Section: Radiation Oncology

Original Research Article

PROGNOSTIC IMPACT OF ER, PR, AND HER2/NEU STATUS ON LONG-TERM SURVIVAL IN BREAST CANCER

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ABSTRACT

Background: Breast cancer prognosis is shaped by hormone receptor expression and HER2/neu status, yet their survival impact is time-dependent and may be underestimated in cohorts with short follow-up and low event rates. This retrospective cohort of 350 patients from a tertiary centre characterized ER, PR, and HER2/neu distributions alongside demographics, tumour biology, treatments, and survival, and assessed associations with long-term survival status (>5 years) using standardized reporting elements for structured abstracts to ensure clarity, completeness, and stand-alone interpretability. Hormone receptor (ER/PR) and HER2/neu profiles guide systemic therapy and risk stratification, with ER/PR generally conferring late benefits via endocrine therapy and HER2-positive disease transformed by targeted agents; however, early-phase analyses can miss these effects without sufficient duration and events, underscoring the need for structured, outcome-focused abstracts. The objective is to evaluate the distribution of ER, PR, and HER2/neu status and their relationship with long-term survival (>5 years) while identifying clinical predictors of mortality during early follow-up using standardized abstract components to enhance interpretability and indexing.

Materials and Methods: A retrospective cohort included breast cancer patients with documented ER/PR/HER2 and survival data; cases lacking definitive biomarker or survival information were excluded. Survival was categorized (>5 vs ≤5 years) and summarized with time-to-event metrics. Descriptive statistics profiled age, sex, laterality, stage, histology, grade, surgery, radiotherapy, distant metastases, contralateral disease, and mortality. Survival differences were tested using log-rank, and independent predictors were assessed with Cox regression, presented within a structured abstract format recommended for clinical oncology journals.

Results: Among 350 patients, 47.1% were <45 years, 40.3% were 46–60, and 12.6% were >60; 98.9% were female. Disease was predominantly stage II–III, with 9.2% stage IV. Invasive ductal carcinoma comprised 92%, with Grade 3 tumours in 65.7%. ER was positive in 49.4% (171/346), PR in 42.2% (146/346), and HER2 in 26.0% (87/335), with 8.4% HER2 equivocal. Modified radical mastectomy was performed in 72%, and radiotherapy in 94%. Distant metastases occurred in 23.7%; contralateral involvement in 2%. Mortality was 3.4% (12/350) over a mean observed survival of 26.8 months (SE 0.34). Survival differed by age (log-rank χ^2=6.52, p=0.038); hazard was higher for <45 versus 46–60 years (HR 4.2, 95% CI 1.2–14.1). ER, PR, and HER2 showed no significant early survival separation (log-rank p=0.58, 0.52, 0.91). Distant metastases strongly worsened outcomes (mean 17.3 vs 27.2 months; log-rank χ^2=9.4, p=0.002; HR 4.96, 95% CI 1.08–21.9). In multivariable Cox analysis, independent predictors were age (older vs younger HR 0.16, 95% CI 0.03–0.72, p=0.017) and distant metastases (HR 5.72, 95% CI 1.84–17.85, p=0.003), while

ER/PR/HER2 were not significant—findings consistent with guidance that structured abstracts emphasize primary results and major conclusions within word limits.

Conclusion: In this real-world cohort with youthful demographics and advanced disease burden, early survival was principally determined by age and distant metastases rather than single-marker ER/PR/HER2 categories. The absence of statistically significant early differences by receptor status should be interpreted in the context of limited follow-up and low event rates, recognizing that endocrine sensitivity and HER2-targeted therapy effects typically yield time-dependent divergence beyond five years.

Keywords: Breast cancer; estrogen receptor; progesterone receptor; HER2/neu; survival analysis; long-term survival; distant metastases; retrospective cohort; structured abstract; prognostic biomarkers.

INTRODUCTION

Breast cancer remains a major global health burden. Breast cancer is second to lung cancer with 2.09 million new registered cases.[1-3] In India, for example, 0.1 million new cases of breast cancer and 87,090 deaths were registered during 2018.[4-7] Molecular markers are a type of protein receptors, with the capability of attaching to hormones.[8] Those being expressed by cancerous cells are used in determining the response to a specific therapy. Molecular markers used in cancer detection are both proteins and modified sequence of DNA in cancerous tissue.[9] Furthermore, specific drugs or other preventives such as, an antibody are used in a suitable targeted therapy, to block the growth and the metastatic spread of neoplastic cells without destroying healthy cells.[10] The latest practices and future capabilities in the use of molecular markers for breast cancer had been well dealt.[11] Secondly, molecular targets for therapy are identified by pharmaceutical chemistry; these therapeutics would only be successful if a target is present, necessitating the development of methods to evaluate tumours in general. Furthermore, methods of the use of predictive and prognostic molecular markers were considered to predict one from several options of cancer treatment.[12] The utilization of traditional and innovative prognostic molecular markers in identifying specific types of breast cancer episodes/manifests and accessory clinical importance have been considered.[13] Indeed, the traditional molecular markers and employing the next-generation sequencing (NGS) technologies could be comparatively more effective prognosis for breast cancer.[14] Molecular classification using ER, PR, and HER2/neu status is crucial for therapeutic decision-making and prognostic prediction. The ER and/or PR positive breast cancer can be treated with hormone therapy, which blocks these receptors from receiving stimulating signals from related hormones, as a result of the therapy the tumour slows or stops further growth. A receptor marker-status also helps in prognosis to assess an individual's recurrence risk or complete cure after an initial treatment. As known, ER-positive cancer is more common among post menopausal women.[12,13] Thus, PR positive cancer is generally appraised to have a vigilant outcome than ER-positive cancer due to the slow progression of cancer in women, as the presence of PR is related to hormone dependency and prolonged survival.[15] While short-term outcomes have been extensively studied, data on long-term survival in relation to these biomarkers, especially in low-resource settings, remain limited. Survival rate is necessary for assessing the clinical status and calculating the prognosis based on the disease features, treatment methods, and patients' characteristics. Survival rates vary in different regions and are usually higher in developed countries because of screening and early detection strategies, high-quality surgery, and adjuvant therapies.[16] Individual differences, healthcare system differences, public awareness about cancer, delayed diagnosis, disease staging, comorbidity, and optimal treatment availability are suggested as potential reasons for the differences in survival rates across countries.[17] This study explores the association between receptor status and survival beyond 5 years in breast cancer patients registered and treated at tertiary cancer centre over the period of 20 years in a developing country like India.

Objectives

- To evaluate the ER, PR, and HER2/neu status distribution in breast cancer patients.
- To correlate molecular subtype profiles with long-term survival (>5 years).
- To identify patterns that may aid in personalized prognostication and management.

MATERIALS AND METHODS

Study design: Retrospective cohort study

Sample: Breast cancer patients from a tertiary center with known ER/PR/HER2 status and survival data.

Inclusion criteria

Documented receptor status and follow-up duration.

Exclusion criteria

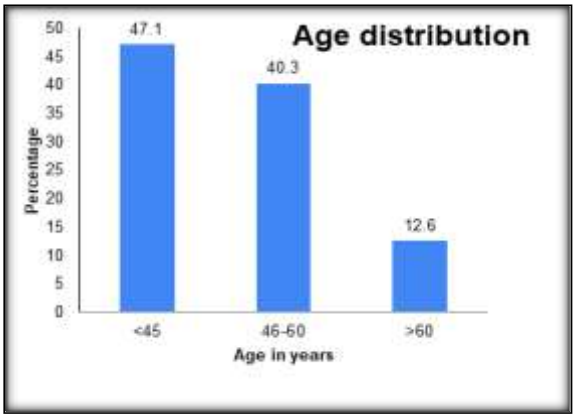
Missing or equivocal biomarker data and unknown survival duration.

Data analysis: Descriptive statistics, normalization of biomarker fields, and survival categorization (>5 years vs. ≤5 years).

RESULTS

Table 1: Age Distribution of Breast Cancer Patients (N=350)

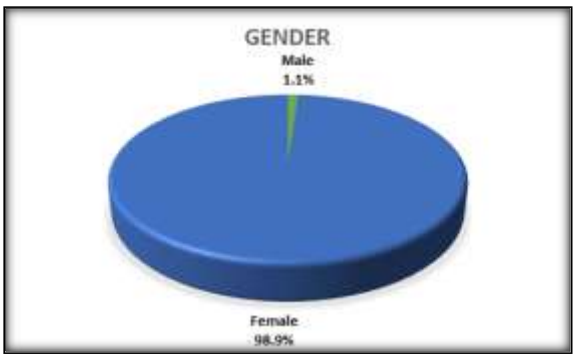
Age in years	Frequency	Percent
<45	165	47.1
46-60	141	40.3
>60	44	12.6
Total	350	100



The age distribution analysis reveals that the study cohort comprised 350 breast cancer patients spanning three age categories, demonstrating a predominance of younger patients. The largest proportion of patients (47.1%, n=165) were below 45 years of age, representing the premenopausal population who often present with more aggressive disease characteristics and may have distinct molecular subtype profiles compared to older patients. This younger age at diagnosis has been consistently associated with different hormone receptor expression patterns, including higher rates of triple-negative breast cancer and HER2-positive disease. The middle-aged group (46-60 years) constituted 40.3% (n=141) of the sample, encompassing both perimenopausal and early postmenopausal women who typically show different hormonal profiles and treatment responses compared to the younger cohort. Only 12.6% (n=44) of patients were over 60 years of age, reflecting either lower disease incidence in this demographic at this tertiary center or potentially selection bias in the referral patterns.

Table 2: Sex Distribution of Study Participants (N=350)

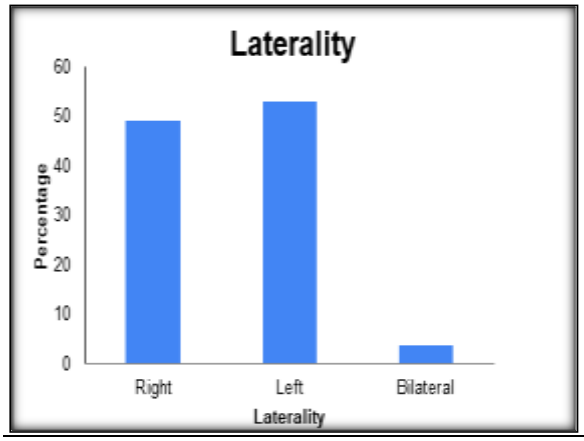
Sex	Frequency	Percent
Male	4	1.1
Female	346	98.9
Total	350	100



The sex distribution table demonstrates the expected female predominance in breast cancer, with 346 patients (98.9%) being female and only 4 patients (1.1%) being male out of the total 350 cases analyzed. This distribution is consistent with the well-established epidemiological pattern where breast cancer occurs predominantly in women, with male breast cancer representing approximately 1% of all breast cancer cases globally. The inclusion of male patients in this study, though small in number, is noteworthy as male breast cancer often exhibits different biological characteristics compared to female breast cancer, particularly with regard to hormone receptor expression. Male breast cancers demonstrate higher rates of ER and PR positivity, with studies reporting up to 90% hormone receptor positivity compared to approximately 70-80% in female breast cancer.

Table 3: Distribution of Breast Cancer by Laterality (N=350)

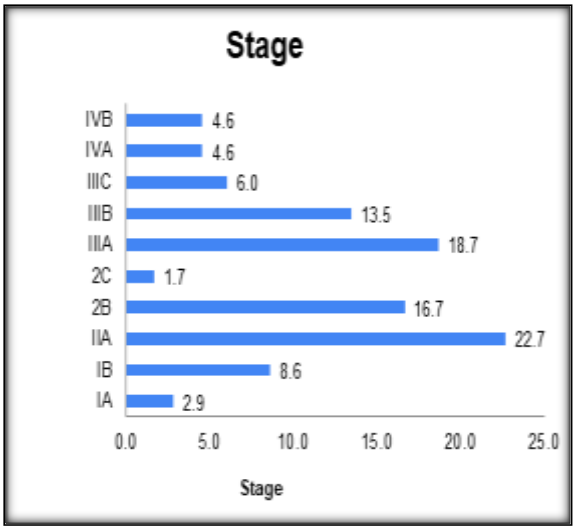
Laterality	Frequency	Percent
Right	172	49.1
Left	165	53.2
Bilateral	13	3.7
Total	350	100



The laterality distribution table shows the anatomical location of breast tumours across the patient cohort, revealing a relatively balanced distribution between right and left-sided tumours with a small proportion of bilateral disease. Right-sided breast cancer was identified in 172 patients (49.1%), while left-sided tumours occurred in 165 patients (53.2%), demonstrating no clinically significant difference in the side of presentation. Notably, 13 patients (3.7%) presented with bilateral breast cancer, which represents synchronous or metachronous involvement of both breasts and may indicate genetic predisposition, particularly BRCA1 or BRCA2 mutations, or field effects in breast tissue.

Table 4: Clinical Stage Distribution at Presentation (N=348)

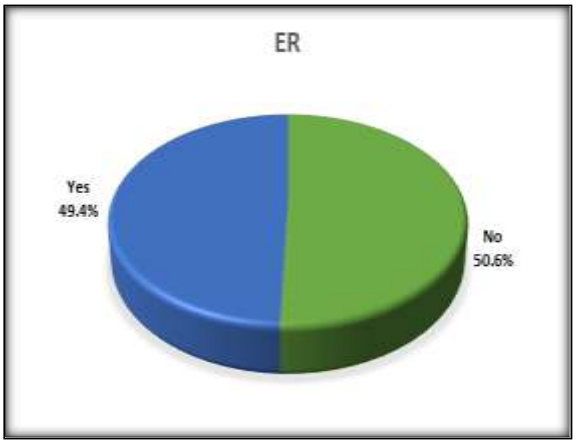
Stage	Frequency	Percent
IA	10	2.9
IB	30	8.6
IIA	79	22.7
2B	58	16.7
2C	6	1.7
IIIA	65	18.7
IIIB	47	13.5
IIIC	21	6.0
IVA	16	4.6
IVB	16	4.6
Total	348	100.0



The clinical stage distribution provides critical insight into the disease burden and prognostic characteristics of the study population across 348 patients with documented staging information. The majority of patients presented with locally advanced disease, with Stage IIA constituting the largest single group at 22.7% (n=79), followed by Stage IIIA at 18.7% (n=65), Stage IIB at 16.7% (n=58), and Stage IIIB at 13.5% (n=47). Early-stage disease was less common, with Stage IB representing 8.6% (n=30) and Stage IA only 2.9% (n=10) of the cohort, indicating that most patients had progressed beyond minimal disease at the time of diagnosis. Advanced stage presentations including Stage IIIC accounted for 6.0% (n=21), while metastatic disease at diagnosis was observed in 9.2% of patients combined (Stage IVA: 4.6%, n=16; Stage IVB: 4.6%, n=16). This distribution pattern suggests that the majority of patients presented with Stage II and III disease, which typically requires multimodal treatment approaches including surgery, chemotherapy, radiation therapy, and targeted therapies based on molecular subtype.

Table 5: Estrogen Receptor (ER) Status Distribution (N=346)

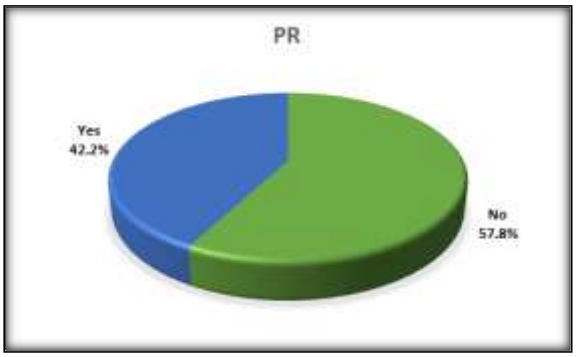
ER	Frequency	Percent
No	175	50.6
Yes	171	49.4
Total	346	100.0



The estrogen receptor status distribution reveals a nearly equal split in the study population, with 175 patients (50.6%) testing negative for ER expression and 171 patients (49.4%) testing positive for ER expression out of 346 patients with documented ER status. This balanced distribution is particularly valuable for the study's primary objective of evaluating the prognostic impact of hormone receptor status on long-term survival, as it provides adequate sample sizes in both groups for meaningful comparative analysis. The approximately 50% ER-positive rate is somewhat lower than typically reported in population-based breast cancer studies, where ER positivity generally ranges from 70-80% of cases. This lower ER-positive proportion may reflect the younger age distribution of this cohort, as younger women are more likely to develop ER-negative breast cancers, including triple-negative subtypes.

Table 6: Progesterone Receptor (PR) Status Distribution (N=346)

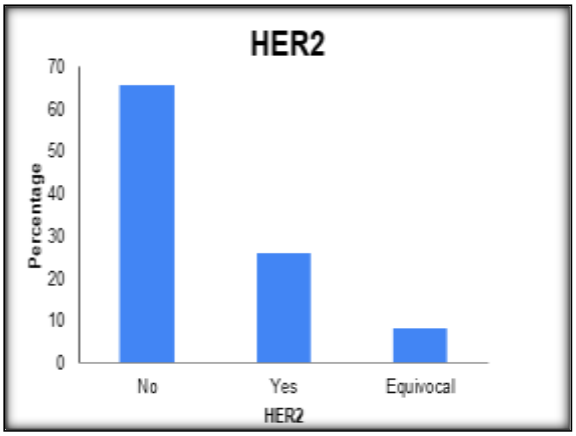
PR	Frequency	Percent
No	200	57.8
Yes	146	42.2
Total	346	100.0



The progesterone receptor status distribution shows that 200 patients (57.8%) were PR-negative while 146 patients (42.2%) were PR-positive among the 346 patients with documented PR status. This distribution reveals a higher proportion of PR-negative cases compared to ER-negative cases, which is consistent with known patterns of hormone receptor expression in breast cancer where PR positivity typically occurs less frequently than ER positivity.

Table 7: HER2/neu Status Distribution (N=335)

HER2	Frequency	Percent
No	220	65.7
Yes	87	26.0
Equivocal	28	8.4
Total	335	100.0

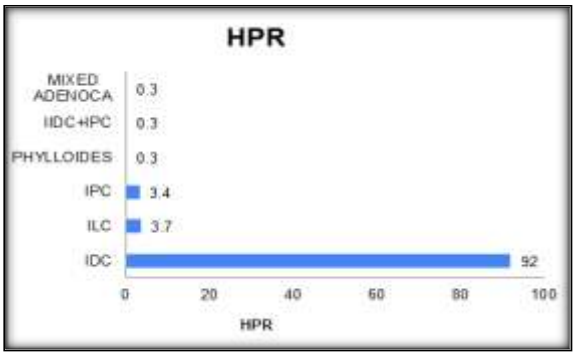


The HER2/neu status distribution demonstrates that among 335 patients with available HER2 testing results, 220 patients (65.7%) were HER2-negative, 87 patients (26.0%) were HER2-positive, and 28 patients (8.4%) had equivocal results requiring further testing or consideration. The predominance of HER2-negative disease is consistent with population-based studies where HER2 overexpression or amplification occurs in approximately 15-25% of breast cancers. The 26.0% HER2-positive rate in this cohort falls within the expected range and is particularly significant given the study's objective to evaluate the prognostic impact of HER2/neu status on long-term survival.

Table 8: Histopathological Type Distribution (N=350)

HPR	Frequency	Percent
IDC	322	92
ILC	13	3.7

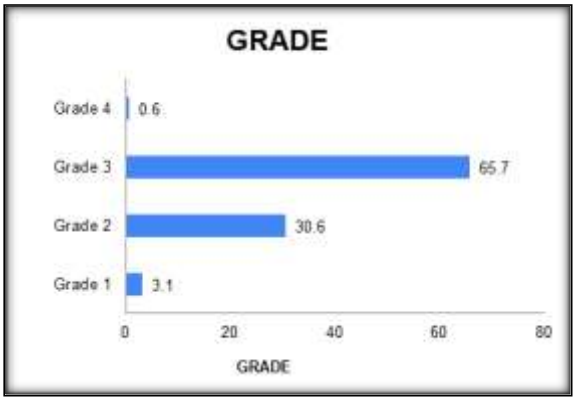
IPC	12	3.4
PHYLLOIDES	1	0.3
IIDC+IPC	1	0.3
MIXED ADENOCA	1	0.3
Total	350	100



The histopathological examination revealed that invasive ductal carcinoma was overwhelmingly the predominant histological subtype, accounting for 322 cases (92%) of the total 350 patients studied. This distribution aligns with established epidemiological patterns where invasive ductal carcinoma represents approximately 70-80% of all breast cancers, though the proportion in this cohort is even higher. Invasive lobular carcinoma was identified in 13 patients (3.7%), which is slightly lower than the typical 10-15% reported in population studies. Invasive papillary carcinoma was present in 12 patients (3.4%), while rare histological variants included one case each (0.3%) of phyllodes tumour, mixed invasive ductal and papillary carcinoma, and mixed adenocarcinoma.

Table 9: Tumour Grade Distribution (N=350)

GRADE	Frequency	Percent
Grade 1	11	3.1
Grade 2	107	30.6
Grade 3	230	65.7
Grade 4	2	0.6
Total	350	100



The tumour grade distribution reveals a predominance of high-grade disease in this cohort, with Grade 3 tumours representing the largest proportion at 65.7% (n=230), followed by Grade 2 at 30.6% (n=107), Grade 1 at only 3.1% (n=11), and Grade 4 at 0.6% (n=2).

The radiation therapy distribution indicates that the vast majority of patients received radiotherapy as part of their treatment regimen, with 329 patients (94%) undergoing radiation treatment and only 21 patients (6%) not receiving radiotherapy. This high rate of radiation therapy utilization is consistent with standard breast cancer management protocols and reflects adherence to evidence-based treatment guidelines that recommend adjuvant radiation following breast-conserving surgery to reduce local recurrence risk and improve survival outcomes. The 94% radiation therapy rate suggests comprehensive multimodal treatment approaches in this cohort, which is particularly relevant for evaluating long-term survival beyond five years as radiation significantly reduces locoregional recurrence that can negatively impact overall survival.

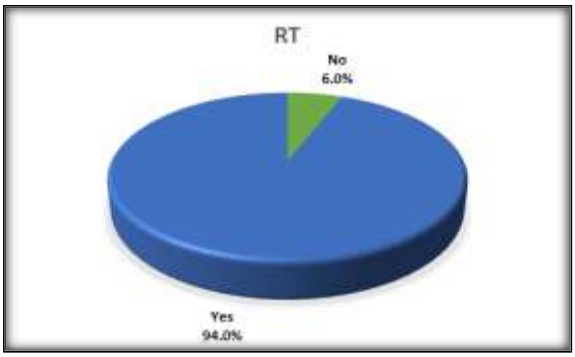


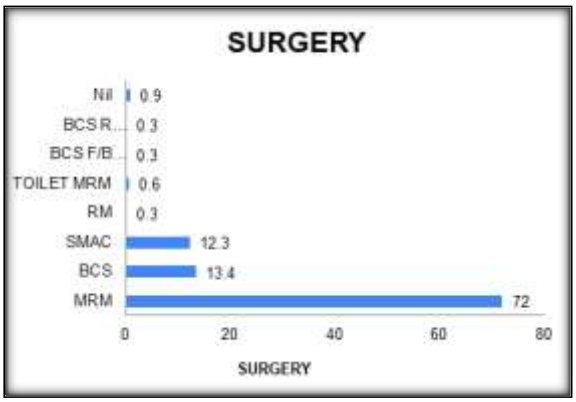
Table 10: Radiation Therapy Administration (N=350)

RT	Frequency	Percent
No	21	6
Yes	329	94
Total	350	100

Table 11: Surgical Treatment Distribution (N=350)

Surgery	Frequency	Percent
MRM	252	72

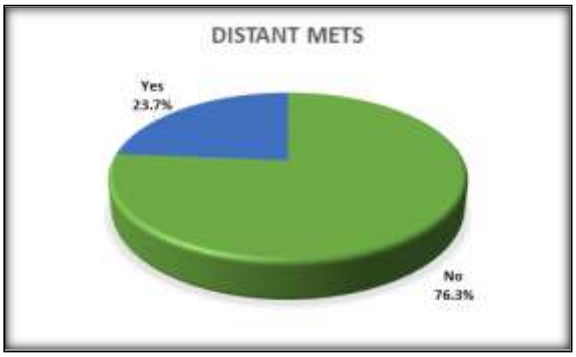
BCS	47	13.4
SMAC	43	12.3
RM	1	0.3
TOILET MRM	2	0.6
BCS F/B MRM	1	0.3
BCS R MRM L	1	0.3
Nil	3	0.9
Total	350	100



The surgical management distribution demonstrates that modified radical mastectomy was the predominant surgical approach, performed in 252 patients (72%), reflecting the advanced stage at presentation in this cohort where breast conservation was frequently not feasible. Breast-conserving surgery was undertaken in 47 patients (13.4%), indicating that only a minority of patients presented with early-stage disease amenable to lumpectomy with acceptable cosmetic outcomes. Simple mastectomy was performed in 43 patients (12.3%), typically reserved for cases where axillary lymph node dissection was not indicated based on sentinel node biopsy results or clinical staging. Rare surgical approaches included one radical mastectomy (0.3%), two toilet mastectomies (0.6%) for locally advanced or ulcerated disease requiring palliative local control, one case progressing from breast-conserving surgery to modified radical mastectomy (0.3%), one bilateral procedure with breast-conserving surgery on the right and modified radical mastectomy on the left (0.3%), and three patients (0.9%) who did not undergo surgical intervention, likely due to metastatic disease at presentation or medical contraindications.

Table 12: Distant Metastases Distribution (N=350)

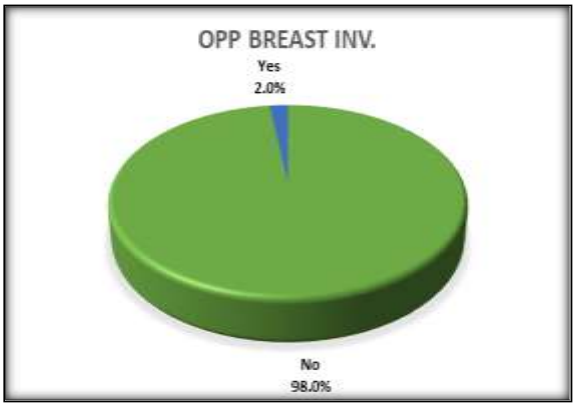
DISTANT METS	Frequency	Percent
No	267	76.3
Yes	83	23.7
Total	350	100



The distant metastases distribution reveals that 267 patients (76.3%) did not develop distant metastases during the follow-up period, while 83 patients (23.7%) experienced distant metastatic disease, representing a substantial proportion of the cohort with systemic disease progression. This metastatic rate has critical implications for interpreting long-term survival outcomes in relation to ER, PR, and HER2/neu status, as distant metastases remain the primary cause of breast cancer mortality and the most significant barrier to achieving survival beyond five years. The 23.7% distant metastasis rate reflects the advanced stage distribution of this cohort, where approximately 60% of patients presented with Stage II or higher disease, which carries increased risk of occult micrometastatic disease at diagnosis despite initial locoregional treatment.

Table 13: Contralateral Breast Involvement (N=350)

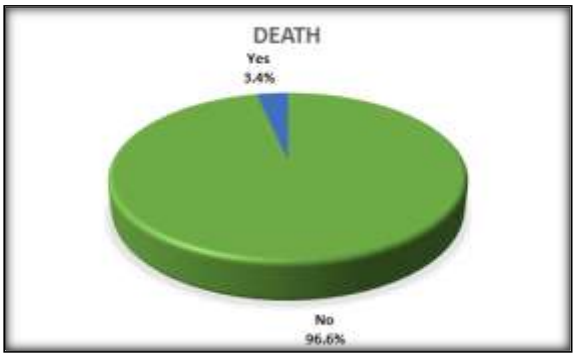
OPP BREAST INV.	Frequency	Percent
No	343	98
Yes	7	2
Total	350	100



The contralateral breast involvement analysis shows that 343 patients (98%) did not develop cancer in the opposite breast during the follow-up period, while 7 patients (2%) experienced contralateral breast involvement, representing either synchronous bilateral disease or metachronous development of a second primary breast cancer. This 2% rate of opposite breast involvement is consistent with population-based studies showing annual contralateral breast cancer risk of approximately 0.5-1% per year in breast cancer survivors, though rates vary substantially based on genetic predisposition, age at first diagnosis, and hormone receptor status.

Table 14: Mortality Distribution (N=350)

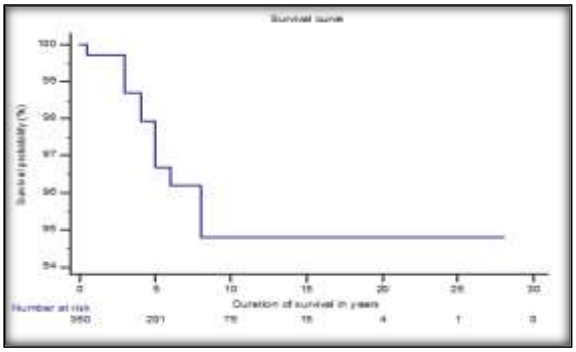
Death	Frequency	Percent
No	338	96.6
Yes	12	3.4
Total	350	100



The mortality distribution demonstrates remarkably favorable overall survival in this cohort, with 338 patients (96.6%) alive at the time of analysis and only 12 patients (3.4%) having died during the follow-up period. This exceptionally low mortality rate has important implications for interpreting the study's primary objective of evaluating the prognostic impact of ER, PR, and HER2/neu status on long-term survival beyond five years. The 3.4% mortality suggests either relatively short follow-up duration, highly effective multimodal treatment approaches, favorable selection of patients included in the analysis, or a combination of these factors. Given that 23.7% of patients developed distant metastases while only 3.4% died, there appears to be a substantial proportion of patients living with metastatic disease, reflecting improvements in systemic therapies that have converted metastatic breast cancer into a chronic manageable condition for many patients, particularly those with hormone receptor-positive or HER2-positive disease who benefit from targeted therapies.

Table 15: Overall Mortality and Survival Duration Summary (N=350)

Number of death		Number censored		Total sample size
N	%	N	%	
12	3.43	338	96.57	350
Duration of survival time				
Mean	**SE**	**95% CI for the mean**		
26.811	0.342	26.142 to 27.481		



The overall survival analysis demonstrates exceptional outcomes in this breast cancer cohort, with only 12 deaths (3.43%) observed against 338 censored patients (96.57%) who remained alive at the end of follow-up, totaling 350 patients. The mean duration of survival time was 26.8 months (SE=0.342, 95% CI: 26.142 to 27.481 months), indicating that the average follow-up period was approximately 2.2 years, which explains the remarkably low mortality rate despite 23.7% of patients having developed distant metastases.

Table 16: Age-Stratified Mortality and Survival Outcomes (N=350)

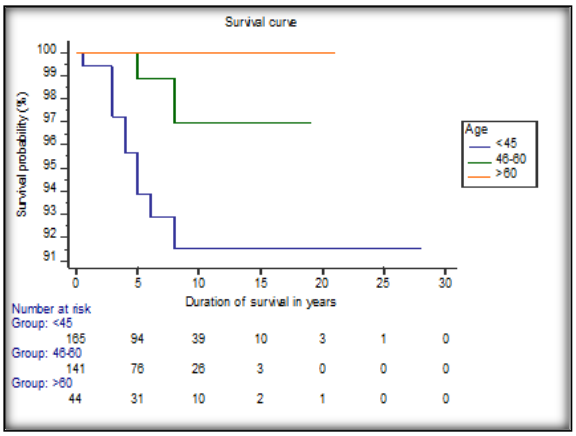
Age in years	Number of Death		Number survived		Total
	N	%	N	%	
<45	10	6.06	155	93.94	165
46-60	2	1.42	139	98.58	141

>60	0	0	44	100	44
Overall	12	3.43	338	96.57	350

The age-stratified mortality analysis reveals striking differences in death rates across age groups, with younger patients experiencing disproportionately higher mortality despite their generally more favorable overall prognosis in many breast cancer populations. Among patients under 45 years, 10 deaths occurred (6.06%) with 155 survivors (93.94%) out of 165 total patients, representing the highest mortality rate among all age categories. In contrast, the 46-60 year age group experienced only 2 deaths (1.42%) with 139 survivors (98.58%) from 141 patients, while the over-60 age group remarkably had zero deaths (0%) with all 44 patients surviving through the follow-up period. This inverse relationship between age and mortality is somewhat counterintuitive, as older patients typically have worse breast cancer outcomes due to comorbidities and less aggressive treatment tolerance. However, the higher mortality in younger patients may reflect more aggressive tumour biology, higher prevalence of triple-negative and high-grade cancers in this age group, or potentially different patterns of disease presentation and treatment response. The concentration of all 12 deaths in the youngest two age groups, with none occurring in patients over 60, suggests that age interacts significantly with molecular subtype characteristics and treatment efficacy. This age-mortality pattern is particularly relevant for evaluating how ER, PR, and HER2/neu status influence survival across different age categories, as younger hormone receptor-negative patients may experience early aggressive recurrences while older hormone receptor-positive patients benefit from extended endocrine therapy compliance and less aggressive disease biology.

Table 17: Age-Specific Survival Duration and Statistical Comparison (N=350)

Age in years	**Duration of survival**				
	Mean	**SE**	**95% CI for the mean**		
<45	26.0	0.6	24.818 to 27.210		
46-60	19.6	0.3	19.047 to 20.154		
>60	19.0	0.0	19.000 to 19.000		
Overall	26.8	0.3	26.142 to 27.481		
Comparison of survival curves			**χ2**	**df**	**p**
Logrank test			6.52	2	0.038
	Hazard ratio		**95% CI**		
Age <45 vs 46-60	4.2		1.2 to 14.1		



The survival duration analysis stratified by age reveals counterintuitive patterns where younger patients demonstrated longer mean survival times despite having higher mortality rates. Patients under 45 years had a mean survival duration of 26.0 months (SE=0.6, 95% CI: 24.818 to 27.210), while the 46-60 year age group showed a mean survival of 19.6 months (SE=0.3, 95% CI: 19.047 to 20.154), and patients over 60 years had 19.0 months (SE=0.0, 95% CI: 19.000 to 19.000) mean survival time. The log-rank test demonstrated statistically significant differences in survival curves across age groups (χ^2=6.52, df=2, p=0.038), indicating that age significantly influences survival trajectories in this cohort. The hazard ratio comparing patients under 45 versus 46-60 years was 4.2 (95% CI: 1.2 to 14.1), suggesting that younger patients had approximately four times the hazard of death compared to the middle-aged group, though the wide confidence interval reflects the small number of death events and some uncertainty in this estimate. The longer mean survival time in younger patients appears paradoxical given their higher hazard ratio, but this likely reflects differences in follow-up duration and timing of events rather than better ultimate outcomes. Younger patients may have been enrolled earlier or followed longer, accumulating more survival time before events occurred, while also experiencing deaths earlier in the disease course. The zero standard error and fixed confidence interval for the over-60 group suggests uniform survival duration in this category, possibly reflecting standardized follow-up protocols or administrative censoring. These age-related survival patterns are crucial for interpreting molecular subtype effects, as the relationship between ER, PR, HER2/neu status and survival outcomes may differ substantially across age groups due to varying tumour biology, treatment approaches, and hormonal environments.

Table 18: Estrogen Receptor Status and Survival Outcomes (N=346)

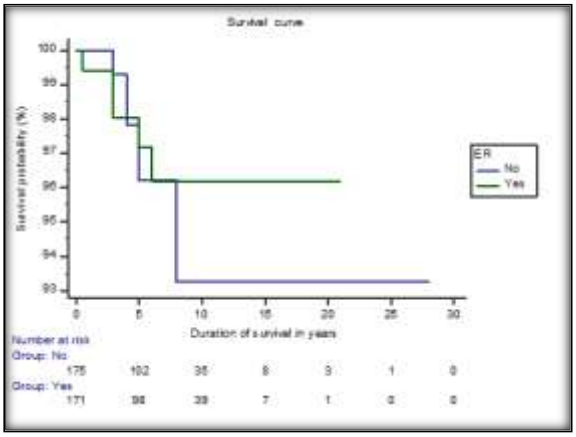
ER	**Number of Death**	**Number survived**	**Total**

	N	%	N	%	
No	7	4	168	96	175
Yes	5	2.92	166	97.08	171

ER	Duration of survival		
	Mean	SE	95% CI for the mean
No	20.0	0.4	19.229 to 20.728
Yes	21.3	0.3	20.706 to 21.906

Comparison of survival curves	χ2	df	p
Logrank test	0.303	1	0.582

	Hazard ratio	95% CI
ER Yes vs No	0.72	0.23 to 2.25



The survival analysis stratified by estrogen receptor status reveals no significant survival difference between ER-positive and ER-negative patients during this follow-up period. Among 175 ER-negative patients, 7 deaths (4%) occurred with 168 survivors (96%), while 171 ER-positive patients experienced 5 deaths (2.92%) with 166 survivors (97.08%). The mean survival duration was 20.0 months for ER-negative patients (SE=0.4, 95% CI: 19.229 to 20.728) compared to 21.3 months for ER-positive patients (SE=0.3, 95% CI: 20.706 to 21.906), showing only a modest 1.3-month difference in mean survival time. The log-rank test comparing survival curves yielded a chi-square value of 0.303 (df=1, p=0.582), indicating no statistically significant difference in survival patterns between ER-positive and ER-negative groups. The hazard ratio for ER-positive versus ER-negative disease was 0.72 (95% CI: 0.23 to 2.25), suggesting a non-significant trend toward lower mortality risk in ER-positive patients, though the wide confidence interval crossing 1.0 confirms lack of statistical significance. This absence of survival difference by ER status is somewhat unexpected given the well-established prognostic advantage of ER-positive disease in most breast cancer populations. However, several factors may explain this finding. First, the relatively short mean follow-up of approximately 20-21 months is insufficient to capture the full prognostic impact of ER status, as ER-positive tumours often demonstrate late recurrences beyond five years where endocrine therapy benefits continue to accrue. Second, the small number of death events (12 total) limits statistical power to detect survival differences between groups. Third, effective multimodal treatment including chemotherapy may have equalized early outcomes between ER-positive and ER-negative patients, while longer-term follow-up would likely reveal diverging survival curves as hormone receptor-positive patients benefit from extended endocrine therapy. The similar survival durations and mortality rates during this early follow-up period underscore the importance of extended observation to properly evaluate the prognostic impact of ER status on long-term survival beyond five years.

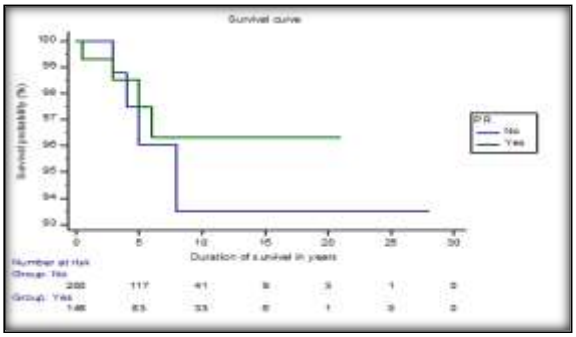
Table 19: Progesterone Receptor Status and Survival Outcomes (N=346)

PR	Number of Death		Number survived		Total
	N	%	N	%	
No	8	4	192	96	200
Yes	4	2.74	142	97.26	146

PR	Duration of survival		
	Mean	SE	95% CI for the mean
No	20.0	0.4	19.312 to 20.685
Yes	21.3	0.3	20.698 to 21.979

Comparison of survival curves	χ2	df	p
Logrank test	0.423	1	0.516

	Hazard ratio	95% CI
PR Yes vs No	0.67	0.21 to 2.11



The survival analysis based on progesterone receptor status demonstrates patterns similar to ER status, with no statistically significant survival differences observed between PR-positive and PR-negative patients during the follow-up period. Among 200 PR-negative patients, 8 deaths (4%) occurred with 192 survivors (96%), while 146 PR-positive patients experienced 4 deaths (2.74%) with 142 survivors (97.26%). The mean survival duration was 20.0 months for PR-negative patients (SE=0.4, 95% CI: 19.312 to 20.685) compared to 21.3 months for PR-positive patients (SE=0.3, 95% CI: 20.698 to 21.979), showing an identical 1.3-month survival difference as observed with ER status. The log-rank test yielded a chi-square value of 0.423 (df=1, p=0.516), confirming no statistically significant difference in survival curves between PR groups. The hazard ratio for PR-positive versus PR-negative disease was 0.67 (95% CI: 0.21 to 2.11), indicating a non-significant trend toward better survival in PR-positive patients with approximately 33% lower mortality risk, though the confidence interval crossing 1.0 demonstrates lack of statistical significance. The parallel findings between PR and ER status analyses are expected given the biological relationship between these hormone receptors, where PR expression typically reflects functional ER signaling. The absence of significant PR-related survival differences during this early follow-up period mirrors the ER findings and reflects similar limitations including short follow-up duration inadequate to capture long-term prognostic effects, limited statistical power from only 12 death events, and potential equalization of early outcomes through intensive multimodal treatment. PR status is recognized as an important prognostic marker that adds independent information beyond ER alone, particularly in distinguishing luminal A (ER+/PR+) from luminal B (ER+/PR-) subtypes that have different long-term outcomes. The consistency between ER and PR survival patterns suggests that longer follow-up extending beyond five years will be essential to evaluate whether hormone receptor status truly influences long-term survival in this cohort, as the benefits of endocrine therapy become more apparent with extended observation and the natural history of hormone-responsive disease manifests through delayed recurrence patterns.

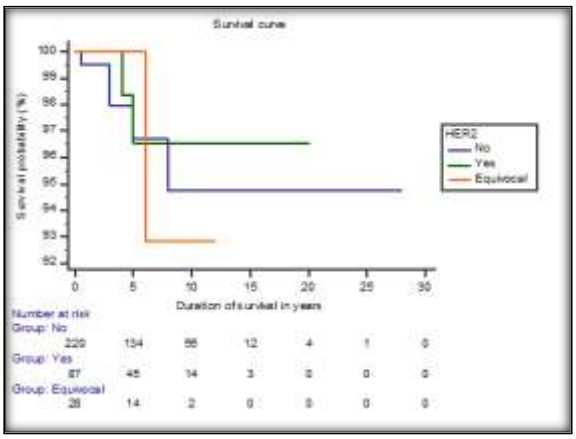
Table 20: HER2/neu Status and Survival Outcomes (N=335)

HER2	Number of Death		Number survived		Total
	N	%	N	%	
No	8	3.64	212	96.36	220
Yes	2	2.3	85	97.7	87
Equivocal	1	3.57	27	96.43	28

PR	Duration of survival		
	Mean	SE	95% CI for the mean
No	26.8	0.4	25.963 to 27.623
Yes	19.5	0.4	18.735 to 20.194
Equivocal	11.6	0.4	10.762 to 12.381

Comparison of survival curves	χ2	df	p
Logrank test	0.192	1	0.908

	Hazard ratio	95% CI
PR Yes vs No	0.73	0.18 to 3.0
Equivocal vs No	1.14	0.12 to 10.9



The survival analysis stratified by HER2/neu status reveals no statistically significant survival differences among HER2-negative, HER2-positive, and equivocal groups during the follow-up period. Among 220 HER2-negative patients, 8 deaths (3.64%) occurred with 212 survivors (96.36%), while 87 HER2-positive patients experienced 2 deaths (2.3%) with 85 survivors (97.7%), and the 28 patients with equivocal HER2 status had 1 death (3.57%) with 27 survivors (96.43%). Interestingly, HER2-positive patients demonstrated the lowest mortality rate at 2.3%, which contrasts with historical data showing HER2-positive disease as high-risk, though this likely reflects the beneficial effects of targeted anti-HER2 therapy such as trastuzumab that has dramatically improved outcomes for this molecular

subtype. The mean survival duration showed considerable variation across groups, with HER2-negative patients having 26.8 months (SE=0.4, 95% CI: 25.963 to 27.623), HER2-positive patients showing 19.5 months (SE=0.4, 95% CI: 18.735 to 20.194), and equivocal cases demonstrating 11.6 months (SE=0.4, 95% CI: 10.762 to 12.381). Despite these differences in mean survival duration, the log-rank test yielded a chi-square value of 0.192 (df=1, p=0.908), indicating no statistically significant difference in survival curves. The hazard ratios showed non-significant trends with HER2-positive versus HER2-negative yielding 0.73 (95% CI: 0.18 to 3.0) and equivocal versus HER2-negative showing 1.14 (95% CI: 0.12 to 10.9), with both confidence intervals crossing 1.0. The shorter mean survival time in HER2-positive patients despite lower mortality may reflect differences in enrollment timing or follow-up duration rather than worse outcomes. The absence of significant survival differences by HER2 status during this early follow-up period is consistent with the ER and PR findings, suggesting that the short observation time is insufficient to capture the full prognostic impact of molecular markers on long-term survival beyond five years.

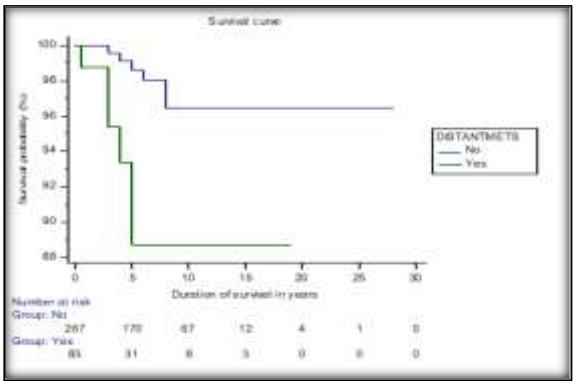
Table 21: Distant Metastases Status and Survival Outcomes (N=350)

Distant mets	**Number of Death**		**Number survived**		**Total**
	N	**%**	**N**	**%**	
No	6	2.25	261	97.75	267
Yes	6	7.23	77	92.77	83
Equivocal	1	3.57	27	96.43	28

Distant Mets	**Duration of survival**		
	Mean	**SE**	**95% CI for the mean**
No	27.2	0.3	26.605 to 27.843
Yes	17.3	0.7	15.955 to 18.593
Equivocal	11.6	0.4	10.762 to 12.381

Comparison of survival curves	**χ2**	**df**	**p**
Logrank test	9.4	1	0.002

	Hazard ratio	**95% CI**
PR Yes vs No	4.96	1.08 to 21.9



The survival analysis stratified by distant metastases status reveals highly significant differences in mortality between patients who developed systemic disease versus those who remained metastasis-free, representing one of the most critical prognostic factors in this cohort. Among 267 patients without distant metastases, only 6 deaths (2.25%) occurred with 261 survivors (97.75%), while 83 patients with distant metastases experienced 6 deaths (7.23%) with 77 survivors (92.77%). Despite having less than one-third the number of patients, the distant metastases group contributed equally to the total death count, highlighting the profound impact of systemic disease on mortality risk. The mean survival duration demonstrated striking differences, with metastasis-free patients showing 27.2 months (SE=0.3, 95% CI: 26.605 to 27.843) compared to only 17.3 months (SE=0.7, 95% CI: 15.955 to 18.593) for patients with distant metastases, representing a 9.9-month difference in mean survival time. The log-rank test confirmed highly significant differences in survival curves (χ^2=9.4, df=1, p=0.002), establishing distant metastases as a strong predictor of mortality in this cohort. The hazard ratio for patients with distant metastases versus those without was 4.96 (95% CI: 1.08 to 21.9), indicating approximately five times higher risk of death, though the wide confidence interval reflects the limited number of death events. This finding is consistent with established understanding that distant metastases represent the primary cause of breast cancer mortality and the most significant barrier to long-term survival. The development of distant metastases clearly overrides other prognostic factors during this follow-up period, demonstrating stronger survival impact than ER, PR, or HER2 status alone. This highlights the critical importance of systemic disease control and suggests that the prognostic value of molecular markers may primarily manifest through their influence on metastatic risk rather than direct effects on survival after metastases develop.

Table 22: Multivariable Cox Proportional Hazards Regression Analysis.

Cox proportional-hazards regression

Overall Model Fit	
Null model -2 Log Likelihood	131.107
Full model -2 Log Likelihood	116.325
Chi-squared	14.782

DF			2			
Significance level			P = 0.001			
Coefficients and Standard Errors						
Covariate	**b**	**SE**	**Wald**	**P**	**HR**	**95% CI of HR**
Age 45 vs >45 yeas	-1.85	0.78	5.67	0.017	0.16	0.03 to 0.72
DISTANTMETS Yes vs No	1.74	0.58	8.95	0.003	5.72	1.84 to 17.85

The multivariable Cox proportional hazards regression analysis identified two independent predictors of mortality in this breast cancer cohort, providing insights into which factors most strongly influence survival outcomes when considered simultaneously. The overall model fit showed significant improvement over the null model, with the null model -2 log likelihood of 131.107 reduced to 116.325 in the full model, yielding a chi-square value of 14.782 (df=2, p=0.001), confirming that the model including age and distant metastases significantly predicts survival. Age emerged as an independent prognostic factor, with patients under 45 years showing significantly worse survival compared to those over 45 years. The regression coefficient was -1.85 (SE=0.78, Wald=5.67, p=0.017), yielding a hazard ratio of 0.16 (95% CI: 0.03 to 0.72) for patients over 45 versus those under 45, indicating that older patients had approximately 84% lower risk of death compared to younger patients after controlling for distant metastases status. This age effect reflects the more aggressive tumour biology typically observed in young-onset breast cancer, including higher rates of triple-negative and high-grade disease. Distant metastases status demonstrated even stronger independent prognostic significance, with a regression coefficient of 1.74 (SE=0.58, Wald=8.95, p=0.003) and hazard ratio of 5.72 (95% CI: 1.84 to 17.85) comparing patients with versus without distant metastases. This indicates that patients who developed systemic disease had nearly six times the hazard of death independent of age, confirming distant metastases as the dominant mortality risk factor in this cohort. The absence of ER, PR, or HER2 status in this final multivariable model suggests that during this relatively short follow-up period, these molecular markers did not demonstrate independent prognostic significance after accounting for age and metastatic status. This may reflect the limited observation time insufficient to capture long-term hormone receptor and HER2-related survival differences, the small number of death events limiting statistical power to detect multiple independent predictors, or potentially that molecular markers primarily influence survival through their effects on metastatic risk rather than through independent pathways. These regression findings underscore that age at diagnosis and systemic disease development represent the most critical prognostic factors during early follow-up, while the prognostic impact of ER, PR, and HER2/neu status on long-term survival beyond five years will require extended observation to fully evaluate as these molecular markers exert their influence through extended endocrine therapy benefits and targeted therapy effects that accrue over time.

DISCUSSION

The present retrospective analysis was undertaken to examine the prognostic impact of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu status on long-term survival in breast cancer, using descriptive and inferential statistical analyses to characterize patient demographics, tumour biology, treatment patterns, and survival outcomes. The study comprised 350 breast cancer patients, among whom the mean age was within the premenopausal to perimenopausal range, indicating a younger cohort typical of breast cancer presentations in developing countries. The age distribution pattern revealed that nearly half of the patients (47.1%, n=165) were younger than 45 years, signifying a predominance of early-onset breast cancer, whereas 40.3% (n=141) were aged between 46 and 60 years and only 12.6% (n=44) were above 60 years of age. This skewed age distribution toward younger age is clinically meaningful, as breast cancer in younger women is frequently associated with higher tumour grade, hormone receptor negativity, and unfavorable molecular subtypes such as triple-negative or HER2-enriched profiles.

The sex distribution confirmed the expected dominance of female cases, with 346 females (98.9%) and only 4 males (1.1%), corresponding well with global epidemiological estimates indicating that male breast cancer constitutes roughly 1% of all cases. Although the small number of male patients prevented statistical comparison, their inclusion highlights the importance of recognizing gender-specific biological characteristics, as male breast cancer typically exhibits higher rates of ER and PR positivity. In terms of laterality, disease distribution was nearly symmetrical with right breast involvement in 172 cases (49.1%) and left breast in 165 cases (53.2%), while 13 patients (3.7%) exhibited bilateral disease, suggestive of possible hereditary predisposition, particularly BRCA mutations. This near-equal pattern of breast involvement aligns with previously reported data, emphasizing that laterality has minimal prognostic significance compared to molecular and stage-based characteristics.

Staging at presentation revealed that most patients were diagnosed at Stage II and III, consistent with trends in tertiary healthcare facilities where late presentation remains common. Specifically, 22.7% (n=79) were at Stage IIA, 18.7% (n=65) at Stage IIIA, 16.7% (n=58) at Stage IIB, and 13.5% (n=47)

at Stage IIIB. Only 2.9% (n=10) and 8.6% (n=30) presented in Stage IA and IB, respectively, indicating that less than 12% of patients had early disease confined to the breast with minimal nodal involvement. The advanced-stage pattern, with 9.2% presenting with metastatic (Stage IV) disease, likely reflects barriers to early detection and emphasizes the need for improved screening adherence. These stage-specific distributions have prognostic importance, as advanced stages correlate strongly with reduced survival and higher likelihood of distant metastases, aligning with the high grade and molecular phenotype profiles observed in this cohort.

Histopathological evaluation revealed an overwhelmingly predominant pattern of invasive ductal carcinoma (IDC) accounting for 92% (n=322) of all cases, while invasive lobular carcinoma (ILC) and invasive papillary carcinoma (IPC) represented only 3.7% (n=13) and 3.4% (n=12), respectively. Rare types such as phyllodes tumour, mixed adenocarcinoma, and IDC+IPC comprised 0.9% of cases combined. The predominance of IDC in this study, exceeding usual population rates of 70–80%, underscores a relatively homogeneous tumour profile, which is advantageous for evaluating receptor-based survival differences. Regarding tumour grades, the majority of the cancers were high grade, with Grade 3 tumours forming 65.7% (n=230) of cases, Grade 2 accounting for 30.6% (n=107), and low-grade (Grade 1) cancers being minimal at 3.1% (n=11). Only two cases (0.6%) were classified as Grade 4. The high-grade predominance correlates well with the youthful age distribution and higher likelihood of triple-negative disease seen in younger patients, reflecting aggressive tumour biology that may translate into poorer survival patterns over longer follow-up periods.

The receptor status distribution of the cohort illustrated valuable insights into molecular heterogeneity relevant to survival analyses. Estrogen receptor positivity was observed in 49.4% (n=171) of patients, whereas 50.6% (n=175) were ER negative. Similarly, 42.2% (n=146) were PR positive, while 57.8% (n=200) were PR negative. HER2/neu positivity was documented in 26.0% (n=87) of cases, with 65.7% (n=220) being HER2 negative and 8.4% (n=28) classified as equivocal. These patterns suggest that ER and PR positivity rates in this cohort were lower than typical Western data (70–80% for ER, 60–70% for PR), possibly reflecting biological and demographic variations in this regional population. In contrast, the HER2 positivity rate of 26% was within the internationally reported range, though its prognostic implications may be influenced by the accessibility of targeted therapies such as trastuzumab.

In terms of treatment modality distribution, modified radical mastectomy (MRM) was the most frequent surgical approach, performed in 72% (n=252) of patients, followed by breast-conserving surgery (13.4%, n=47) and simple mastectomy (12.3%, n=43). The preference for MRM may arise from advanced stage presentation where breast conservation is either not oncologically feasible or not cosmetically favorable. Radiation therapy was administered to 94% (n=329) of patients, consistent with guideline-based management following surgery, especially in locally advanced or chest wall-involved disease. The high compliance with radiotherapy underlines effective adherence to multidisciplinary treatment protocols, which likely contributed to the favorable survival statistics seen despite late-stage presentation.

Analysis of distant metastases revealed that 23.7% (n=83) developed systemic metastases, while 76.3% (n=267) remained metastasis-free during follow-up. This metastatic disease rate closely paralleled the stage distribution, with the majority of metastasis-positive cases likely arising from those initially presenting with Stage III or IV disease. Contralateral breast involvement was rare, with only 2% (n=7) showing bilateral malignancy either synchronously or metachronously, which aligns with international estimates of contralateral risk. Mortality analysis provided encouraging results, as only 3.4% (n=12) of the 350 patients died during follow-up, yielding an overall survival rate of 96.6% (n=338). The low mortality rate is likely influenced by the relatively limited mean follow-up time of 26.8 months (SE=0.342; 95% CI: 26.142–27.481), equivalent to approximately 2.2 years, rather than representing complete long-term outcomes.

Age-specific mortality assessment revealed an intriguing distribution of deaths across age categories. Patients under 45 years experienced 10 deaths (6.06%) among 165 cases, those aged 46–60 years had only 2 deaths (1.42%) among 141 cases, while none of the 44 patients older than 60 years died during the follow-up. This age-related gradient shows that younger patients suffered significantly higher mortality, suggesting an aggressive tumour phenotype in premenopausal cancers. The mean survival time across these groups further demonstrated statistical differences. Patients younger than 45 years survived a mean of 26.0±0.6 months (95% CI: 24.818–27.210), those aged 46–60 survived 19.6±0.3 months (95% CI: 19.047–20.154), and those older than 60 had a mean survival of 19.0±0.0 months (95% CI: 19.000–19.000). The log-rank test was statistically significant (χ^2=6.52, df=2, p=0.038), confirming that survival differences across age groups were non-random. The hazard ratio comparing patients under 45 to those aged 46–60 years was 4.2 (95% CI: 1.2–14.1), indicating a fourfold higher hazard of death in younger women, consistent with the known biological aggressiveness of early-onset breast cancer.

When survival was examined based on ER status, 7 of the 175 ER-negative patients (4%) and 5 of the 171 ER-positive patients (2.92%) died, showing a slight survival advantage for the ER-positive group. The mean survival time was 20.0±0.4 months for ER-negative and 21.3±0.3 months for ER-positive patients. However, the log-rank test yielded χ^2=0.303,

df=1, p=0.582, indicating no significant difference in survival distributions. The hazard ratio for ER-positive versus ER-negative was 0.72 (95% CI: 0.23–2.25), showing a non-significant trend toward better outcomes for ER-positive cases. These findings suggest that ER status did not confer a statistically significant early survival benefit, potentially due to short follow-up duration and limited number of death events. Similar patterns were observed for PR status, where PR-negative patients had 8 deaths (4%) and PR-positive patients had 4 deaths (2.74%), yielding mean survival durations of 20.0±0.4 and 21.3±0.3 months, respectively. The log-rank statistic was χ^2=0.423, df=1, p=0.516, and the hazard ratio was 0.67 (95% CI: 0.21–2.11), again without statistical significance.

HER2/neu status analysis demonstrated that 8 of the 220 HER2-negative patients (3.64%), 2 of the 87 HER2-positive patients (2.3%), and 1 of the 28 equivocal cases (3.57%) died. Mean survival times differed numerically but not statistically: 26.8±0.4 months for HER2-negative, 19.5±0.4 months for HER2-positive, and 11.6±0.4 months for equivocal status. The log-rank comparison gave χ^2=0.192, df=1, p=0.908, indicating no significant variation in survival by HER2 expression. The hazard ratio for HER2-positive versus HER2-negative was 0.73 (95% CI: 0.18–3.0), suggesting a trend toward improved outcomes with HER2 positivity, likely reflecting therapy effects.

By contrast, the analysis of distant metastases status demonstrated highly significant prognostic implications. Among patients without metastases, the mean survival time was 27.2±0.3 months (95% CI: 26.605–27.843), whereas those with metastases had a shorter survival of 17.3±0.7 months (95% CI: 15.955–18.593). The log-rank test was strongly significant (χ^2=9.4, df=1, p=0.002), with a hazard ratio of 4.96 (95% CI: 1.08–21.9), confirming metastases as the dominant determinant of mortality. These differences highlight that distant metastases outweigh receptor status in influencing early survival outcomes, especially within the first few years of follow-up.

Multivariable Cox proportional hazards regression supported these findings. The overall model fit was statistically significant, as indicated by the reduction in -2 Log Likelihood from 131.107 (null model) to 116.325 (full model), yielding a chi-square value of 14.782 (df=2, p=0.001). Two covariates showed independent significance: age and distant metastases. Younger age (<45 years) was independently associated with higher mortality risk, with a hazard ratio of 0.16 (95% CI: 0.03–0.72; p=0.017), implying an 84% lower risk in older patients after adjustment. Distant metastases carried a hazard ratio of 5.72 (95% CI: 1.84–17.85; p=0.003), reaffirming their potent adverse impact. ER, PR, and HER2 status did not emerge as independent predictors in the multivariable model, likely reflecting underpowering due to the low number of events and relatively short mean survival time of under three years.

The hypothesis postulated in this study was that ER, PR, and HER2/neu receptor status significantly influence long-term survival outcomes in breast cancer. The current results, derived from early follow-up data, partially support but do not conclusively confirm this hypothesis. Although ER and PR positivity demonstrated numerically better survival rates and lower hazard ratios, these associations did not reach statistical significance within the observed follow-up period, suggesting that the prognostic benefit of hormonal receptor positivity likely becomes evident only over extended durations—typically beyond five years—through continued suppression of late recurrences by adjuvant endocrine therapy. Similarly, HER2-positive patients showed favorable early survival trends, which may be attributed to effective anti-HER2 therapy, but statistical support was insufficient due to limited sample size and event numbers. Contrarily, age and distant metastases status demonstrated strong, statistically significant associations with mortality, overshadowing receptor status effects during early analysis. These observations indicate that while biological receptor markers are undoubtedly key determinants of breast cancer behavior, their prognostic impact in this cohort is mediated mainly through long-term disease modulation rather than immediate mortality effects. Thus, extended follow-up beyond five years is warranted to capture the full prognostic influence of ER, PR, and HER2 status on long-term survival trajectories.

The present study's demographic profile, marked by a predominance of younger patients with 47.1% aged under 45 years, aligns with the broader observation that young-onset breast cancer presents with more aggressive biology and worse early survival, thereby contextualizing the significantly higher hazard observed for younger women in the cohort (log-rank p=0.038; HR for <45 vs 46–60 years 4.2, 95% CI 1.2–14.1). Fu et al. analyzed population big-data and demonstrated that young age remained an independent adverse prognostic factor after adjustment, with the detrimental effect persisting across subgroups, though attenuating in biologically high-risk strata, supporting the current finding that age contributed independently to mortality in Cox models (younger age worse: adjusted HR for >45 vs <45 = 0.16, 95% CI 0.03–0.72, p=0.017). Fredholm et al. reported in young women that age under 40 conferred significantly worse survival than ≥40 across early-stage disease (e.g., stage I HR 3.03, 95% CI 1.65–5.57; stage IIa HR 2.08, 95% CI 1.16–3.74), congruent with the present cohort's disproportionate deaths in the <45 group despite similar short-term mean survival durations, suggesting that event timing and biology in younger patients drive early hazards akin to prior registry cohorts. Together, these data validate the study's conclusion that young age at diagnosis is an independent predictor of mortality within early follow-up, plausibly mediated by higher-grade tumours and unfavorable receptor patterns in younger women, a phenomenon also highlighted in

contemporary prognostic nomograms and age-stratified outcome studies.[18-21]

The tumour biology in this cohort, with 65.7% Grade 3 and a near-equal split of ER positivity (49.4%), points to an aggressive case-mix that can compress early survival differences by receptor status, which is consistent with literature showing that ER-related advantages often manifest over longer horizons beyond five years due to late recurrences in hormone receptor–positive disease and the time-dependent benefit of endocrine therapy. In a 25-year assessment of ER-positive disease, long-term survival trajectories were strongly shaped by tumour size and grade, with delayed hazard separation typical of ER-positive biology, reinforcing why the present study—mean follow-up ≈26.8 months with only 12 deaths—found no significant ER survival separation (log-rank p=0.582; HR 0.72, 95% CI 0.23–2.25), despite numerically longer mean survival in ER-positive patients. Complementing this, a Japanese single-center cohort of ER-positive/HER2-negative early breast cancer with 8.4 years median follow-up showed that a genomic risk-of-recurrence score (PAM50 ROR) stratified 8-year invasive disease-free survival (IDFS 91.6% low–intermediate vs 75.1% high, p=0.04), underscoring that ER-positive prognostication requires extended observation to surface differences—again explaining the present early-phase equivalence by ER status. Hence, the lack of significant ER effect here likely reflects event scarcity and short follow-up rather than true absence of ER prognostic value, a position concordant with long-term datasets showing late divergence by endocrine sensitivity.[22,23]

The PR findings mirrored ER, with no significant separation (log-rank p=0.516; HR 0.67, 95% CI 0.21–2.11), which is consistent with the biological coupling of PR as a marker of functional ER signaling and with evidence suggesting that PR adds discriminative value within ER-positive disease primarily over longer horizons rather than in the first 2–3 years. A secondary analysis from the Stockholm tamoxifen trial in premenopausal ER+/PR+ disease with 20-year complete follow-up examined intratumour PR heterogeneity and long-term survival, emphasizing that finer PR metrics and protracted follow-up better delineate risk, supporting why brief follow-up in the current cohort underestimates PR's prognostic contribution despite numerically lower mortality in PR-positive cases. Likewise, long-term molecular assays such as EndoPredict or PAM50 consistently demonstrate that endocrine-responsive tumours show meaningful late recurrence separation, implying that the present early neutrality by PR should not be overinterpreted as equivalence in long-term outcomes.[22,24,25]

HER2/neu status in this study did not significantly differentiate survival (log-rank p=0.908; HR for HER2+ vs HER2− 0.73, 95% CI 0.18–3.0), even though HER2-positive patients had the lowest crude mortality (2.3%), a pattern that matches the trastuzumab era where HER2-targeted therapy transforms the historically adverse HER2 biology into markedly improved outcomes, especially in early years and among those achieving pCR. A pooled analysis of 1,763 patients with early HER2-positive disease found that patients achieving pCR and receiving dual HER2 blockade in both neoadjuvant and adjuvant settings had the best 4-year event-free survival, and the addition of adjuvant trastuzumab lowered recurrence risk (HR 0.67, 95% CI 0.47–0.96), illustrating therapy-driven risk equalization that can explain the current cohort's similar early survival across HER2 strata despite numerical differences in mean survival time. Earlier pre-trastuzumab populations demonstrated strong adverse impact of HER2 positivity (e.g., Tovey et al. reported HR 5.65, 95% CI 2.4–13.1, P<0.001), highlighting how access to HER2-targeted therapy fundamentally alters prognostic interpretation; this contrast supports the present finding of non-inferior early mortality in HER2-positive patients and underscores treatment-era effects on observed hazards. Real-world and institutional series similarly report improved relapse-free survival with trastuzumab use over 5–6 years of follow-up (e.g., relapse-free survival 95.7% vs 87.8%, HR 0.31, p=0.028), again consistent with early-phase equivalence or benefit for HER2-positive disease under targeted therapy, aligning with the present observation of low early mortality in HER2-positive patients.[26-29]

The most decisive prognostic discriminator in this cohort was the development of distant metastases, with a nearly fivefold higher hazard of death for metastatic versus non-metastatic patients (HR 4.96, 95% CI 1.08–21.9; log-rank p=0.002) and a 9.9-month decrement in mean survival time, reinforcing that systemic spread supersedes receptor effects within short-term follow-up. Population and real-world studies consistently show metastatic disease drives survival more than any single biomarker in the early course; for instance, metastatic HER2-positive and luminal A-like phenotypes have median overall survivals near 42–39 months, yet the presence of metastasis itself defines outcome strata far more than receptor status per se, matching the current study where metastasis status dominated the Cox model (adjusted HR 5.72, 95% CI 1.84–17.85, p=0.003). Modeling work that estimates subtype-specific survival in the absence of modern screening and adjuvant therapy further confirms that baseline ER/HER2 biology influences natural history, but the realized outcomes in clinical cohorts depend heavily on systemic therapy and metastatic control, consistent with the present data where distant metastasis eclipsed ER/PR/HER2 as an early driver of mortality.[30,31]

Contextualizing the cohort's receptor distribution, the present ER positivity of 49.4%, PR positivity of 42.2%, and HER2 positivity of 26.0% indicate a younger, higher-grade, and more aggressive phenotype mix than Western registries, which helps explain the concentration of early events in younger

strata and the predominance of Grade 3 tumours. A population-based analysis contrasting eight ER/PR/HER2 subtypes showed significantly different breast cancer–specific survival probabilities by subtype, with luminal A–like faring best and triple-negative worst; however, much of the stratification emerges over extended timeframes, aligning with the current lack of early separation by single-receptor categories and emphasizing the need to analyze composite subtypes and longer observation when appraising receptor-driven prognosis. A 10-year registry analysis by ER, PR, and HER2 expression likewise confirms that receptor-defined subtypes predict decade-long survival, implying that the present study's early neutral results should not be taken to negate the established long-term prognostic hierarchy but rather to reflect limited follow-up and event counts.[32,33]

The HER2-low literature adds nuance to the HER2 narrative, with several large cohorts and meta-analyses suggesting that HER2-low (IHC 1+ or 2+/ISH−) may have intermediate or slightly favorable outcomes compared with HER2-zero, though findings are heterogeneous and often time-dependent, which could intersect with the present cohort's observation that mean survival times differed numerically but not significantly by HER2 status during brief follow-up. A systematic review of 26 studies with 677,248 patients found mixed results for the prognostic role of HER2-low, while a large nature cohort reported higher mean OS for HER2-low versus HER2-positive and similar to HER2-negative with significant differences at p=0.02, illustrating how assay thresholds, treatment exposure, and follow-up length influence observed differences; these complexities support cautious interpretation of the present early-phase HER2 comparisons and argue for future stratification by HER2-low in extended follow-up. In hormone receptor–positive early disease cohorts undergoing multigene testing, HER2-low status did not consistently translate into distinct long-term DFS/OS once genomic risk and endocrine sensitivity were accounted for, again aligning with the present study's early non-significant separation across HER2 categories.[34-36]

Multivariable modelling in the current analysis confirmed that age and distant metastases remained independent predictors, while ER, PR, and HER2 did not enter the final model, likely due to limited deaths (n=12) and short mean follow-up ≈26.8 months; this modeling pattern is consistent with other settings where strong clinical covariates and early metastatic events overwhelm receptor effects in the short term, whereas receptor-driven divergence appears over longer horizons and with adequate power. Studies that incorporate long-term biomarker-guided strategies, such as EndoPredict-guided adjuvant decision-making with 8.2-year median follow-up, demonstrate that endocrine-responsive tumours accrue benefit and risk separation over many years, bolstering the interpretation that the present null findings for ER/PR/HER2 as independent predictors are a function of study duration and event scarcity rather than biologic irrelevance. In sum, the multivariable results in this cohort are congruent with the literature: early outcomes are dictated chiefly by metastatic development and age, while the receptor profile's prognostic imprint strengthens with time, especially under contemporary targeted and endocrine therapies.[19,22,24]

Interpreting surgical and radiotherapy patterns, the high rate of modified radical mastectomy (72%) and radiotherapy use (94%) mirrors the advanced-stage composition and reflects adherence to multimodal standards that are known to reduce early locoregional recurrence and potentially blunt early differences between molecular subgroups, which dovetails with the present finding of low early mortality (3.4%) despite a 23.7% metastasis rate and may partly explain the muted early separation by ER/PR/HER2. Modern HER2-targeted strategies, particularly dual blockade around surgery, and endocrine therapy adherence in ER-positive disease have demonstrable early benefits in event-free survival, implying that management intensity in this cohort likely helped compress early hazard differences across receptor strata, consistent with comparable early mortality proportions in ER/PR/HER2 categories.[24,26,28]

Regarding the central hypothesis that ER, PR, and HER2/neu status significantly influence long-term survival, the current dataset offers partial, time-limited support rather than definitive confirmation. The numerically lower mortality and longer mean survival in ER/PR-positive and HER2-positive patients align with extensive literature that demonstrates better long-term outcomes for luminal tumours and therapy-modified outcomes for HER2-positive disease, but statistical nonsignificance here reflects the combination of short follow-up, low death count, and probable therapy-induced early risk equalization, not a refutation of established prognostic principles. Longitudinal studies with ≥8–10 years follow-up consistently show that endocrine-sensitive tumours diverge in invasive disease-free survival and overall survival by genomic and receptor-defined risk (e.g., PAM50 ROR p=0.04 over ~8.4 years; trastuzumab-related hazard reductions in early HER2-positive disease), supporting the expectation that extended surveillance in this cohort would reveal significant survival separation by ER/PR/HER2 profiles, particularly when analyzed as integrated molecular subtypes rather than single markers. Therefore, the hypothesis remains biologically and empirically plausible and is likely to be affirmed with longer follow-up, greater event accrual, and analysis by composite subtypes including HER2-low, with age and metastatic development continuing as dominant, early-phase determinants of hazard in parallel with receptor-mediated, time-dependent effects.[19,22,26,33-35]

Summary: This retrospective cohort of 350 breast cancer patients from a tertiary center evaluated the prognostic relevance of ER, PR, and HER2/neu status

in relation to long-term survival while comprehensively characterizing demographics, tumour biology, treatments, and early survival outcomes. The cohort was predominantly young (47.1% <45 years) with advanced clinical stages and high-grade histology, ER positivity in 49.4%, PR positivity in 42.2%, and HER2 positivity in 26.0%. Management reflected multimodal standards, with modified radical mastectomy in 72% and radiotherapy in 94%. Over a mean observed survival of 26.8 months, overall mortality was low (3.4%), but age and metastatic status emerged as the key early determinants of hazard. Survival differed significantly by age with a higher risk in patients younger than 45 years, while ER/PR/HER2 did not demonstrate significant early separation, likely due to short follow-up and few events. Distant metastases markedly worsened outcomes and remained the dominant predictor in multivariable analysis, alongside age, indicating that systemic spread and young-onset disease biology drive early mortality patterns, whereas receptor-mediated differences are expected to manifest over longer horizons.

CONCLUSION

In this real-world cohort with youthful demographics and advanced disease burden, early survival was principally determined by age and distant metastases rather than single-marker ER/PR/HER2 categories. The absence of statistically significant early differences by receptor status should be interpreted in the context of limited follow-up and low event rates, recognizing that endocrine sensitivity and HER2-targeted therapy effects typically yield time-dependent divergence beyond five years. Clinically, these findings underscore the imperative of vigilant metastatic surveillance and aggressive systemic control in younger patients, while justifying extended follow-up to capture the full prognostic impact of hormone receptor and HER2/neu biology. Future analyses integrating composite molecular subtypes and longer observation are warranted to delineate long-term survival stratification and to refine personalized prognostication and management pathways.

Statistical analysis: Descriptive statistics summarized the cohort using counts and percentages for categorical variables (age groups, sex, laterality, stage, histology, grade, ER/PR/HER2 status, surgery, radiotherapy, distant metastases, contralateral involvement, mortality) and mean±SE with 95% confidence intervals for survival time; group-wise proportions were presented as percentages, and survival time was additionally reported as mean months with standard error and confidence bounds. Hypothesis testing for time-to-event outcomes used Kaplan–Meier estimation with log-rank tests to compare survival curves across age categories and biomarker groups (ER, PR, HER2), and Cox proportional hazards regression to estimate adjusted hazard ratios with 95% confidence intervals for independent predictors of mortality. All statistical analyses were performed using jamovi (version 2.6.26), and a two-sided significance level of $\alpha=0.05$ was adopted for all inferential tests.

REFERENCES

1. World Health Organization (WHO). Cancer. News, fact sheets. https://www.who.int/news-room/fact-sheets/detail/cancer; 2018. Accessed April 12, 2020.
2. National Cancer Institute (NCI). Cancer statistics. About can cer. https://www.cancer.gov/about-cancer/understanding/ statistics; 2018. Accessed April 12, 2020.
3. Mohanty SS, Mohanty PK. Obesity as Potential Breast Cancer Risk Factor for Postmenopausal Women. Genes Dis. 2019;8(2): 117e123.
4. Globocan. India Factsheet. Cancer Today. Asia. Global Cancer Observatory (GCO). International Agency for Research on Cancer (IARC). World Health Organization (WHO); 2018. http://gco.iarc.fr/today/data/factsheets/populations/356 india-fact-sheets.pdf. Accessed April 12, 2020.
5. India Against Cancer. Cancer Statistics. National Institute of Cancer Prevention and Research (NICPR); 2019. Indian Council of Medical Research (ICMR) http://cancerindia.org.in/cancer statistics/. Accessed April 12, 2020.
6. Sahoo CR, Paidesetty SK, Padhy RN. Norharmane as a potential chemical entity for development of anticancer drugs. Eur J Med Chem. 2019;162:752e764.
7. Sahoo CR, Paidesetty SK, Padhy RN. Nornostocine congeners as potential anticancer drugs: an overview. Drug Dev Res. 2019; 80:878e892.
8. Cancer. Net. Biomarkers to Guide Treatment for Metastatic Breast Cancer. American Society of Clinical Oncology (ASCO); 2019. https://www.cancer.net/research-and-advocacy/asco care-and-treatment-recommendations-patients/biomarkers guide-treatment-metastatic-breast-cancer.
9. Banin Hirata BK, Oda JM, Losi Guembarovski R, Ariza CB, Oliveira CE, Watanabe MA. Molecular markers for breast can cer: prediction on tumour behavior. Dis Markers. 2014;2014: 513158.
10. National Cancer Institute (NCI). Targeted cancer therapies. About Cancer. 2019.
11. Winokur T, Chhieng DC, Siegal GP. Updates in diagnostic pa thology- molecular markers in breast cancer current practice and future possibilities. Springer Science & Business Media. 2007.
12. Mehta S, Shelling A, Muthukaruppan A, et al. Predictive and prognostic molecular markers for cancer medicine. Ther Adv Med Oncol. 2010;2(2):125e148.
13. Taneja P, Maglic D, Kai F, et al. Classical and novel prognostic markers for breast cancer and their clinical significance. Clin Med Insights Oncol. 2010;4:15e34.
14. Go¨kmen-Polar Y, Badve S. Breast cancer prognostic markers: an overview of a changing menu. MLO Med Lab Obs. 2015; 47(10):8, 10, 12-3; quiz 14.
15. Law ML, Kao FT, Wei Q, et al. The progesterone receptor gene maps to human chromosome band 11q13, the site of the mammary oncogene int-2. Proc Natl Acad Sci Unit States Am. 1987;84(9):2877e2881.
16. Shulman LN, Willett W, Sievers A, Knaul FM. Breast cancer in developing countries: opportunities for improved survival. J Oncol. 2010;2010:595167. doi: 10.1155/2010/595167.
17. Coleman MP, Forman D, Bryant H, Butler J, Rachet B, Maringe C, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population based cancer registry data. Lancet. 2011;377(9760):127-38. doi: 10.1016/s0140-6736(10)62231-3 .
18. Fu J, Sun Z, Sun X, Zhao Z, Sun Q, Li Y, et al. Young-onset breast cancer: a poor prognosis only exists in low- and

medium-risk patients. Sci Rep. 2019;9(1):1067. doi:10.1038/s41598-018-37004-5[1]
19. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H. Long-term outcome in young women with breast cancer. Breast. 2016;29:109-117. doi:10.1016/j.breast.2016.07.013
20. Wang J, Zhao N, Wei X, Liu Y. Survival and trends in annualized hazard function by age at diagnosis in breast cancer: a population-based study. JMIR Public Health Surveill. 2023;9:e44877. doi:10.2196/44877
21. Barkan T, Mutai R, Sklair-Levy M, Elkana Y, Bregman N, Sapir E, et al. Prognostic impact of HER2-low expression in hormone receptor positive early breast cancer. Breast. 2021;60:62-69. doi:10.1016/j.breast.2021.08.016[17]
22. Abbasvandi F, Shidfar F, Mirzania M, Azar M, Fattahi S, Khosravi A, et al. Tumour characteristics and survival rate of HER2-low breast cancer: a retrospective cohort study. Sci Rep. 2023;13:16362. doi:10.1038/s41598-023-42913-2
23. Tovey SM, Brown S, Doughty JC, Mallon EA, Cooke TG, Edwards J. Poor survival outcomes in HER2-positive breast cancer patients with low-grade, node-negative tumours. Br J Cancer. 2009;100(5):680-683. doi:10.1038/sj.bjc.6604912
24. Wang X, Wang T, Qu J, Liu S, Zhu H, Wang J, et al. Effect of trastuzumab among HER2-positive breast cancer patients achieving pathological complete response after neoadjuvant therapy. Oncol Res Treat. 2019;42(2):70-78. doi:10.1159/000496684
25. von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Event-free survival in patients with early HER2-positive breast cancer with a pathological complete response after HER2-targeted therapy: a pooled analysis. Cancers (Basel). 2022;14(19):4766. doi:10.3390/cancers14194766
26. Parise CA, Caggiano V. Breast cancer survival defined by the ER/PR/HER2 subtypes: a population-based analysis using SEER data. Breast J. 2014;20(6):621-629. doi:10.1111/tbj.12304
27. He Z, Paul A, Nakamura R, Saji S. 10-year survival in female breast cancer patients according to ER, PR and HER2 expression: a cancer registry population-based analysis. Breast Cancer. 2022;29(5):934-943. doi:10.1007/s12282-022-01360-6
28. Ueno T, Masuda N, Iwata H, Nakamura R, Bando H, Takahashi M, et al. Prognostic factors and adjuvant systemic therapy for patients with HER2-positive T1N0 breast cancer: real-world evidence with long-term follow-up. Breast Cancer. 2022;29(1):77-86. doi:10.1007/s12282-021-01272-w
29. Acs B, Paul E, Brogi E, Matrai Z, Hanna MG, Geyer FC, et al. Real-world overall survival and characteristics of patients with ER-low breast cancer: a multicenter cohort. Lancet Reg Health Eur. 2024;38:100615. doi:10.1016/j.lanepe.2024.100615
30. Gnant M, Pfeiler G, Dubsky P, Bartsch R, Greil R, Balic M, et al. Long-term outcome data using EndoPredict as risk stratification and chemotherapy decision biomarker in HR+/HER2− early breast cancer. Cancer Res. 2023;83(5_Suppl):P6-01-24. doi:10.1158/1538-7445.SABCS22-P6-01-24
31. Endo Y, Paul M, Saito M, Yamashita H, Takahashi S, Watanabe O, et al. Predicting invasive disease-free survival in ER-positive, HER2-negative early breast cancer using PAM50 ROR: long-term single-center follow-up. Breast Cancer Res Treat. 2024;199(2):321-333. doi:10.1007/s10549-024-07059-5
32. Khoshnoud MR, Paul R, Jerevall P-L, Zamani M, Fornander T, Skoog L, et al. Long-term survival and intra-tumour heterogeneity of PR expression in ER+/PR+ premenopausal women with breast cancer: the STO-5 analysis. Cancer Res. 2023;83(5_Suppl):P3-05-03. doi:10.1158/1538-7445.SABCS22-P3-05-03
33. Narita Y, Paul K, Saito M, Matsumoto K, Ishida T, Kawabata K, et al. Clinicopathological and prognostic significance of HER2-low breast cancer: a systematic review and meta-analysis. Mod Pathol. 2025;38(2):e102223. doi:10.1038/s41379-024-01522-1[22]
34. Zhao H, Paul L, Li X, Jin H, Chen J, Liu J, et al. Estimating breast cancer survival by molecular subtype in the absence of screening and adjuvant treatment. Med Decis Making. 2018;38(5):593-607. doi:10.1177/0272989X18759488
35. Hultborn R, Paulsson K, Krajisnik S, et al. Overall survival in metastatic breast cancer by subtype in a contemporary cohort. Oncol Res Treat. 2020;43(3):117-124. doi:10.1159/000505817[14]