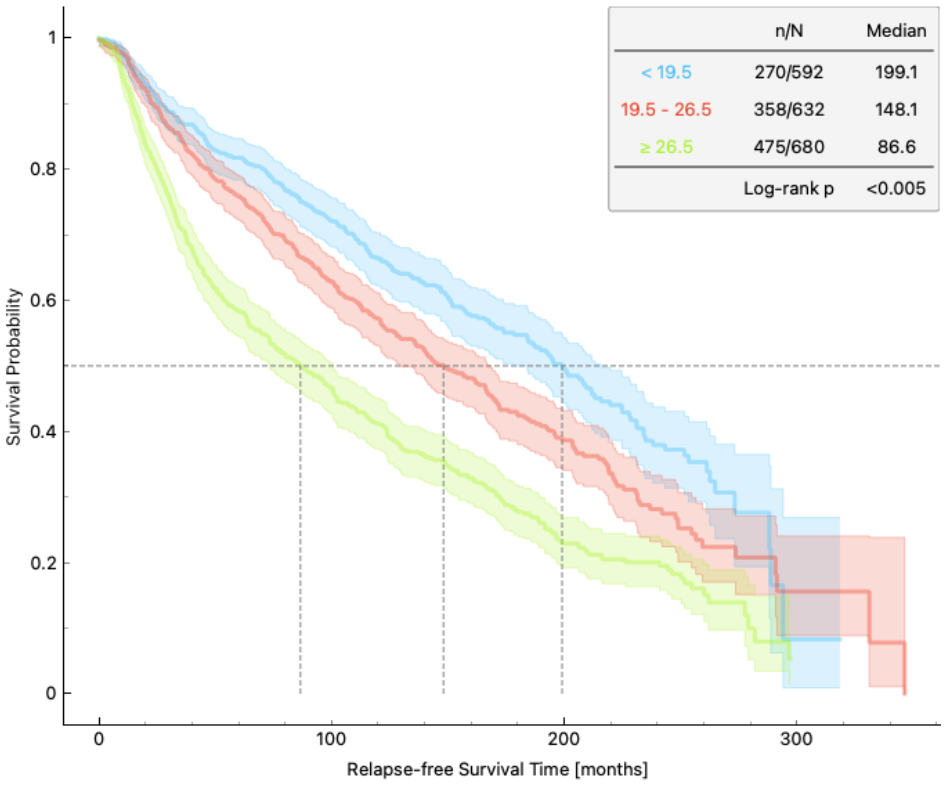

Figure 1. Kaplan-Meier curves of RFS stratified by tumor size

Figure 2 presents Kaplan–Meier curves stratified by age at diagnosis. Patients diagnosed at a younger age ($<$ 55.6 years, blue curve) have markedly better survival than older patients ($\geq$ 67.9 years, green curve), with the middle-age group (55.6–67.9 years, red) in between. The median RFS is 246.2 months for the youngest group and only 101.6 months for the oldest group. The confidence intervals for the youngest and oldest groups barely overlap, and the log-rank test yields $p < 0.005$. This indicates a highly significant trend toward worse outcomes with increasing age. Early in follow-up, the difference is already apparent: at 80 months about 60% of the youngest group are still relapse-free compared to roughly 40% of the oldest group. By 150 months the survival gap has widened further. The consistent ordering and parallel decline of the curves suggest that the HR for age remains roughly constant over time (no crossing of curves). These results imply that older age at diagnosis confers a substantially higher relapse risk. In practical terms, younger patients in this dataset enjoy significantly longer RFS. This trend may reflect age-related differences in tumor biology and patient resilience, but regardless of cause, age is clearly an important prognostic covariate in the METABRIC cohort.

Figure 3 shows RFS stratified by chemotherapy status. In this case, patients who received chemotherapy (red curve) have worse survival than those who did not (blue curve). The median RFS for the chemotherapy group is 102.7 months, compared to 145.0 months for the no-chemotherapy group. The confidence bands overlap somewhat, and the log-rank test yields $p = 0.03$, indicating a statistically significant (albeit weaker) difference. Notably, at early times (e.g. 50 months) the no-chemotherapy curve is around 90% survival versus about 80% for the chemotherapy curve. Over the first 100 months the gap persists such that by 100 months roughly 70% of the no-chemotherapy patients are event-free compared to only 50% of the chemotherapy group. Beyond 150 months the curves tend to converge due to small numbers. These findings suggest that patients who received chemotherapy had a higher hazard of relapse. However, this result likely reflects confounding by indication: patients selected for chemotherapy often had more aggressive tumor features at baseline. Without adjustment, the Kaplan–Meier plot cannot distinguish between a true harmful effect of chemotherapy and the fact that the chemo group was inherently higher-risk. Therefore, while the

log-rank test indicates a significant survival difference (p = 0.03), this should not be interpreted as evidence that chemotherapy reduces survival; rather, it highlights the clinical reality that treated patients in this sample fared worse on average, presumably due to more advanced disease.

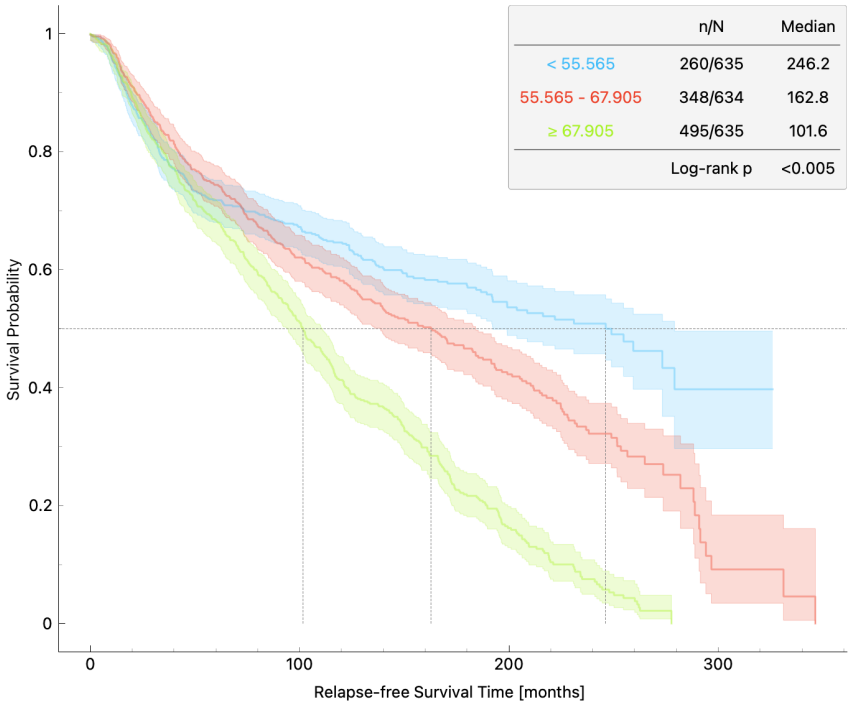

Figure 2. Kaplan-Meier curves stratified by age at diagnosis

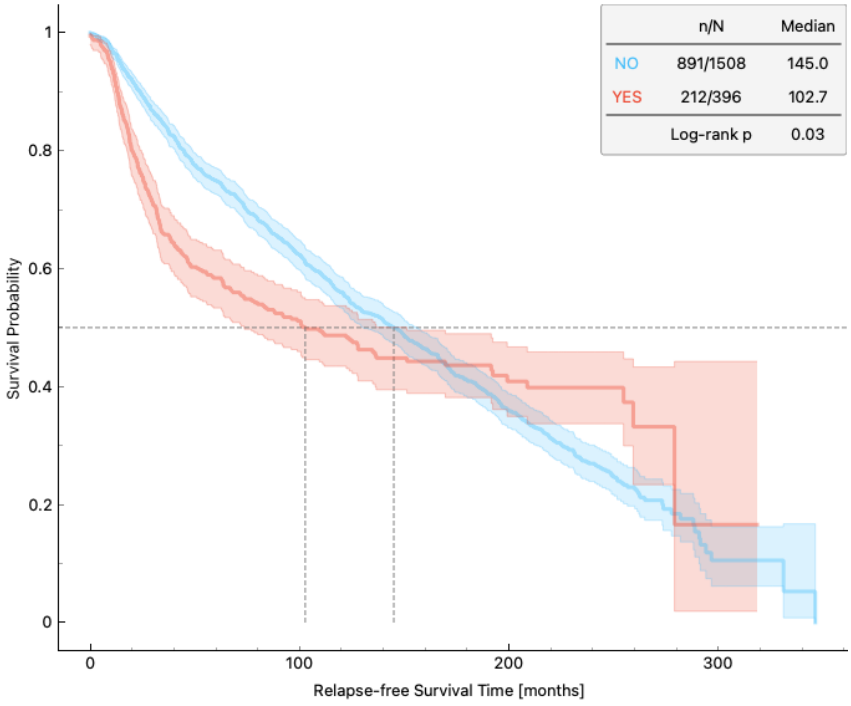

Figure 3. Kaplan-Meier chemotherapy status

Figure 4 demonstrate that patients with < 0.5 positive lymph nodes had the highest median RFS, reaching 171.9 months, whereas patients with ≥ 2.5 positive lymph nodes exhibited the lowest median RFS of 64.2 months. This difference was statistically significant ($p < 0.005$), providing further evidence that the extent of lymph node involvement is strongly associated with the risk of disease recurrence. An increasing number of positive lymph nodes was associated with a progressively poorer prognosis, as greater lymphatic involvement may indicate more extensive dissemination of malignant cells and a higher likelihood of systemic metastasis. Consequently, patients in the group with ≥ 2.5 positive lymph nodes demonstrated substantially shorter RFS and may represent a subgroup with a higher risk of recurrence requiring closer clinical surveillance and potentially more intensive therapeutic management.

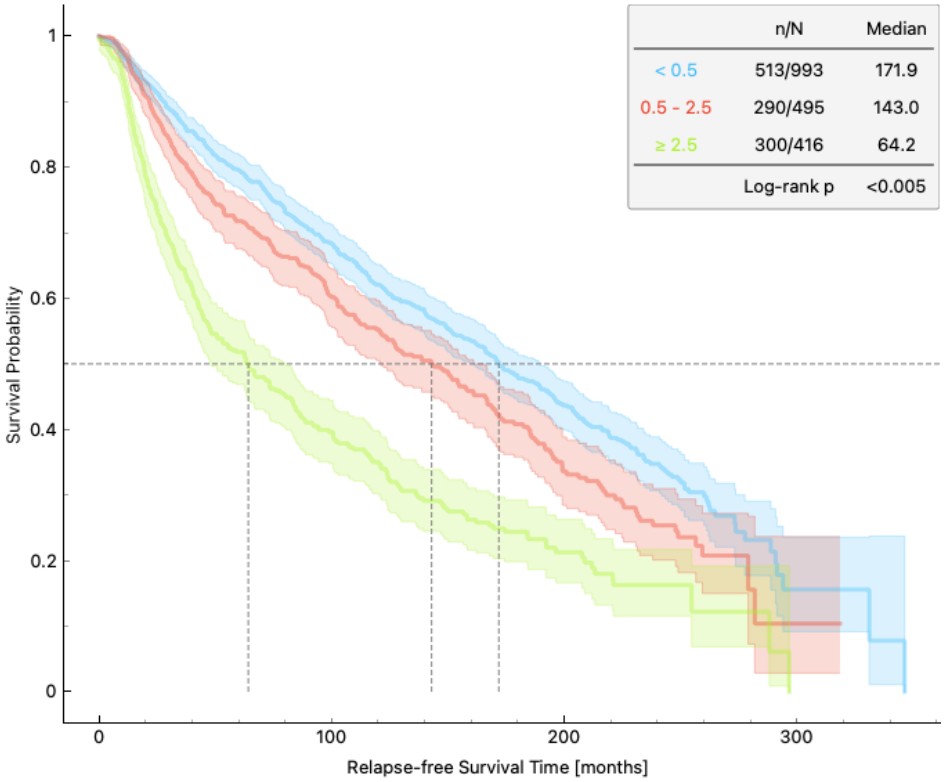

Figure 4. Kaplan-Meier lymph nodes

Figure 5 compares RFS between patients who did (red curve) versus did not (blue curve) receive postoperative radiotherapy. The radiotherapy group has a noticeably better survival curve, with a median RFS of 153.7 months versus 119.1 months in the no-radiotherapy group. The shaded confidence intervals for the two groups remain largely separated after the first 50 months of follow-up. The log-rank test yields $p < 0.005$, indicating a statistically significant difference. For example, at 100 months approximately 60% of patients who received radiotherapy are still relapse-free, whereas only about 50% of patients without radiotherapy remain event-free. This pattern implies a protective effect of radiotherapy–patients who received radiation have consistently lower hazard of relapse. In fact, by 200 months the majority of the radiotherapy group remain event-free, whereas the non-radiotherapy group has declined to a much smaller survival fraction. In summary, the Kaplan–Meier analysis suggests that radiotherapy is associated with an appreciable improvement in RFS in this cohort.

Figure 6 shows Kaplan–Meier curves by histological tumor grade (1, 2, or 3). Lower-grade tumors (blue curve, grade 1) are associated with the best survival: median RFS is 195.1 months for grade 1. In contrast, high-grade tumors (green curve, grade 3) have a median of only 115.8 months. Grade 2 (red) is intermediate at 152.5 months. The curves are well separated, and the log-rank test gives $p < 0.005$. Early on (up to 50 months) over 90% of grade 1 patients remain event-free versus about 80% of grade 3. By 150 months, only 20% of grade 3 patients are relapse-free compared to 50% of grade 1. The shaded confidence regions show

limited overlap among the grades. These patterns reflect the expected biology: higher-grade tumors are more aggressive and recur earlier. The sizable differences in median survival (nearly 80 months between grade 1 and grade 3) indicate that tumor grade is a significant determinant of prognosis in this cohort.

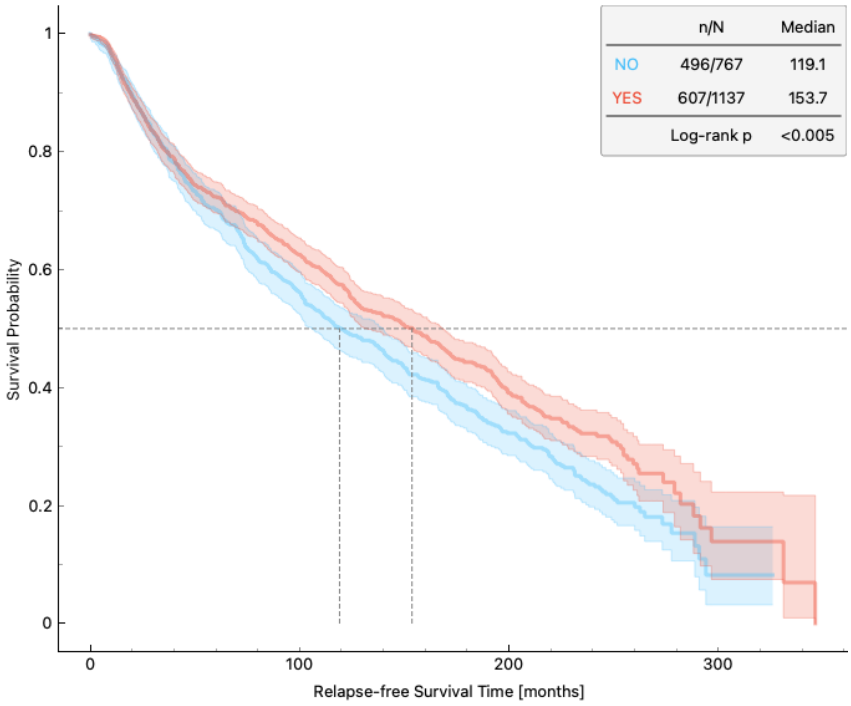

Figure 5. Kaplan-Meier curves postoperative radiotherapy

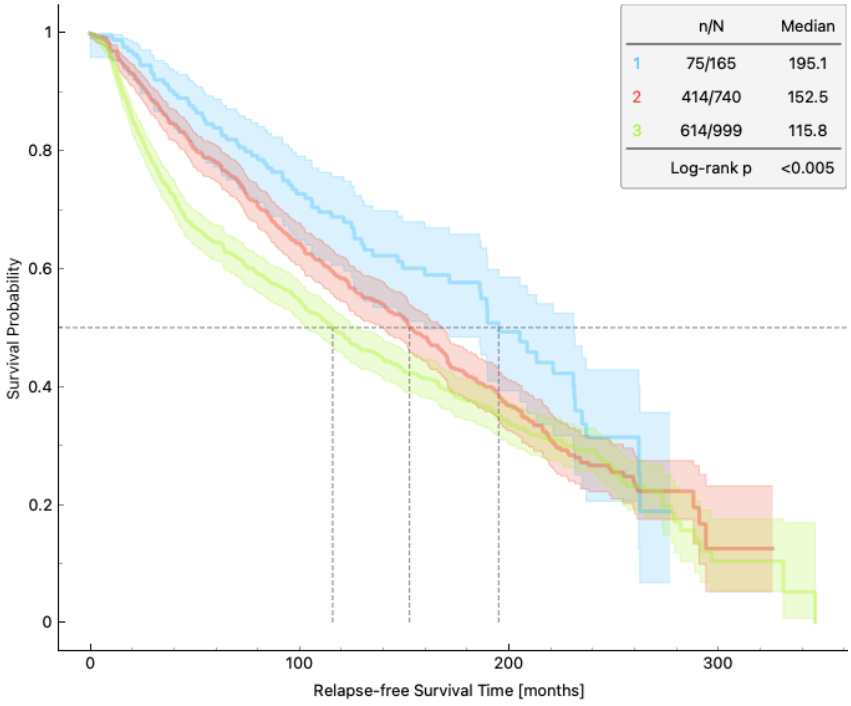

Figure 6. Kaplan–Meier curves by histological tumor grade

In identifying feature ranking based on Cox log-likelihood ratio test, each variable is assessed by how much it improves the model's fit, with larger values indicating greater importance, as explicated in Table 1. Age at diagnosis is ranked first (log-likelihood ratio (LLR) 130.4, p = 3.31×10^{-30}, false discovery rate (FDR) 1.98×10^{-29}), followed by number of positive lymph nodes (102.9, p = 3.45×10^{-24}, FDR 1.03×10^{-23}) and tumor size (98.8, p = 2.78×10^{-23}, FDR 5.55×10^{-23}). These three have extremely high significance–their FDR-corrected p-values remain $<10^{-22}$ – reflecting that they dominate the survival model. Tumor grade is fourth (LLR-meaning the recurrence of cancer within the breast and surrounding areas after initial treatment - 22.7, p = 1.92×10^{-6}, FDR $\approx 2.89 \times 10^{-5}$), a much smaller but still significant contribution. Radiotherapy (LLR 9.71, p = 0.002, FDR 0.002) and chemotherapy (LLR 4.546, p = 0.033, FDR 0.033) have the lowest scores. These correspond to weaker prognostic information in a univariate sense. The drop from LLR ~ 100 for the top features to < 10 for treatments is notable: it indicates that age, nodal status, and tumor burden explain most of the variability in outcome. In effect, age alone accounts for a 130-point increase in log-likelihood–an enormous effect (by comparison, a likelihood ratio of 3.84 corresponds to p = 0.05 for one degree of freedom). The chemotherapy variable's LLR of only ~ 4.55 suggests a marginal univariate effect (just under p = 0.05). The FDR column confirms that even after correcting for multiple tests, all six factors are statistically significant (the largest FDR being 0.033 for chemotherapy). Thus, the ranking reinforces the Cox regression and Kaplan–Meier results: patient age, lymph node involvement, and tumor size carry the greatest prognostic weight, while tumor grade is moderately important and treatment variables, though statistically relevant, contribute less to prediction.

Table 1. Rank survival features

Features	Log-likelihood ratio test	p	FDR
Age at diagnosis [years]	130.4	$3.31\text{x}10^{-30}$	$1.98\text{x}10^{-29}$
Lymph nodes examined positive	102.9	$3.45\text{x}10^{-24}$	$1.03\text{x}10^{-23}$
Tumor size [mm]	98.8	$2.78\text{x}10^{-23}$	$5.55\text{x}10^{-23}$
Tumor grade	22.7	$1.92\text{x}10^{-6}$	$2.89\text{x}10^{-23}$
Radiotherapy	9.713	0.002	0.002
Chemotherapy	4.546	0.033	0.033

4. CONCLUSION

This comprehensive SA reinforces the critical role of traditional clinical factors—age, tumor size, lymph node involvement, and tumor grade—as significant predictors of RFS in breast cancer patients. Findings from Kaplan–Meier curves and Cox proportional hazards models confirm and quantify their prognostic relevance, while rare histological subtypes and adjuvant radiotherapy show strong protective associations. The observed correlation between chemotherapy and reduced RFS highlights the impact of clinical selection bias and cautions against overinterpretation of observational outcomes. Clinically, these insights aid in precise risk stratification, enabling more tailored treatment decisions. However, this retrospective analysis has inherent limitations, such as the absence of molecular biomarkers and genetic data. Thus, while the study provides robust validation of established knowledge, future research integrating multi-omics data and advanced modeling techniques is essential to refine predictive accuracy and unravel the complexity of breast cancer prognosis.

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AUTHOR CONTRIBUTIONS STATEMENT

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Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Boby Al Qurthuby		✓	✓	✓		✓		✓	✓		✓			
I Made Murwantara	✓	✓			✓	✓	✓	✓		✓	✓	✓	✓	✓

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal Analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject Administration
Fu : **Fu**nding Acquisition

CONFLICT OF INTEREST STATEMENT

Authors state no conflict of interest.

INFORMED CONSENT

This section not applicable. This study did not involve human participants, human data, or any personally identifiable information. All data used were either publicly available, fully anonymized, or derived from non-human sources, and therefore no informed consent was required from individuals.

ETHICAL APPROVAL

This section applicable. This research did not involve human subjects, human biological materials, or experimental procedures on animals. The work was conducted solely on computational models, publicly available datasets, or non-sensitive data that did not require intervention with living organisms. Therefore, ethical approval from an institutional review board or animal ethics committee was not necessary for this study.

DATA AVAILABILITY

The supporting data of this study are openly available in cBioPortal at https://www.cbioportal.org/study/summary?id=brca_metabric.

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