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IMPACT OF TUMOUR GRADE AND INDIVIDUAL HETEROGENEITY ON BREAST CANCER SURVIVAL: A RELATIVE TIME TO EVENT INDEX-FRAILTY APPROACH

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Abstract

Background: Breast cancer survival is influenced by multiple clinical and pathological factors, and appropriate modelling is required to obtain reliable prognostic estimates while accounting for unobserved heterogeneity.

Methodology: A population-based retrospective survival analysis was conducted among women diagnosed with primary breast cancer. Survival time from diagnosis to death or event was analysed using proportional hazards (PH) and accelerated failure time (AFT) models across multiple parametric distributions. Shared gamma frailty models were fitted at the age-group level to account for unobserved heterogeneity.

Results: Higher tumour grade and lymph node ratio (LNR) were the strongest predictors of poor survival. Compared with grade 1 tumours, grade 3 tumours were associated with substantially shorter survival times (time ratio ≈0.55 – 0.59) and increased hazard (hazard ratio ≈1.8 - 1.9). Patients with LNR > 0.68 experienced markedly earlier events (time ratio ≈ 0.33 – 0.38) and higher hazard (hazard ratio ≈ 3.1). Advanced age showed the largest adverse effect, with patients older than 78.5 years experiencing events approximately three to four times earlier (time ratio ≈ 0.26 – 0.29). Hormone receptor-negative tumours were associated with reduced survival (time ratio ≈ 0.71 – 0.86). Flexible AFT models, particularly the generalized gamma distribution, demonstrated superior fit. Frailty modelling revealed moderate

unobserved heterogeneity (θ≈ 0.30), with attenuation of effect sizes but preserved inference.

Conclusion: Key prognostic factors for breast cancer survival remained robust across modelling frameworks and after accounting for unobserved heterogeneity. The combined use of PH, AFT, and frailty models provides clinically interpretable and reliable survival estimates.

Keywords: Survival analysis, Cox model, Frailty model, Breast cancer, Tumour grade, Heterogeneity

I. Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide and remains a leading cause of cancer-related mortality despite advances in screening and treatment strategies [XXII]. The prognosis of breast cancer depends on clinical, pathological, and biological factors, among which tumour grade has a crucial impact. Tumour grade is a measure of the differentiation of cancer cells and reflects features such as nuclear pleomorphism and mitotic activity. Higher-grade tumours, particularly Grade 3, show more aggressive biology, a more rapid disease course, and poorer survival compared with low-grade tumours [XVII, IX]. Numerous epidemiological and clinical studies have consistently demonstrated tumour grade as an independent predictor of overall survival and disease-free survival in breast cancer patients [XI].

The main statistical framework for examining time-to-event outcomes in oncology research is survival analysis. “Due to its interpretability and semi-parametric nature, the Cox proportional hazards (PH) [XV] model is the most commonly used approach. Without requiring the baseline hazard to be specified, the Cox model calculates the relative impact of covariates on the hazard function [V]. However, this model is based on important assumptions, such as homogeneity among individuals with identical covariate patterns and proportional hazards over time. These presumptions are frequently violated in real-world clinical datasets because of unmeasured biological, genetic, environmental, or treatment-related factors, resulting in unobserved heterogeneity. Ignoring such heterogeneity could lead to biased regression coefficients, understated standard errors, and inaccurate conclusions about prognostic variables like tumour grade [XXIII].

To address these limitations, frailty models have been developed as extensions of the Cox model by incorporating random effects, referred to as frailty terms, to account for unobserved or latent heterogeneity in survival data [XXVI]. In a frailty framework, the hazard function is modified by a multiplicative random effect that captures individual- or group-level susceptibility to the event. Frailty may be modelled at the individual level (univariate frailty) or at the group level (shared frailty), where individuals within the same cluster (e.g., hospital, region, or treatment centre) share a common frailty term. The gamma frailty model is the most commonly used specification due to its mathematical tractability and interpretability, with the frailty term typically assumed to have a mean of one [VII].

Frailty models explicitly account for unobserved heterogeneity and help capture dependence arising from unmeasured risk factors, thereby improving model fit and inference compared with standard Cox models [XIX]. In oncology research, where patient populations are naturally diverse, these models have gained increasing attention. Frailty models have been widely applied in breast cancer research to analyze survival variability among treatment facilities, genetic subtypes, and therapeutic regimens. For instance, when taking center-level variability in breast cancer survival outcomes into account, Kheiri et al. demonstrated that shared frailty models offered better model fit than traditional Cox models [XIV]. Similarly, previous studies have shown that incorporating frailty effects in breast cancer survival models improves predictive performance and helps identify significant prognostic factors [XXI].

Despite these methodological advantages, clinical survival studies continue to underutilize frailty models, especially when examining tumour grade and individual-level heterogeneity. The majority of current analyses of breast cancer survival still rely primarily on the conventional Cox proportional hazards (Cox PH) model, which may underestimate the influence of latent heterogeneity on patient outcomes. Furthermore, there is a lack of direct comparisons between Cox and frailty models in relation to tumour grade-specific survival, which creates a significant methodological and clinical gap in the literature.

In this context, the present study aims to evaluate the impact of tumour grade on breast cancer survival while explicitly accounting for individual heterogeneity through frailty modelling. By comparing the performance and inference of the Cox PH model with frailty-based survival models, this study seeks to evaluate the added value of incorporating unobserved heterogeneity in survival analysis and to provide methodological insights for more robust prognostic modelling in breast cancer research. To our knowledge, this study represents the first application of a Relative Time-to-Event Index-Frailty modelling framework to breast cancer survival data, incorporating tumour grade and individual heterogeneity.

II. Materials and Methods

II.i. Study Design and Data Source

This study employed a retrospective survival analysis using data obtained from the Surveillance, Epidemiology, and End Results (SEER) program, a population-based cancer registry [XX]. The dataset included female patients diagnosed with primary breast cancer with complete information on survival time, event status, tumour grade, and relevant clinicopathological variables. Patients with missing key covariates or incomplete follow-up information were excluded from the analysis. The primary outcome was time-to-event, defined as the duration from the date of breast cancer diagnosis to death or a disease-related event. Patients who were alive or event-free at the end of follow-up were treated as right-censored.

The main exposure of interest was tumour grade, categorized into Grade 1 (reference), Grade 2, Grade 3, and Grade 4. Additional covariates included age at diagnosis, lymph node ratio categories, number of primary tumours, first primary tumour status, tumour location, estrogen receptor (ER) status, and progesterone receptor (PR) status. These

variables were selected based on clinical relevance and prior evidence of prognostic importance.

II.ii. Survival Modelling Strategy

Survival outcomes were analysed using both PH and accelerated failure time (AFT) modelling frameworks with appropriate handling of right-censored data. To account for unobserved heterogeneity, shared gamma frailty models were additionally fitted at the age-group level, enabling assessment of covariate effects on both risk and survival time scales.

II.ii.i. Survival Function:

The survival function [I], denoted as S(t), represents the probability that an individual will "survive" or remain event-free past time '*t*' as:

$$S(t) = P(T > t) \quad (1)$$

where T denotes the survival time. It can be represented as a smooth curve, as '*t*' varies from 0 to infinity. The survival function is non-increasing, i.e., as time '*t*' increases, the probability of surviving beyond time '*t*' either decreases or remains constant.

The hazard function [IV] measures the risk of an event occurring at time 't', given that the event has not yet occurred. Unlike the survival function, which gives the probability of surviving past a time '*t*', the hazard function represents the instantaneous likelihood of an event in the immediate future [XXVI]. Denoted as h(t), it describes the instantaneous rate of occurrence at time t. Mathematically, the hazard function is defined as:

$$h(t) = \lim_{\triangle t \to 0} \frac{p(t \le T < t + \triangle t \mid T \ge t)}{\triangle t} \quad (2)$$

The cumulative hazard function, denoted as H(t), represents the accumulated risk of the event occurring up to time '*t*' and is related to the survival function. It sums up the instantaneous hazard (risk rate) at each time point, providing an overall measure of risk. The cumulative hazard function is defined as:

$$H(t) = - \log S(t) \quad (3)$$

The cumulative hazard also represents the expected number of events occurring between the time origin and '*t*' [XXVI].

II.ii.ii. Cox Proportional Hazards Model

The Cox PH model was used as the primary semi-parametric approach to estimate hazard ratios (HR) for tumour grade and other covariates. This model assumes proportional hazards over time and independence among individuals. The Cox PH model specifies the hazard function for individual i with covariate vector xi, which is defined as:

$$h_i(t) = h_0(t) \exp(\beta^T x_i) \quad (4)$$

where,

- $h_0(t)$ is the unspecified baseline hazard function,
- β is the vector of regression coefficients.

The HR for a one-unit increase in covariate xk is

$$HR = \exp(\beta_K) \tag{5}$$

where HR > 1 indicates increased risk, whereas HR < 1 indicates reduced risk. The PH assumption entails that HRs remain constant over time.

II.ii.iii. Parametric Survival Models and Accelerated Failure Time Framework

To examine time-based interpretations of covariate effects, several parametric models were fitted under both PH and AFT formulations, including Weibull, Gompertz, lognormal, log-logistic, and generalized gamma distributions. In the AFT model [XXV], covariate effects were expressed as time ratios (TRs), indicating acceleration or deceleration of survival time. Under the AFT framework, survival time is modelled as:

$$\log(T_i) = \beta^T x_i + \varepsilon_i \tag{6}$$

where ε_i follows a specified distribution. Covariate effects are expressed as TRs, with TR < 1 indicating shorter survival time and TR > 1 indicating prolonged survival.

II.ii.iv. Relative Time to Event Index (rTIO)

For improved clinical interpretability, AFT model estimates were additionally expressed using the rTIO [XIII], where rTIO < 1 indicates earlier event occurrence (shorter survival) and rTIO > 1 indicates delayed event occurrence, and it is defined as:

$$rTIO = \exp(\beta_k) \tag{7}$$

II.ii.v. Frailty Modelling for Unobserved Heterogeneity

To account for unobserved individual heterogeneity, shared frailty models with a gamma-distributed random effect were fitted. Frailty was defined at the age-group level to capture latent risk factors shared among patients within the same age strata. Both PH-frailty and AFT-frailty models were estimated. The hazard function with frailty term u_j is expressed as:

$$h_{ij}(t) = u_j h_0(t) \exp(\beta^T x_{ij}) \tag{8}$$

The term u_j captures latent risk shared among individuals within the same age-group cluster. The frailty terms were assumed to follow a gamma distribution with a mean of 1, and the variance parameter θ quantifies the degree of unobserved heterogeneity. Likelihood ratio tests were used to assess the significance of frailty effects.

II.iii. Model Comparison and Statistical Inference

Model performance was assessed with the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), where lower values reflect better model fits. Parameters of the models were estimated using maximum likelihood estimation. Results from PH models are reported as hazard ratios with corresponding confidence intervals and p-values, while AFT models are reported as time ratios and rTIO values. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

III. Results

III.i. Overview of Survival Analysis

All patients diagnosed with primary breast cancer were included in the survival analysis. To determine the robustness of prognostic effects under various assumptions about the baseline hazard and survival time distribution, a variety of parametric and semi-parametric survival models were applied to evaluate survival outcomes. Clinically significant covariates such as tumour grade, lymph node (LN) ratio, age at diagnosis, hormone receptor status, tumour location, number of primary tumours, and first primary tumour status were included in the analysis. Higher tumour grade, increased lymph node involvement, advanced age, and negative hormone receptor status were all consistently associated with poorer survival outcomes across all modelling frameworks. These associations were evident both in terms of increased instantaneous risk of the event and shortened survival time, indicating strong and stable prognostic relevance of these factors.

III.ii. Time-Based Effects from Accelerated Failure Time Models

Time-based effects of prognostic factors were evaluated using AFT models, with results expressed as rTIOs. An rTIO value < 1 indicates earlier occurrence of the event, whereas values (rTIO > 1) indicate delayed event occurrence. rTIO estimates derived from Weibull, Lognormal, log-logistic, and generalized gamma models are summarized in Table 1.

Table 1: Time-based effects of prognostic factors across AFT models expressed as rTIO

Factors (comparison)	Weibull AFT rTIO (p)	Lognormal rTIO (p)	Log-logistic rTIO (p)	Gen. Gamma rTIO (p)	Interpretation
Tumour Grade 2 vs 1	0.83*	0.79*	0.80*	0.80*	Event occurs ~20–22% earlier
Grade 3 vs 1	0.59*	0.54*	0.56*	0.55*	Event occurs ~45% earlier
Grade 4 vs 1	0.62*	0.54*	0.57*	0.56*	Marked time acceleration
LN ratio >0.68 vs ref	0.38*	0.33*	0.33*	0.34*	Event ~2/3 earlier
LN ratio 0.35–0.50 vs ref	0.62*	0.59*	0.59*	0.59*	Moderate time shortening
No first primary vs yes	0.77*	0.72*	0.73*	0.73*	Earlier failure
Age >78.5 vs ref	0.28*	0.26*	0.29*	0.27*	Event ~3–4× earlier

ER negative vs positive	0.81*	0.71*	0.73*	0.74*	Reduced survival time
PR negative vs positive	0.86*	0.82*	0.83*	0.83*	Modest acceleration
Central location vs ref	0.89*	0.88*	0.89*	0.89*	Small but consistent effect
No. of primaries (per unit)	1.04*	1.07*	1.06*	1.06*	Delayed event

*p-value<0.05

Across all AFT specifications, rTIO estimates were highly consistent in both magnitude and direction, demonstrating robust time-based effects. Higher tumour grade was associated with substantial acceleration of event timing. Compared with Grade 1 tumours, Grade 2 tumours showed a modest but statistically significant shortening of survival time, with rTIO values ranging from 0.79 to 0.83 across models, corresponding to events occurring approximately 20 to 22% earlier. In contrast, higher-grade tumours exhibited substantially stronger effects. Grade 3 tumours were associated with pronounced time acceleration, with rTIO values between 0.54 and 0.59, indicating that events occurred roughly 40 to 45% earlier than in Grade 1 tumours. Grade 4 tumours demonstrated a similar pattern of marked time acceleration, with rTIO estimates closely aligned with those observed for Grade 3. Taken together, these findings highlight a graded and clinically meaningful relationship between tumour grade and survival time, with even intermediate-grade disease showing earlier event occurrence, and high-grade tumours associated with substantially shortened survival. LN ratio exhibited a strong and graded association with survival time. Patients in the highest LN ratio category (> 0.68) experienced markedly earlier events, with rTIO values consistently below 0.35, indicating that events occurred nearly two-thirds earlier compared with the reference group. Intermediate lymph node ratio categories also showed significant time acceleration, suggesting a dose-response relationship.

Age at diagnosis demonstrated the strongest time-based effect among all the covariates. Patients aged above 78.5 years experienced events approximately three to four times earlier than the youngest reference group, with rTIO values ranging from 0.26 to 0.29 across models. Hormone receptor-negative status was associated with moderate acceleration of event timing, with rTIO values ranging from 0.71 to 0.81 for estrogen receptor-negative tumours and 0.82 to 0.86 for progesterone receptor-negative tumours. rTIO values consistently exceeded one across all AFT models, indicating a modest prolongation of survival time.

III.iii. Comparison of Proportional Hazards and AFT Model Estimates

A comprehensive comparison of covariate effects across PH and AFT models is presented in Table 2. Tumour grade demonstrated a strong and consistent association with survival across all parametric specifications. In AFT models, a graded reduction in survival time was observed, ranging from modest shortening for grade 2 tumours to

substantial acceleration for grades 3 and 4. These time-based effects were mirrored in PH models, where increasing tumour grade was associated with progressively higher hazard relative to grade 1, while grade 3 and grade 4 tumours were associated with nearly two-fold elevations in hazard. The consistency in direction, relative magnitude, and statistical significance of tumour grade effects across parametric AFT models and PH formulations underscores the robustness of tumour grade as a key prognostic factor influencing both the timing and instantaneous risk of mortality.

LN ratio showed pronounced effects in both modelling frameworks. In AFT models, higher LN ratio categories were associated with progressively shorter survival times. Patients with LN ratio > 0.68 experienced substantial survival reduction (Weibull AFT TR ≈ 0.38, $p < 0.001$), with similar estimates across other parametric distributions. Correspondingly, PH models showed more than a threefold increase in hazard for this category (Gompertz HR ≈ 3.10, $p < 0.001$). These findings indicate a strong and graded relationship between nodal involvement and mortality risk. The number of primary tumours demonstrated a statistically significant but modest association with survival. In AFT models, each additional primary tumour was associated with a small increase in survival time (Weibull AFT TR ≈ 1.01, $p < 0.001$), while PH models showed a corresponding modest reduction in hazard (Gompertz HR ≈ 0.96, $p < 0.001$).

Table 2: Comparison of PH and AFT model estimates across parametric distributions

Factor	Weibull AFT (TR, p)	Gompertz PH (HR, p)	Lognormal AFT (TR, p)	Log-logistic AFT (TR, p)	Gen. Gamma AFT (TR, p)	Weibull PH + Frailty (HR, p)
Tumour grade (Grade 2 vs 1)	0.82*	1.28*	0.78*	0.79*	0.79*	1.30*
Tumour grade (Grade 3 vs 1)	0.59*	1.86*	0.54*	0.56*	0.55*	1.87*
Tumour grade (Grade 4 vs 1)	0.62*	1.79*	0.54*	0.57*	0.56*	1.78*
LN ratio >0.68 vs ref	0.38*	3.10*	0.33*	0.33*	0.34*	3.19*
LN ratio 0.35–0.50 vs ref	0.62*	1.75*	0.59*	0.59*	0.59*	1.77*
Number of primaries (per unit)	1.04*	0.96*	1.07*	1.06*	1.06*	0.95*
First primary (No vs Yes)	0.77*	1.34*	0.72*	0.73*	0.73*	1.36*
Age >78.5 yrs vs ref	0.28*	4.51*	0.26*	0.29*	0.27*	3.19*
ER neg vs pos	0.81*	1.27*	0.71*	0.73*	0.74*	1.28*
PR neg vs pos	0.86*	1.19*	0.82*	0.83*	0.83*	1.20*
Central breast location	0.89*	1.15*	0.88*	0.89*	0.89*	1.15*

*p-value<0.05

Patients without a first primary tumour consistently exhibited poorer outcomes. AFT models showed significantly shorter survival times (TRs approximately 0.72 – 0.77, $p < 0.001$), while PH models demonstrated increased hazard of death (HR ≈ 1.34, $p < 0.001$). Age at diagnosis remained a dominant prognostic factor across all models. In AFT formulations, patients older than 78.5 years experienced markedly shorter survival times (TRs approximately 0.26 – 0.29, $p < 0.001$). In the Gompertz PH model, this age group exhibited a substantially increased hazard of death (HR ≈ 4.51, $p < 0.001$). Intermediate age categories also showed statistically significant effects, supporting a monotonic association between age and mortality risk.

Hormone receptor status showed consistent associations with survival outcomes. Estrogen receptor-negative tumours were associated with shorter survival times in AFT models (TRs approximately 0.71 – 0.81, $p < 0.001$) and higher hazards in PH models (HR ≈ 1.27, $p < 0.001$). Progesterone receptor-negative status showed similar but slightly weaker effects. Tumour location demonstrated statistically significant but comparatively smaller effects. Central and entire-breast tumour locations were associated with modest reductions in survival time and modest increases in hazard across models, whereas other locations showed weaker or non-significant associations.

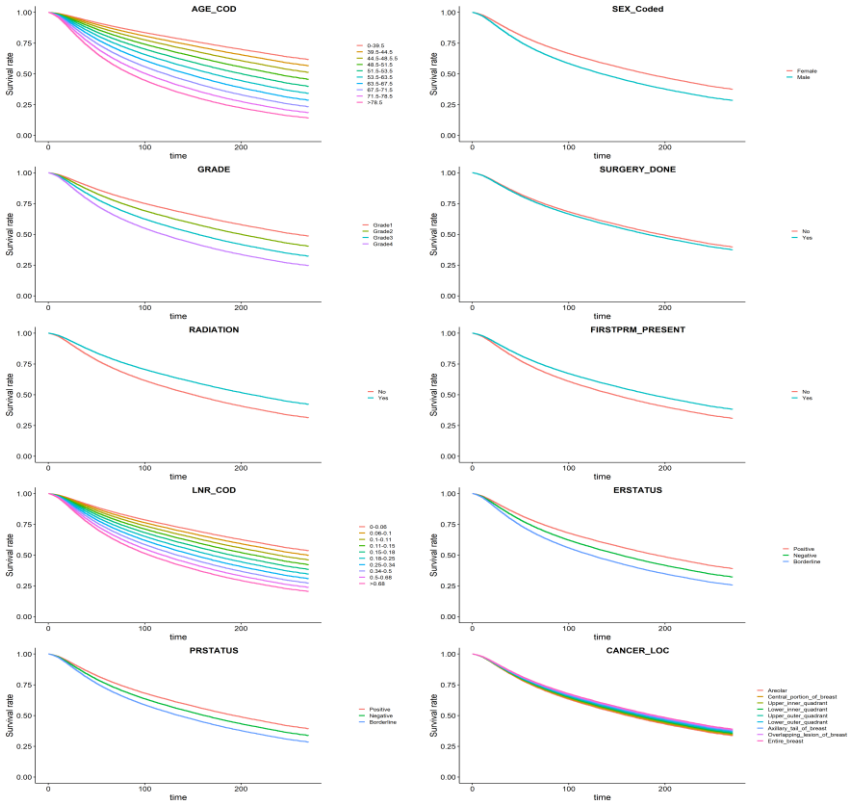

Fig. 1. Adjusted survival curves for key prognostic factors in Breast Cancer

The figure displays model-adjusted survival probabilities over time for major prognostic variables. Curves were obtained from multivariable survival models with all

other covariates held constant. Separation between curves indicates differences in survival experience across categories of each variable.

Figure 1 presents the adjusted survival curves for key prognostic variables derived from the multivariable survival models. Clear separation of curves was observed for age, tumour grade, and LN ratio, indicating progressively poorer survival with increasing age, higher tumour grade, and greater nodal involvement. Patients in the oldest age group and those with the highest LN ratio experienced the most rapid decline in survival probability over time. Distinct differences in survival were also evident according to hormone receptor status, with estrogen receptor-negative and progesterone receptor-negative tumours showing lower survival probabilities compared with receptor-positive tumours. In contrast, survival curves for tumour location and sex showed relatively modest separation, suggesting weaker associations with survival after adjustment for other covariates. Overall, the adjusted curves visually support the multivariable model findings and demonstrate consistent patterns across prognostic factors.

III.iv. Model Comparison and Goodness-of-Fit Assessment

Model comparison based on AIC and BIC values is presented in Table 3. Among classical parametric models, flexible AFT specifications consistently outperformed simpler PH models. The generalized gamma distribution yielded the lowest AIC and BIC values, indicating superior goodness-of-fit after accounting for model complexity. The log-logistic model also demonstrated favourable performance, whereas the Weibull and Gompertz models showed comparatively higher information-criterion values.

Table 3: Information-criterion comparison for parametric models with shared frailty

Model	Scale	Log-likelihood	AIC	BIC
Gompertz	PH	−66623.9	133267	133459
Weibull	AFT	−66178.1	132396	132594
Lognormal	AFT	−65697.5	131435	131641
Log-logistic	AFT	−65680.9	131401	131608
Generalized gamma	AFT	−65549.9	131099	131315
Model (Frailty-adjusted)				
Exponential + frailty	PH	−66639.1	133318	133534
Gompertz + frailty	PH	−66442.5	132925	133140
Weibull PH + frailty	PH	−65870.4	131760	131976
Weibull AFT + frailty	AFT	−65861.9	131743	131968
Lognormal + frailty	AFT	−65690.3	131400	131633
Log-logistic + frailty	AFT	−65674.6	131369	131602
Generalized gamma + frailty	AFT	**−65548.1**	**131116**	**131357**

III.v. Shared Frailty Models and Unobserved Heterogeneity

Shared frailty models incorporating a gamma-distributed random effect revealed statistically significant unobserved heterogeneity. The estimated frailty variance

parameter ($\theta \approx 0.30$) was significantly different from zero ($p < 0.001$), corresponding to a Kendall's tau of approximately 0.13, indicating modest intra-cluster dependence. Likelihood ratio tests strongly rejected the null hypothesis of no frailty. Empirical residual-based correlations were consistent with the model-implied dependence structure, further supporting the presence of modest within-cluster association. Inclusion of shared frailty resulted in modest attenuation of effect estimates while preserving their direction and statistical significance. For example, in the Weibull PH frailty model, the hazard ratio for grade 3 tumours relative to grade 1 tumours was approximately 1.87 ($p<0.001$), and the hazard ratio for LN ratio > 0.68 was approximately 3.19 ($p<0.001$). These results suggest that classical models may slightly overestimate effect sizes but do not alter overall inference. Sensitivity analyses using log-normal frailty yielded comparable results, reinforcing the robustness of the inferred dependence structure and model conclusions.

Across a wide range of parametric survival models, tumour grade, lymph node ratio, age at diagnosis, hormone receptor status, and first primary tumour status were consistently associated with survival outcomes. Results were robust to assumptions regarding the baseline hazard function and remained stable after accounting for unobserved heterogeneity using shared frailty models. Flexible AFT models, particularly the generalized gamma distribution, provided superior model fit and enabled clinically intuitive interpretation through time-based measures. Reporting both hazard-based and time-based estimates offers complementary insights into survival dynamics and strengthens the transparency and reliability of the findings.

III.vi. Robustness and Model Validation Analyses

To ensure the reliability of the estimated effects, additional robustness and validation analyses were conducted using the Cox proportional hazards framework with robust (sandwich) variance estimation. The model demonstrated stable and consistent estimates across all covariates, with no indication of instability arising from model specification. Simulation-based calibration using a parametric bootstrap approach (1,000 replications) further supported the validity of the model. The bootstrap-derived coefficients closely matched the original estimates, with comparable standard deviations, indicating asymptotic normality and absence of meaningful estimation bias. This consistency confirms that the estimated hazard ratios are not driven by sampling variability and are robust to repeated sampling.

Across the validated models, lymph node ratio (LNR), tumour grade, hormone receptor status, and number of primary tumours remained statistically significant predictors of survival (*Table 4*). In particular, LNR showed a strong and consistent association with increased hazard, reinforcing its importance as a reliable indicator of disease burden beyond conventional staging systems. Estrogen receptor (ER) positivity was associated with improved survival outcomes, in line with its established clinical relevance, while progesterone receptor (PR) status demonstrated a statistically significant but comparatively modest effect. Tumour grade also exhibited a significant association with survival; however, the direction and magnitude of this effect should be interpreted with some caution, as it may reflect underlying coding structure or reference category selection. Similarly, the observed association between the number of primary tumours and increased hazard is likely influenced by confounding by indication, where patients

with more severe disease profiles are more likely to undergo additional clinical interventions.

Table 4. Cox Proportional Hazards Model with Robust Variance Estimation and Parametric Bootstrap Validation of Model Stability

Cox Proportional Hazards Model with Robust (Sandwich) Variance					Parametric Bootstrap Validation (Simulation-Based Calibration)		
Variable	**HR**	**95% CI**	**Robust SE**	**p-value**	**Mean Coefficient**	**Bootstrap SD**	**Approx HR**
AGE_DX	1	0.99 – 1.00	0.0004	0.652	0.00016	0.00037	1
GRADE	0.855	0.84 – 0.87	0.0063	***<0.001***	-0.156	0.0062	0.856
LNR	1.211	1.16 – 1.26	0.02	***<0.001***	0.19	0.0194	1.209
ER_STATUS	0.852	0.83 – 0.87	0.013	***<0.001***	-0.159	0.0135	0.853
PR_STATUS	1.045	1.02 – 1.07	0.0112	***<0.001***	0.043	0.0111	1.044
Number of primaries	1.403	1.38 – 1.49	0.0091	***<0.001***	0.338	0.0093	1.403

Notably, age at diagnosis did not emerge as an independent predictor after adjustment for other covariates, suggesting that its effect may be mediated through disease severity or other clinical factors. Overall, the combined use of robust variance estimation and parametric bootstrap validation provides strong evidence for the stability, consistency, and reliability of the model estimates. These findings further strengthen the overall conclusions of the study by demonstrating that the identified prognostic factors are not sensitive to model assumptions or sampling variability.

IV. Discussion

This population-based survival analysis found that tumour grade, LN ratio, age at diagnosis, hormone receptor status, and first primary tumour status were "consistently" and independently associated with breast cancer survival. These associations were robust across multiple parametric and semi-parametric models and remained statistically significant after accounting for shared frailty at the age-group level, indicating that the findings are robust to both modelling assumptions and unobserved heterogeneity. Tumour grade and LN ratio emerged as the strongest and most consistent prognostic factors. Higher histologic grade was consistently associated with markedly shorter survival time and higher instantaneous hazards across both AFT and PH frameworks, supporting the established role of grade as a core prognostic marker in breast cancer. This finding is in close agreement with earlier studies that have identified histologic grade as a key marker of tumour aggressiveness and biological behaviour, with higher grades consistently linked to poorer outcomes irrespective of

molecular subtype or treatment era [XVIII]. The consistency of this association across multiple model formulations in the present analysis further reinforces the central prognostic importance of tumour grade in breast cancer.

LN ratio demonstrated a clear dose-response relationship with survival outcomes: increasing LN ratio categories were associated with progressive shortening of survival time and rising hazards. Similar graded associations have been reported in large cohort studies and meta-analyses, which suggest that the LN ratio provides a more refined measure of nodal disease burden than absolute LN counts (Liyu et al., 2014; Chang et al., 2015). Our findings support the growing evidence that ratio-based nodal metrics may enhance prognostic stratification, particularly among node-positive patients, and highlight their relevance in survival modelling. [III], [XVI].

Advanced age at diagnosis was associated with the most pronounced adverse effect on survival, particularly for patients older than 78.5 years, consistent with population-level studies that report markedly worse survival among the oldest patients even after adjustment for stage and other covariates [II]. Age-related survival disparities likely reflect a complex interplay of biological vulnerability, comorbid conditions, differences in treatment intensity, and competing causes of mortality, underscoring the need for careful clinical interpretation and individualized management strategies in elderly patients. Hormone receptor status also showed a consistent association with survival outcomes. Estrogen receptor-negative and progesterone receptor-negative tumours were associated with significantly shorter survival times across both modelling frameworks. This finding aligns with contemporary evidence emphasizing the prognostic and predictive importance of hormone receptor expression, including recent studies highlighting the independent prognostic contribution of progesterone receptor status in addition to estrogen receptor expression [VI]. The stability of these effects across parametric distributions further supports the clinical relevance of receptor profiling in breast cancer prognosis.

Incorporation of shared frailty models revealed statistically significant unobserved heterogeneity ($\theta \approx 0.30$), suggesting that patients within the same age strata shared latent risk factors not fully captured by observed covariates. Although adjustment for frailty resulted in modest attenuation of effect estimates, the direction and statistical significance of key prognostic associations remained unchanged. This indicates that conventional survival models may slightly overestimate effect magnitudes but do not materially alter overall inference. Similar conclusions have been reported in methodological studies highlighting the importance of frailty modelling in clustered survival data to obtain more realistic effect estimates [XII], [X], [XXVII], [VIII], [XXIV].

Flexible AFT models, particularly the generalized gamma, provided superior fit in our cohort as judged by information-criterion comparisons, and yielded clinically interpretable time-scale estimates (time ratios, rTIO) that complement hazard-based inference. In addition to improved statistical performance, these models yielded clinically interpretable time-scale estimates, including time ratios and relative time-to-event indices, which directly quantify how much earlier or later events are expected to occur. Such time-based measures complement hazard-based inference and may facilitate clearer communication of prognosis in clinical settings, especially when

discussing expected survival trajectories with patients. Together, these findings highlight the value of considering both hazard- and time-scale parametrizations to achieve robust and interpretable survival analyses.

Overall, the consistent prognostic impact of tumour grade, LN ratio, age at diagnosis, hormone receptor status, and first primary tumour status across modelling frameworks underscores their importance in breast cancer survival. The combined use of PH and AFT approaches, along with frailty adjustment, provides a transparent and clinically meaningful assessment of survival dynamics and supports the integration of both hazard-based and time-based measures in future observational cancer survival studies.

V. Conclusion

In this large population-based study, several routinely recorded clinical factors were found to be strongly related to survival in women with breast cancer. Higher tumour grade, greater LN ratio involvement, older age at diagnosis, and negative hormone receptor status were consistently linked to poorer survival outcomes. These relationships remained stable even when different statistical approaches were used and after accounting for hidden differences between patient groups. Importantly, methods that focus on survival time, in addition to traditional risk-based measures, helped describe how much earlier or later an event occurred in a way that is easier to understand clinically. Together, these findings support the use of flexible and transparent survival models to better communicate prognosis and to strengthen evidence-based decision-making in breast cancer care.

Competing interests:

The authors have declared that no competing interests exist.

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