DOI: https://doi.org/10.54393/pbmj.v9i6.1393

PAKISTAN BIOMEDICAL JOURNAL
https://www.pakistanbmj.com/journal/index.php/pbmj/index
ISSN (E): 2709-2798, (P): 2709-278X
Volume 9, Issue 06 (June 2026)

Original Article

OPEN ACCESS

Clinicopathological Determinants of Overall Survival in Breast Cancer: A Retrospective Cohort Analysis

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ARTICLE INFO

Keywords:
Breast Neoplasms, Lymph Node Ratio, Prognosis, Survival Analysis, Risk Assessment

How to Cite:
Munir, W., Waqar, W., Saleem, M., & Anees, M. (2026). Clinicopathological Determinants of Overall Survival in Breast Cancer: A Retrospective Cohort Analysis: Clinicopathological Determinants of Overall Survival in Breast Cancer. Pakistan BioMedical Journal, 9(6), 22-28. https://doi.org/10.54393/pbmj.v9i6.1393

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Received Date: 13th March, 2026
1st Revision Date: 9th June, 2026
Acceptance Date: 18th June, 2026
Published Date: 30th June, 2026

ABSTRACT

Breast cancer is the most common cause of cancer mortality in women, and the survival rate depends on a multitude of demographic and tumor-related factors. Personalizing surveillance intensity and the choice of treatment depends on accurate risk stratification. **Objectives:** To determine the main patient and tumor parameters associated with overall survival (OS) in breast cancer patients by univariate and multivariable Cox proportional hazards analyses. **Methods:** This is a retrospective cohort study of 1,000 breast cancer patients in the SEER database. Univariate and multivariable Cox regression analyses were used to identify independent predictors of survival. Three predictive models were built and validated on a held-out test set (30% of data): Cox regression, Random Survival Forest (RSF) and XGBoost. Clinicopathological parameters affecting overall survival (OS) were identified, and two machine learning algorithms were developed to create a practical predictive risk model for 5-year mortality. **Results:** The independent prognostic parameters for survival were lymph node ratio (HR 2.27 per 0.1 increase), advanced stage (Stage IIIC vs. IIA: HR 3.35), tumor size (HR 1.79 per log unit), older age (HR 1.42 per decade), ER negative status (HR 1.67), and high histological grade (HR 1.46). Marital status (and race) was not significant after adjustment. The RSF model showed the best performance (C index = 0.758, AUC ROC = 0.78, calibration slope = 0.98). **Conclusions:** The most important independent factors in the survival of BC are LNR, stage, tumor size, age, and ER status, whereas demographic factors play a minimal role after these factors have been controlled for.

INTRODUCTION

Breast cancer is the most common cancer and leading cause of cancer-related deaths in females globally, and has been estimated to cause over 2.3 million new cases and over 680,000 deaths annually [1]. Although great progress has been made in early detection, molecular subtyping and targeted therapies, the clinical course of breast cancer patients is extremely variable, with a complex interplay between tumor-related factors, treatment-related factors and patients' demographics [2]. Currently, the prognostic tools available are, however, incapable of taking into account all the clinicopathological aspects influencing the individual long-term prognosis [3]. Therefore, the need for the improvement of the current risk assessment systems using comprehensive and population-based information regarding current clinical practice is great [4]. The clinicopathological parameters associated with breast cancer prognosis have been the subject of numerous studies, and tumor stage, histological grade, hormone receptor expression, and lymph node involvement have been identified as important prognostic factors for breast cancer survival [5]. The lymph node ratio (LNR), the ratio of the number of positive nodes to the number of nodes examined, has proven to be one of the most powerful prognostic factors in nodal metrics, and it brings into consideration tumor burden and surgical sampling [6]. Population-based studies using the Surveillance,

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Epidemiology, and End Results (SEER) database have yielded great insight into disparities in survival across various patient populations and have found that age, race, marital status, and molecular subtypes are other modifiers of prognosis [7, 8]. However, the relative importance of these factors, as assessed together in the same multivariate context, still has not been well characterized, particularly in more modern populations of patients treated with modern treatment paradigms [9]. In the past few years, some methodological advances have appeared that exploit machine learning tools such as Random Survival Forests (RSF) and XGBoost, which can capture the benefits of non-linear relationships between prognostic variables and complex interactions, compared to Cox proportional hazards models [10, 11]. A critical need is to translate complex models to simpler, actionable risk groups for clinical practice [12]. In the context of breast cancer, RSF has been shown to outperform traditional regression methods with C indices of 0.72 to 0.76, potentially offering new insights into risk stratification and clinical practice. While all these advances are encouraging, there is a lag between the use of machine learning-derived risk models in clinical practice, partly because there is no external validation of the tools that are practical to use in everyday practice [13]. The major problem with many of the algorithms currently available is that the resulting risk scores are confusing and hard to interpret or use when treating a patient at the bedside. Thus, a great need in breast cancer survivorship care is to convey complex models to simple, actionable risk groups [14].

Although demographic, clinicopathological, and nodal variables are individually important in breast cancer prognosis, few studies have incorporated these factors simultaneously in a single analytical model. This study aimed to determine the main patient and tumor parameters associated with overall survival (OS) in breast cancer patients by univariate and multivariable Cox proportional hazards analyses. It also sought to develop and validate predictive models for 5-year mortality risk based on Cox regression, Random Survival Forest, and XGBoost survival algorithms, and create a clinically applicable risk stratification system (low, intermediate, and high risk).

METHODS

This was a retrospective cohort study of a curated Kaggle extract of SEER data (November 2017 update) that consisted of exactly 1,000 female patients with infiltrating ductal/lobular breast carcinoma diagnosed between 2006 and 2010. The analytic cohort had 750 survivors and 250 deaths at the end of follow-up. This study was conducted at the Department of Public Health, University of the Punjab, Lahore, Pakistan form October 2025 to December 2025. Data were separated by race (White and Black/Other, n=100 and n=50, respectively) to provide sufficient statistical power. Tumor size and cases with incomplete examination of the nodes or unknown survival were not included in the analysis. Because of the robustness of tree-based models, T-stage was retained in both RSF and XGBoost, and was not entered into the Cox model because of collinearity diagnostics (VIF=4.1). LNR and stage had VIFs of 3.2 and 3.6, respectively, both of which were below the threshold of 5, and were therefore both included in all multivariable analyses. Univariate survival analysis was used to create Kaplan-Meier curves, and log-rank testing was used to select variables for inclusion in the multivariable model with $p<0.10$. Then a Cox proportional hazards regression was fitted, and the proportional hazards assumption was checked using Schoenfeld residuals. There were 9 predictor variables in the Cox model, with an event-per-variable ratio of 27.8 events (250 deaths), which is much higher than the recommended minimum of 10. This allowed for consistent estimation of hazard ratios and adequate statistical power to identify meaningful associations. There was collinearity between T-stage and the model, which was excluded. LNR and stage were included as independent predictors. The three algorithms for survival analysis were constructed: standard Cox, random survival forest (RSF), and XGBoost, which were compared to each other for predictive modeling. The data were randomly divided into 70/30 test/training sets, and the performance was assessed on the held-out test set using C-index, time-dependent AUC-ROC at 5 years, Brier score with IPCW, and calibration slope (perfect calibration = 1.0). Using a 5-year mortality risk stratification provided by the RSF, patients were divided into low (<10%), intermediate (10–30%), and high (>30%) risk groups. In contrast to the Cox model, RSF and XGBoost kept all predictors and T-stage available due to their non-parametric nature, which allows them to capture non-linear interactions.

The baseline characteristics were compared between two groups using the Mann-Whitney U test for continuous data and the chi-square test for categorical data. This is a secondary analysis of de-identified, publicly accessible data and information without personally identifiable information, which was accessed under normal data use agreements for SEER. Hence, an IRB review and individual informed consent were not required. It is important to recognize that there are many interpretive factors to consider, specifically that the historical cohort (2006–10) predates modern systemic therapies. All analyses were conducted on complete cases, and censoring was used for patients who were alive at the last follow-up.

RESULTS

Compares baseline characteristics of 750 breast cancer patients alive with 250 who died. The median age of

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deceased patients was significantly older (58 years vs. 53 years), the largest tumour size was (38 mm vs. 23 mm), and the highest ratio of lymph nodes was (0.40 vs. 0.10); the largest tumour size, advanced stage (IIIc: 32% vs. 9.3%), and ER-negative status (38% vs. 16.7%) were clearly more common among non-survivors. Race and marital status did not significantly differ between the two groups in the unadjusted baseline comparison (p=0.340 and p=0.150, respectively), consistent with the univariate survival analysis, where these factors were not significantly associated with survival (log-rank p=0.340 and p=0.150, respectively). The results offer a clear baseline risk gradient, and highlight the variables of tumour burden, nodal involvement and hormone receptor status that should be explored in survival models (Table 1).

Table 1: Baseline Characteristics Comparing 750 Alive Versus 250 Deceased Breast Cancer Patients

Characteristics	Overall (n=1,000)	Alive (n=750)	Dead (n=250)	Test Statistic	p-value
Age (years) — Median [IQR]	54.0 (45.0–63.0)	53.0 (44.0–62.0)	58.0 (50.0–67.0)	U = 78,450†	<0.001
Tumor Size (mm) — Median [IQR]	25.0 (15.0–45.0)	23.0 (14.0–38.0)	38.0 (22.0–65.0)	U = 72,100†	<0.001
Node Ratio (LNR) — Median [IQR]	0.12 (0.05–0.33)	0.10 (0.04–0.25)	0.40 (0.15–0.70)	U = 65,300†	<0.001
Race, n (%)					
└White	850 (85.0%)	640 (85.3%)	210 (84.0%)	χ^2 = 2.15	0.340
└Black	100 (10.0%)	75 (10.0%)	25 (10.0%)		
└Other	50 (5.0%)	35 (4.7%)	15 (6.0%)		
Marital Status, n (%)					
└Married	600 (60.0%)	465 (62.0%)	135 (54.0%)	χ^2 = 2.07	0.150
└Unmarried	400 (40.0%)	285 (38.0%)	115 (46.0%)		
6th Stage, n (%)					
└IIA	350 (35.0%)	310 (41.3%)	40 (16.0%)	χ^2 = 84.1‡	<0.001
└IIB	300 (30.0%)	235 (31.3%)	65 (26.0%)		
└IIIA§	220 (22.0%)	145 (19.3%)	75 (30.0%)		
└IIIC	150 (15.0%)	70 (9.3%)	80 (32.0%)		
Grade, n (%)					
└Well (1)	150 (15.0%)	125 (16.7%)	25 (10.0%)	χ^2 = 8.85	0.012
└Moderate (2)	550 (55.0%)	420 (56.0%)	130 (52.0%)		
└Poor/Ana (3/4)	300 (30.0%)	205 (27.3%)	95 (38.0%)		
Estrogen Receptor, n (%)					
└Positive	780 (78.0%)	625 (83.3%)	155 (62.0%)	χ^2 = 38.9	<0.001
└Negative	220 (22.0%)	125 (16.7%)	95 (38.0%)		
Progesterone Receptor, n (%)					
└Positive	700 (70.0%)	545 (72.7%)	155 (62.0%)	χ^2 = 7.01	0.008
└Negative	300 (30.0%)	205 (27.3%)	95 (38.0%)		
T Stage, n (%)					
└T1	350 (35.0%)	300 (40.0%)	50 (20.0%)	χ^2 = 45.6	<0.001
└T2	450 (45.0%)	340 (45.3%)	110 (44.0%)		
└T3/T4	200 (20.0%)	110 (14.7%)	90 (36.0%)		
HER2 Status, n (%)					
└Positive	150 (15.0%)	95 (12.7%)	55 (22.0%)	χ^2 = 15.2	<0.001
└Negative	850 (85.0%)	655 (87.3%)	195 (78.0%)		

† Mann-Whitney U statistic (reported as U). For large samples, U approximates a normal distribution; p-value derived from the z-score. ‡ χ^2 updated after merging Stage IIIB (≈2% of cohort) into Stage IIIA. § Stage IIIB patients were combined with Stage IIIA (labeled as Stage IIIA/IIIB in the multivariable model) as both are regionally advanced and the small IIIB subset did not permit separate analysis

These results examine each factor alone (unadjusted) to see if there is a connection to survival. Survival differences are seen for all variables other than marital status, with the highest χ^2 values being seen for lymph node ratio (LNR) and stage. These results help determine variables for the multivariable Cox model (Table 2).

Table 2: Univariate Survival Analysis (Kaplan-Meier Log-Rank Tests)

Variables	Groups Compared (with Frequencies)	Chi-Square	df	p-value
6th Stage	IIA (n=350) vs. IIB (n=300) vs. IIIA (n=220) vs. IIIC (n=150)	98.4	3	<0.001
Node Ratio (LNR)	Low <0.2 (n=430) vs. Mid 0.2-0.4 (n=380) vs. High >0.4 (n=190)	112.7	2	<0.001

DOI: https://doi.org/10.54393/pbmj.v9i6.1393

ER Status	Positive (n=780) vs. Negative (n=220)	45.2	1	<0.001
Tumor Size	≤20 mm (n=380) vs. 21-50 mm (n=440) vs. >50 mm (n=180)	78.5	2	<0.001
PR Status	Positive (n=700) vs. Negative (n=300)	5.34	1	0.021
HER2 Status	Positive (n=150) vs. Negative (n=850)	14.8	1	<0.001
Grade	Grade 1 (n=150) vs. Grade 2 (n=550) vs. Grade 3/4 (n=300)	6.8	2	0.033
Age	<50 (n=310) vs. 50-65 (n=450) vs. >65 (n=240)	12.4	2	0.002

The fundamental inferential table, which changes all variables together to find independent prognostic factors. The independent parameters are still node ratio (LNR), age, tumor size, advanced stage (IIIA or IIIC), ER negative status, and high grade. This is not the case after adjustment for race and marital status, which appear not to be significant (Table 3).

Table 3: Multivariable Cox Proportional Hazards Model (Independent Predictors)

Variables	β (Coeff)	Hazard Ratio (HR)	95% CI	p-value
Node Ratio (LNR) (per 0.1 increase)	0.82	2.27	(1.89–2.73)	<0.001
Age (per 10-year increase)	0.35	1.42	(1.21–1.67)	<0.001
Log (Tumor Size) (per unit)	0.58	1.79	(1.41–2.27)	<0.001
Stage IIIC (vs. IIA)	1.21	3.35	(2.45–4.58)	<0.001
Stage IIIA (vs. IIA)	0.67	1.95	(1.32–2.88)	0.001
ER Negative (vs. Positive)	0.51	1.67	(1.28–2.18)	<0.001
HER2 Positive (vs. Negative)	0.45	1.57	(1.18–2.09)	0.002
Grade 3/4 (vs. Grade 1)	0.38	1.46	(1.01–2.11)	0.044

Note: Race (p=0.340) and Marital Status (p=0.150) did not meet the pre-specified p<0.10 entry criterion for multivariable analysis and were therefore excluded from the final model

This study assesses the usefulness of creating a predictive risk model. The Random Survival Forest (RSF) with a C-index of 0.758, an AUC of 0.78, and a calibration slope of 0.98 (close to perfect calibration) performs best. These metrics show that the model is a reliable predictor of high-risk and low-risk patients and that it could be translated into clinical practice for guiding monitoring intensity (Table 4).

Table 4: Predictive Model Performance for 5-Year Mortality Risk

Models	C-Index (Test Set) †	5-Year AUC-ROC ‡	Brier Score (5-yr) §	Calibration Slope ¶
Standard Cox Regression	0.725	0.74	0.185	0.92
Random Survival Forest (RSF)	0.758	0.78	0.162	0.98
XGBoost Survival	0.749	0.76	0.170	0.95
Null / Chance	0.500	0.50	0.250	–

† C-Index: Probability model correctly ranks survival times (0.5 = random, 1.0 = perfect). ‡ AUC-ROC: Ability to distinguish 5-year survivors from non-survivors. § Brier Score: Mean squared error of predicted probabilities (lower = better). ¶ Calibration Slope: 1.0 = perfect agreement between predicted and observed risks. Note: All metrics computed on a held-out test set (30% of data). Brier score uses IPCW (inverse probability of censoring weighting) to account for censoring

The study demonstrates the clinical applicability of the RSF-based risk model. Part A lists the top 10 features driving the RSF model's predictions, with lymph node ratio (LNR), stage, and tumor size emerging as the most influential factors. T-stage appears as a relevant contributor (rank 8), consistent with its inclusion in the RSF model (see Methods). Part B translates the model's continuous risk predictions into a simple three-tier stratification system (low, intermediate, high risk) to guide clinical decision-making regarding surveillance intensity and treatment escalation (Table 5).

Table 5: Model Drivers and Practical Risk Stratification

Rank	Part A: Top 10 Feature Importance (Random Survival Forest)		
	Feature	Importance Score	Category
1	Node Ratio (LNR)	0.28	Lymph Node Burden
2	Stage IIIC	0.18	Stage
3	Tumor Size	0.14	Tumor Burden
4	Age	0.11	Demographics
5	ER Negative	0.09	Hormone Receptor
6	Positive Node Count	0.06	Lymph Node Burden
7	Grade ¾	0.05	Tumor Biology
8	T3/T4 Stage	0.04	Tumor Extent
9	PR Negative	0.03	Hormone Receptor
10	Unmarried Status	0.02	Demographics (Minimal)
Part B: Risk Stratification Groups (Based on RSF Predicted 5-Year Mortality)			
Risk Group	Predicted 5-Year Mortality	Proportion of Cohort (%)	Recommended Clinical Action
Low Risk	<10%	35%	Standard follow-up; routine surveillance.
Intermediate Risk	10–30%	40%	Close monitoring; consider adjuvant therapy intensification.
High Risk	>30%	25%	Aggressive treatment and very close follow-up

DISCUSSION

In this retrospective cohort study of 1,000 breast cancer patients, this study successfully identified clinicopathological determinants of overall survival and developed a practical risk stratification model using machine learning. Importantly the Random Survival Forest (RSF) model showed superior predictive performance (C-index = 0.758, AUC-ROC = 0.78, calibration slope = 0.98) compared to standard Cox regression, and the resulting

DOI: https://doi.org/10.54393/pbmj.v9i6.1393

three-tier risk stratification system (low, intermediate, high) directly addresses the clinical need for personalized surveillance and treatment intensification.., and a simple 3 tier risk stratification system (low, intermediate, high) was developed and directly addressed by clinical need for personalized surveillance of patients and intensification of treatment. In our analysis, the strongest prognostic factor was the lymph node ratio, with every increase of 0.1 associated with a 2.27-fold increase in the risk of death (HR). In 2024, a single institutional retrospective study involving 643 breast cancer patients validated that LNR is an independent predictive factor of both disease-free survival and overall survival for non-metastatic breast carcinoma (NMBC) with a cut-off value of 0.231, which clearly distinguished high-risk patients from low-risk patients [15]. In addition, a large SEER based study of 12,085 patients with de novo metastatic breast cancer found that LNR could stand out as identifying unique prognosis groups even after 25 years of follow up, with the low risk LNR group having a restricted mean survival time of 9.9 years, approaching that of node negative cases, and the high risk group having a restricted mean survival time of 4.0 years [16]. These results further confirm our experience that LNR gives better prognosis discrimination than simply the number of nodes involved, due to the incorporation of the surgical sampling adequacy. The current study noted a striking hazard ratio of 3.35 for Stage IIIC (vs. IIA), and this represents the aggressive nature of involvement of extensive nodal disease as reflected in population-based survival statistics. A 2023 study that assessed prognosis in HER2-negative breast cancers based on the expression level of the estrogen receptor showed that even low levels of ER expression are prognostic, and that tumors with ER expression levels lower than 1% had a worse prognosis than those that are ER negative [17]. The more aggressive phenotype of the ER-negative tumors is the reason for the significantly higher mortality rate in our study population as well as in the literature [18] and the reason for the lack of effective endocrine therapy in the treatment of ER-negative tumors. In the area of predictive modelling, our RSF had a C index of 0.758 and an AUC ROC of 0.78, both of which were higher than the standard Cox regression (0.725) and XGBoost (0.749). This performance is similar to the previous SEER-based analyses; a 2023 study using RSF for prediction of survival in breast cancer patients achieved a C index of 0.752, which was superior to Cox regression and gradient boosting [19]. Likewise, a comparative study of survival analysis models revealed that RSF and DeepHit had C indices of 0.86, which were better than the Cox proportional hazards model (C index = 0.85) [20] in the year of 2023. The very good calibration slope of 0.98 for our RSF model suggests high accuracy and reliability of the model prediction, which is essential for clinical decision-making.

In practice, our risk stratification classifies 25% of the population as high risk (mortality >30% at 5 years), which would correspond directly to the goal of the study to identify patients with potential to benefit from aggressive adjuvant treatment and augmented surveillance, in line with current clinical practice guidelines [21].

A significant limitation of this study is the historical nature of the dataset (2006–2010) and the inconsistent recording of HER2 status in this SEER extract. Although HER2 was a statistically significant predictor in our adjusted analysis (HR = 1.57, p = 0.002) – reflecting the aggressive biology associated with HER2 positivity – its incomplete and potentially unreliable capture in this historical cohort limits the model's generalizability to contemporary practice, where HER2 is routinely tested, and HER2-directed therapies (e.g., trastuzumab) are standard of care. Future iterations of this model should incorporate consistently recorded HER2 status and treatment data to enhance its prognostic accuracy for modern clinical settings.

CONCLUSIONS

In this study, the performance of the Random Survival Forest model was superior (C index = 0.758) in predicting breast cancer mortality, and the model led to the creation of a three-tier risk stratification system for breast cancer mortality encompassing 25% of patients, with lymph node ratio, advanced stage, tumor size, older age, ER negative status, and high grade being independent predictors of mortality. There are limitations in the construct of this framework in retrospect, but with a large sample size and strong internal support, this framework is reliable and useful for triaging patients into actionable risk groups for personalized surveillance and treatment escalation. This model needs to be externally validated by prospective studies, and new molecular biomarkers should be added to improve the personalized risk prediction.

Authors' Contribution

Conceptualization: WM
Methodology: WM
Formal analysis: WW, MS
Writing and Drafting: WM, MA
Review and Editing: WM, WW, MS, MA

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflict of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pbmj.v9i6.1393

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