RESEARCH ARTICLE

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Survival Outcomes of Breast Cancer Patients in South India Over 20 Years

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Abstract

Objective: The study aimed to investigate the distribution and clinicopathologic features of breast cancer patients in South India, while also examining the overall survival (OS) and identifying predictive factors affecting it. Additionally, we aimed to assess the influence of risk factors on Disease Free Survival (DFS) and Distant Disease-Free Survival (DDFS). **Methods:** This retrospective cohort study on breast cancer trends used comprehensive follow-up including regular patient contact, medical record review and collaboration with healthcare providers. Patients without follow-up information for more than 12 months were contacted by telephone, while those with no follow-up after 2 years were labelled as lost to follow-up. **Results:** A total of 3256 patients were identified from a single cancer institute in India. The median follow-up time was 8.1 years. The 5-year survival rates were 89%, 84%, 85%, 88% and 10-year were 82%, 78%, 79%, 83% for luminal cancers, Triple Negative Breast Cancers, HER2 enriched and luminal with HER2 enriched respectively. **Conclusion:** Poorer survival rates were seen among those with pT3/4 tumors, nodal involvement at diagnosis, Estrogen receptor negative status, high Ki67 proliferative index and higher TNM stage at diagnosis of the disease. Although our patients were younger and had more aggressive types of cancer, their DFS, DDFS and overall survival were comparable to other developed nations.

Keywords: Breast cancer- developing countries- distant disease-free survival- disease free survival- overall survival

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Introduction

Breast cancer is characterised by its heterogeneous nature, encompassing various subtypes with distinct cellular composition and clinical behaviors [1] . It remains as one of the leading causes of mortality among women in both developing and developed countries [2]. Due to rapid advancements in treatment paradigms and improved population screening, mortality rates for breast cancer are steadily declining in developed countries. A recent study conducted in Austria, found that there is a decline in breast cancer-related mortality over the past few decades, the annual percent change ranging from 17.5% to -0.8%, indicating a substantial reduction in the number of breast cancer deaths [3]. Similarly, a study conducted in Sweden found a 49% decrease in the 5 year breast cancer-related mortality during the period from 1989-2013 [4]. These positive trends can be attributed to the following developments. Firstly, increased awareness and public education regarding the symptoms of breast cancer, as well as screening programs have helped detect breast cancer in its early stage. Secondly, newer chemotherapeutic agents and targeted therapies have become more affordable and accessible, improving the survival of patients with breast cancer world over. Thirdly, the multidisciplinary approach which involves collaboration with different specialists including surgeons, medical oncologists, radiation oncologists and pathologists provides a comprehensive treatment protocol for each patient. Lastly, several therapeutic options for metastatic breast cancer patients are now available, which allow many women to live longer with the disease [5].

However, while numerous studies have been conducted on breast cancer survival rates in Western populations, limited research has been undertaken in developing countries like India, where breast cancer patients show distinct characteristics and diagnostics and treatment options are more limited. A pooled analysis involving 5 million patients across 195 world countries from 1990 - 2015 showed a notable increase in the breast cancer

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mortality rate in many countries including India [6]. From the limited number of studies, it appears that in the Indian population, breast cancer tends to exhibit a more aggressive nature compared to the Western population [7]. Breast cancer patients in India are notably younger, at around 47 years, compared to the Western population where the median age was 63 [8]. Additionally, there is a higher prevalence of locally advanced breast cancer cases in India compared to the western countries [9]. Approximately 30% of breast cancer cases in India are categorised as triple-negative, which is significantly higher than the 12-15% observed in the Western population [10]. Only a small number of studies have reported long-term outcomes of breast cancer patients in India [11]. Lack of general awareness, social stigma, and severe financial constraints all present several roadblocks in the management of breast cancer in India. Our study aims to showcase the survival rates of Indian women with breast cancer in the state of Kerala, which are comparable to the survival rates of other developed nations, reiterating the fact that quality healthcare can be provided even in the presence of resource limitations. A better understanding of breast cancer characteristics in India will facilitate the development of more tailored treatment strategies with the ultimate aim of improving the survival rates and enhancing quality of life.

This study presents the findings from the Amrita Breast Cancer Cohort. This cohort consists of breast cancer patients from South India who were treated in a tertiary care institute, which provides affordable care as well as charitable care and offers a full range of primary and speciality care medical services. The cohort includes patients who were treated between 2004 to 2020 and were followed up until 2023. This long follow-up is one of the strengths of our cohort. The majority of routine follow-up visits were scheduled as follows: 3 monthly for the first 2 years after completing treatment, followed by 6 monthly for the next 3 years, and annually for the remaining years. As a result, a detailed assessment of the long-term patient outcomes was possible. The current manuscript describes the characteristics of this breast cancer cohort in detail and investigates survival and recurrence outcomes. The results of this study provide a more thorough understanding of the unique features of breast cancer patients in South India and highlight the differences from cohorts in developed countries.

Materials and Methods

Patients

A retrospective cohort study was conducted to analyze the characteristics and survival of female breast cancer patients diagnosed between January 2004 and December 2020 and the patients were followed up till June 2023. Women who completed treatment for breast cancer at the Amrita Institute of Medical Sciences (AIMS), which is a super-speciality tertiary-care hospital in south India, with at least 6 months of follow-up comprised the cohort for this study. Patients who did not come back for any follow-up after the primary treatment or patients who did not complete all the treatments were excluded from the study. Details of patients' characteristics, clinicopathological details, and follow-up after surgery were collected from the hospital-based electronic medical record system. Patients without follow-up information for more than 12 months were contacted by telephone to update this information. 12.6% of patients whose follow-up information was not available after 2 years were tagged as lost to Follow-up and those patients were excluded from the study.

Measurements

Patient details including age, TNM, stage, Grade, molecular type, OS, DFS, DDFS calculated from the dates were available for all 3256 patients. In addition, patient characteristics such as menopausal status, Ki67 proliferative index, histological type and patient treatment details were only available for the subgroup of 1877 patients who were diagnosed in the year between 2010 to 2020.

The molecular classification of all patients was examined histologically based on ER, Progesterone Receptor (PR), and HER2. This leads to 4 molecular classes of breast cancer, namely Luminal Cancers (HR+/HER2-), Luminal with HER2 enriched (HR+/HER2+), HER2 enriched (HR-/HER2+) and TNBC (HR-/HER2-). Ki67 testing was not included in the diagnostic evaluation prior to 2010 in our institution, thus patients prior to that year did not undergo Ki67 evaluation. The cut-off to determine the high and low categories of Ki67 has been under discussion for the past few decades [12]. In our study, we evaluated the survival benefits of Ki67 with a cut-off of 20% and reported that Ki67 is a useful predictor of risk of recurrence in women with breast cancer. Thus Ki67 index could also be added as a factor for prognostic assessment and for guiding adjuvant, local or systemic treatment decisions.

All patients were staged according to the American Joint Committee for Cancer (AJCC 8th edition) TNM staging system for breast cancer. In our study molecular classification was performed through histological examination of *ER, PR, HER2* and *Ki67*. A cut-off value of 20% was used to differentiate between luminal A and luminal B. We have analyzed data based on various parameters including the stage of the disease, molecular classification and treatment undergone. The study was reviewed and approved by the Institutional Review Board of AIMS.

Objectives and Outcomes

The primary objective of this pooled analysis was to determine the distribution, clinicopathologic features, and their survival and to identify the predictive factors affecting the overall survival of breast cancer patients in south India. OS was defined as the time in years from diagnosis to death or the date of last contact. The secondary objectives were to assess the influence of the risk factors on DFS and DDFS. DFS was defined as the time in years from diagnosis of the disease to first relapse (local or distant), Second Malignancy or death from any causes, whichever occurs first. DDFS was defined as time in years from diagnosis to any distant recurrence of

the disease. The impact of potential risk factors such as patients' age at diagnosis, menopausal status, pathological tumor stage, nodal stage, tumor grade, Histologic tumor type, Hormone Receptor and HER2 Status, Ki67 Index, biological subtype, and treatment approaches on DFS, DDFS, and OS were analyzed.

Statistical Analysis

Continuous variables were described by means with standard deviations while categorical variables were described by contingency tables. The effective percentage of clinicopathological characteristics and patient outcomes were calculated. For potential risk factors, DFS, DDFS, and OS rates and their corresponding 95% confidence intervals were calculated and the survival curves were visualized using the Kaplan-Meier plots. The survival rates were additionally analyzed in the subgroups according to the biological subtypes. Patients with missing values for the variable-defining subgroup were excluded from the analysis of this subgroup. Cox regression was used to assess the effect of risk factors. Schoenfeld Residuals were used to check the proportional hazards assumption. Conditional density plots were used to visualize the change over time in the distribution of the clinicopathological characteristics. Cox regression with natural cubic splines was used to investigate trends in the survival rates depending on the years of diagnosis. All tests were two-sided and the reported p-values smaller than 0.05 were considered statistically significant. All analyses were performed using R Version 4.3.0.

Results

Patient characteristics

Between 2004 and 2020, a total of 3256 patients diagnosed with breast cancer were identified from hospital-based cancer registry databases. The median age of patients with breast cancer was 54 (IQR 46 - 62) years. After a median follow-up of 8.1 years, 80.6% were found to be alive and 19.4% of patients were deceased.

Clinicopathological Characteristics and Patient characteristics of the patients are depicted in Table 1. Three-quarters of the patients presented with early-stage breast cancer. Only 10% of patients had a low-grade tumor. The most common molecular type was luminal cancer. Among luminal cancer patients, 53.8% were luminal A and 46.9% were luminal B. Invasive ductal carcinoma was the most common histological tumor type. The number of left-sided and right-sided tumors was roughly equal, with a small number of bilateral tumors (2.1%). Figure 1 shows that the distribution of clinicopathological features has not changed much over time.

Treatment patterns

Patients underwent either Modified Radical Mastectomy or Breast Conserving Surgery (BCS) with the majority being Mastectomy (73.8%). Upfront surgery was performed in 87.48% of luminal cancers, 71.28% of TNBC patients, 64.36% of HER2-enriched patients and 75.45% of Luminal with HER2-enriched breast cancer patients. Among clinically node-positive patients, 72.72% were offered upfront surgery.

Overall, radiotherapy was offered for 57.9% of patients and the schedule followed was either 50Gy/25# or 40Gy/15#. The patients who underwent BCS received radiotherapy with a dose of 40Gy/15# followed by tumor bed boost.

Neoadjuvant Chemotherapy (NACT) was given to 23.34%, The most frequent regimen was a combination of Adriamycin and cyclophosphamide with four cycles of paclitaxel/docetaxel (4AC+4T). 26.7% of patients with NACT achieved pathological complete response (PCR).

Adjuvant chemotherapy was recommended for 68.78% of patients based on clinicopathological characteristics. Chemotherapy was recommended for all TNBC and HER2 enriched patients who could tolerate it. The most common regimens for TNBC patients were 4AC+4T or dose-dense 4AC+4T. HER2-enriched patients were recommended anti-HER2 therapy along with scheduled chemotherapy. Only 40.95% of these patients with Her 2 positive breast cancer actually received anti-HER2 therapy due to financial constraints. Before 2014, only <10% of HER2-positive patients received anti-HER27 while >80% of HER2-enriched patients received anti-HER2 therapy after 2018. 54.79% of luminal A patients and 73.92% of luminal B patients received adjuvant chemotherapy. The chemotherapy schedules used in most luminal cancers were 4AC+4T or 4 cycles of Docetaxel and Cyclophosphamide (4TC).

Patients with hormone receptor-positive status received either tamoxifen or letrozole depending on menopausal status for a minimum period of 5 years. Among premenopausal women with hormone receptor-positive status, 16% of patients underwent oophorectomy as a part of their treatment.

Patient outcomes

Disease Free Survival (DFS), Distant-DFS (DDFS) and Overall Survival (OS) rates over 5 years, 10 years and 15 years of various subgroups are presented in Table 2. In the entire cohort, the 5-year, 10-year and 15-year DFS rate of breast cancer patients were 94.3% (CI: 93.3 – 95.4), 90.5% (CI: 89.1 – 92) and 86.4% (CI: 84.3 – 88.5) while 5 year, 10 year and 15-year DDFS were 95.3% (CI: 94.4 – 96.2), 93.8% (CI: 92.7 – 95) and 91.6 (CI: 90.1 – 93.1). Additionally, OS rates on 5-year, 10-year and 15-year follow-ups were 99.1% (CI: 98.7 - 99.6), 98.9% (CI: 98.4 – 99.5) and 97.7% (CI: 96.8 – 98.7) respectively. Lower DFS, DDFS and OS rates were observed in pT3/4 and pN2/N3 (≥4 positive nodes) diseases. Higher tumor grades also led to worse survival outcomes. *Ki67* was highly predictive of survival outcomes as well. Survival rates of breast cancer molecular subtypes according to various groups were analysed. However, the survival rates among different breast cancer molecular subtypes within various groups did not reveal significant differences in the outcomes. A concise summary of these findings can be found in supplementary Appendix 1.

The Kaplan Meier plots for DFS, DDFS and OS with respect to TNM Staging are shown in Figure 2. Stage 1 and 2 had similar outcomes, while stage 3 and stage 4 were much worse in terms of all three survival

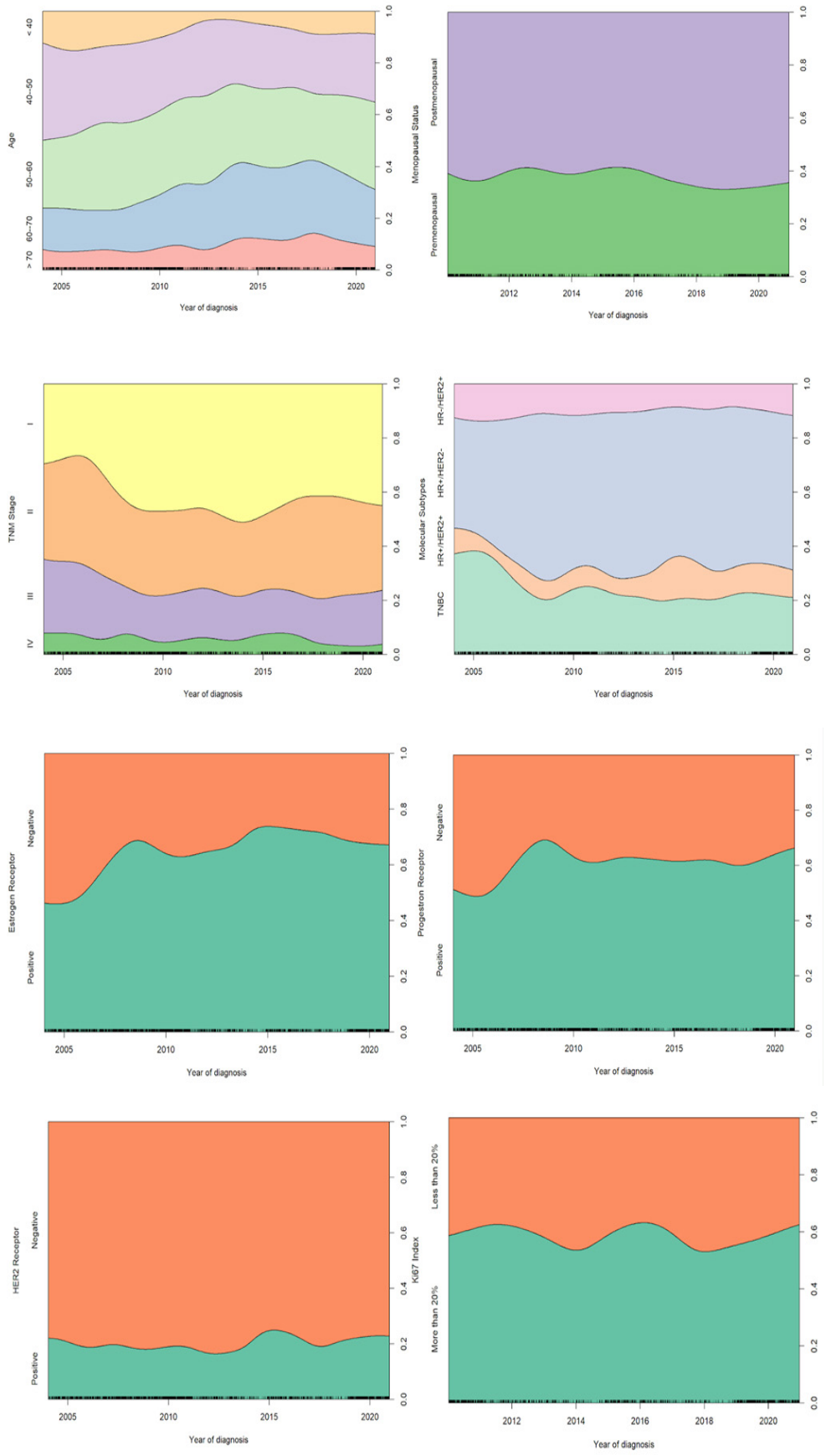

Figure 1. Conditional Density Plots which Shows the Distribution of Patients among Different Categories across the Study Period.

Table 1. Characteristics of the Patients Affected with Breast Cancer who were Included in the Study (N = 3256)

Parameter	Category	N (valid %)
Age	< 40	297 (9.1)
	40--50	898 (27.6)
	50--60	1019 (31.3)
	60--70	731 (22.5)
	> 70	311 (9.6)
Menopausal status	Postmenopausal	1197 (63.8)
	Premenopausal	680 (36.2)
Tumor Stage	T1	582 (18.7)
	T2	1999 (64.2)
	T3	334 (10.7)
	T4	197 (6.3)
Nodal Stage	N0	1496 (46.8)
	N1	1084 (33.9)
	N2	368 (11.5)
	N3	252 (7.9)
Grading	G1	308 (10.2)
	G2	1665 (55.3)
	G3	1039 (34.5)
TNM Stage	I	1397 (43.5)
	II	1037 (32.3)
	III	606 (18.9)
	IV	171 (5.3)
Histotype	ductal	1538 (84.8)
	lobular	105 (5.8)
	mucinous	43 (2.4)
	others	128 (7.1)
Estrogen Receptor	Negative	1110 (34.1)
	Positive	2146 (65.9)
Progestron Receptor	Negative	1204 (37)
	Positive	2052 (63)
HER2 Receptor	Negative	2548 (80.2)
	Positive	630 (19.8)
Ki67 index	Less than 20%	677 (39.6)
	More than 20%	1034 (60.4)
Molecular Profile	Luminal	1792 (56.4)
	TNBC	758 (23.9)
	HER2 Enriched	333 (10.5)
	Luminal with HER2	293 (9.2)
PR after NACT	No PCR	192 (73.3)
	PCR	70 (26.7)
Local recurrence	No	3131 (96.2)
	Yes	125 (3.8)
Site of local recurrence	Same Breast	47 (1.4)
	Chest Wall	21 (0.6)
	Lymph Nodes	67 (2.1)
Distant metastases	No	2805 (86.1)
	Yes	451 (13.9)
Site of distant metastasis	Bone metastasis	218 (6.7)
	Lung metastasis	153 (4.7)
	Liver metastasis	137 (4.2)
	Brain metastasis	79 (2.4)
	Metastasis to other sites	28 (0.9)
Second Malignancy	No	3204 (98.4)
	Yes	52 (1.6)
Site of Second Malignancy	Same Breast	3 (0.2)
	Opposite Breast	22 (1.2)
	Ovary/Uterine Metastasis	9 (0.5)
Death	Alive	2294 (80.6)
	Dead	552 (19.4)

Note: Contains the number of patients of the particular category and their effective percentages. For some categories, data were available for patients who were diagnosed between 2010 and 2020. Abbreviations: ductal, Invasive mammary carcinoma; lobular, Invasive lobular carcinoma; mucinous, Invasive mucinous carcinoma; NACT, NeoAdjuvant Chemotherapy; PCR, Pathological Complete Response.

outcomes. Among postmenopausal early-stage luminal cancers, there were no significant differences between the patients who received chemotherapy and those who received chemotherapy in addition to endocrine therapy. Figure 3 shows significant improvements in breast cancer survival outcomes over time, while the distribution of clinicopathological features did not change much over time as shown in Figure 1. DFS, DDFS, and OS improved over time from 2004 to 2020 by about 10%. This can be seen from the survival rates in Table 2 and the hazard ratios in Table 3.

Risk factors

Table 3 shows the hazard ratios for each potential risk factor for DFS, DDFS, and overall survival. Proportional hazard assumptions were found to be reasonable by investigating Schoenfeld residual plots. Age was a significant predictor for overall survival. Patients aged less than 30 years and more than 75 years showed the worst overall survival. Premenopausal status was also associated with poorer survival. Survival outcomes were significantly worse for patients having advanced tumor stages, higher numbers of positive lymph nodes, and higher gradings. Worse survival outcomes were also observed in patients with high values of the Ki67 index. Patients who received NACT were at higher risk than the patients who didn't receive it for a DFS event, as they were patients who had a higher stage of disease at the time of diagnosis. Finally, patients who had estrogen receptor-positive status had better survival rates compared to estrogen receptor-negative cancer. Similarly, the patients who had positive Progesterone receptor status had better survival. While in case of HER2 Receptor, patients who were identified positive had lower survival.

Discussion

This analysis presents the characteristics and long-

Table 2. Disease-Free Survival Rates, Distant Disease-Free Survival Rates and Overall Survival Rates for Different Categories of Patients having Breast Cancer. Rates for 5-year, 10-year and 15-year is provided along with 95% Confidence Interval.

		5-year rate			10-year rate			15-year rate		
Parameter	Category	DFS rate	DDFS Rate	OS Rate	DFS rate	DDFS Rate	OS Rate	DFS rate	DDFS Rate	OS Rate
Age	< 30	71 (57, 87)	71 (57, 87)	81 (69, 95)	57 (42, 79)	57 (42, 79)	60 (44, 82)	57 (42, 79)	57 (42, 79)	60 (44, 82)
	30 - 50	82 (80, 84)	83 (81, 86)	88 (86, 90)	76 (73, 79)	78 (76, 81)	83 (81, 85)	73 (70, 75)	76 (73, 78)	80 (77, 82)
	50 - 75	82 (80, 84)	83 (81, 85)	88 (86, 89)	73 (71, 76)	76 (74, 79)	80 (78, 83)	68 (65, 71)	71 (69, 74)	76 (73, 78)
	> 75	67 (57, 77)	67 (57, 77)	69 (59, 79)	51 (40, 64)	52 (42, 66)	55 (44, 68)	46 (36, 60)	48 (37, 62)	48 (37, 62)
Menopausal Status	Postmenopausal	84 (82, 86)	85 (83, 87)	90 (88, 92)	75 (72, 79)	78 (75, 81)	81 (78, 85)	60 (46, 79)	65 (53, 80)	64 (51, 80)
	Premenopausal	84 (81, 87)	85 (82, 88)	92 (89, 94)	78 (73, 82)	82 (79, 86)	88 (85, 91)	61 (43, 85)	57 (37, 86)	59 (40, 86)
Type of surgery	Mastectomy	83 (81, 85)	84 (82, 86)	90 (89, 92)	75 (73, 79)	78 (76, 81)	83 (81, 86)	60 (47, 78)	64 (51, 80)	63 (51, 79)
	BCS	89 (86, 93)	91 (88, 94)	92 (89, 95)	78 (72, 86)	85 (80, 91)	87 (82, 93)	52 (29, 94)	51 (26, 97)	52 (27, 98)
Tumor stage	T1	88 (85, 91)	90 (87, 93)	92 (89, 94)	78 (74, 82)	84 (80, 87)	87 (84, 91)	74 (69, 79)	80 (76, 84)	85 (82, 89)
	T2	86 (84, 87)	87 (85, 88)	91 (89, 92)	78 (76, 80)	80 (78, 82)	84 (82, 86)	73 (70, 75)	76 (73, 78)	79 (77, 82)
	T3	74 (69, 79)	74 (70, 79)	81 (77, 85)	67 (61, 72)	69 (64, 75)	74 (70, 80)	64 (59, 70)	66 (61, 72)	70 (64, 76)
	T4	50 (43, 58)	51 (44, 59)	63 (56, 70)	43 (36, 51)	43 (36, 52)	50 (42, 58)	43 (36, 51)	43 (36, 52)	49 (42, 57)
Nodal stage	N0	91 (89, 92)	92 (90, 93)	93 (92, 95)	83 (80, 85)	86 (84, 88)	89 (88, 91)	78 (75, 81)	82 (79, 84)	85 (82, 87)
	N1	81 (79, 84)	82 (80, 85)	87 (85, 90)	74 (71, 77)	75 (73, 78)	80 (77, 83)	69 (66, 73)	72 (69, 75)	76 (73, 79)
	N2	73 (68, 77)	74 (70, 79)	82 (77, 86)	65 (60, 70)	66 (61, 72)	72 (67, 78)	60 (54, 66)	62 (57, 68)	69 (64, 75)
	N3	53 (47, 60)	55 (49, 62)	69 (63, 75)	45 (39, 52)	47 (41, 54)	57 (50, 64)	45 (38, 52)	46 (40, 53)	54 (48, 62)
Grade	G1	88 (84, 91)	89 (85, 92)	92 (89, 95)	81 (77, 86)	83 (79, 87)	87 (83, 91)	74 (68, 81)	78 (73, 84)	82 (77, 88)
	G2	83 (81, 85)	84 (82, 85)	88 (87, 90)	74 (72, 77)	77 (74, 79)	81 (79, 84)	70 (68, 73)	73 (70, 75)	77 (75, 80)
	G3	79 (77, 82)	81 (78, 83)	86 (83, 88)	73 (70, 76)	76 (73, 79)	80 (77, 82)	69 (65, 73)	73 (70, 77)	77 (74, 81)
Molecular profile	Luminal	84 (82, 85)	85 (83, 86)	89 (88, 91)	75 (73, 77)	77 (75, 79)	82 (80, 84)	70 (67, 73)	73 (71, 76)	78 (75, 80)
	TNBC	79 (76, 82)	80 (77, 83)	84 (81, 87)	73 (70, 77)	75 (72, 79)	78 (75, 81)	68 (64, 72)	70 (66, 74)	73 (70, 77)
	HER2 Enriched	78 (74, 83)	80 (76, 85)	85 (81, 89)	71 (66, 77)	75 (70, 80)	79 (74, 84)	69 (64, 75)	74 (69, 79)	77 (72, 83)
	Luminal with HER2	81 (76, 86)	82 (77, 87)	88 (84, 92)	74 (68, 80)	78 (73, 84)	83 (78, 88)	72 (66, 79)	76 (71, 82)	81 (76, 87)
Ki67 index	< 20%	87 (84, 90)	88 (85, 91)	92 (90, 95)	77 (73, 82)	81 (77, 85)	84 (80, 89)	69 (57, 83)	55 (31, 99)	56 (31, 100)
	> 20%	83 (81, 86)	84 (81, 86)	90 (88, 92)	76 (72, 80)	80 (77, 83)	84 (81, 87)	44 (24, 79)	50 (30, 81)	49 (30, 82)
TNM Stage	I	90 (89, 92)	91 (90, 93)	93 (92, 95)	82 (80, 85)	86 (83, 88)	89 (87, 91)	77 (74, 80)	81 (78, 83)	85 (82, 87)
	II	87 (85, 90)	88 (86, 91)	91 (89, 93)	79 (76, 82)	81 (79, 84)	85 (82, 87)	74 (70, 77)	77 (74, 81)	80 (77, 83)
	III	74 (70, 77)	75 (72, 79)	81 (77, 84)	65 (61, 70)	67 (62, 71)	72 (68, 76)	63 (59, 68)	64 (60, 69)	69 (64, 73)

Abbreviations: BCS, Breast Conservation Surgery; luminal contains both luminal A and luminal B; Luminal with HER2, luminal with HER2 enriched; NACT, Neoadjuvant Chemotherapy; PCR, Pathological Complete Response; PR, Pathological Response.

term survival rates of breast cancer patients in the Amrita Breast Cancer Cohort, the largest cohort from a single center in India described in the literature so far. The breast cancer patients in this cohort are similar to patients in developed countries with respect to some characteristics but also show some distinct peculiarities. Differences and similarities will now be discussed for demographics, molecular subtypes, stage of disease, and survival outcomes.

It is reported that the demographic characteristics of Indian breast cancer patients differ from that of the Western population in terms of the age at diagnosis. Shaoyuan Lei et al. [11] have reported that in the USA, Belgium, Australia, and the United Kingdom, the highest incidence of breast cancer was among women in their 60s. In contrast, women in China, Japan, Iran, Fiji and Morocco were diagnosed in the age range of 55-60 years, while women in India tend to be diagnosed between 45-55 years of age [13, 14]. In the current study, the majority of patients were diagnosed between the ages of 50 and 60 years. This distribution pattern of age is similar to other Asian countries [15,16]. M Khadije et al in their meta-analysis described those patients between the ages 46-50 showed the highest survival rates, with survival rates decreasing in both patients less than 30 years and more than 75 years, which was consistent with the results of our study [17]. It is worth noting that in our cohort, the distribution of age and menopausal status has not changed much since 2004.

A large study conducted in the US reported the distribution of breast cancer subtypes Luminal A, Luminal B, HER2 enriched, and TNBC was 72.6%, 11.2%, 4.8%, and 11.3%17. In a study conducted in southern China, the distribution of breast cancer subtypes was 31.1%, 30.4%, 22.1%, and 16.5% respectively [18]. A meta-analysis of Indian patients showed a prevalence of 33%, 17%, 15%, and 30% respectively [19]. The current study supports this. This indicates that in India, there is a higher proportion of aggressive molecular subtypes compared to the Western population.

When examining the long-term outcomes, the correlation between molecular subtypes and patient prognosis indicates that individuals with luminal cancers had a superior DFS, DDFS and OS as compared to other molecular subtypes. These findings were consistent with previous studies conducted in other countries [20,21]. The most favourable survival pattern was observed among women with luminal cancer, followed by HER2, and TNBC had the worst survival rate. This study further finds that patients who achieved Pathologic Complete Response (PCR) showed better survival outcomes. This finding is in agreement with other studies from low- and middle-income countries [22].

In developed countries, the proportion of women with TNM stage 3 and 4 breast cancer ranges from 8% to 22%. However, in developing countries, including India, this proportion is higher ranging from 40 – 50%. Reasons include lack of awareness, education, affordable healthcare, and social stigma [9, 23-26]. In our cohort, we observed a slightly higher prevalence of locally advanced or metastatic disease (25%) compared to the Western

Table 2. Continued

Parameter	Category	5-year rate			10-year rate			15-year rate		
		DFS rate	DDFS Rate	OS Rate	DFS rate	DDFS Rate	OS Rate	DFS rate	DDFS Rate	OS Rate
PR After NACT	No PCR	66 (59, 74)	69 (62, 76)	83 (77, 90)	61 (52, 72)	69 (62, 76)	75 (67, 85)	51 (34, 75)	59 (43, 81)	65 (47, 89)
	PCR	86 (78, 94)	86 (78, 94)	86 (77, 97)	86 (78, 94)	86 (78, 94)	86 (77, 97)	86 (78, 94)	86 (78, 94)	86 (77, 97)
Year of Diagnosis	2011-'20	86 (84, 88)	87 (85, 89)	92 (91, 94)	79 (76, 81)	82 (79, 84)	87 (85, 90)	76 (73, 79)	79 (76, 82)	85 (82, 87)
	2004-'10	77 (75, 79)	78 (76, 80)	83 (81, 85)	70 (67, 72)	72 (70, 74)	75 (73, 78)	65 (63, 67)	68 (65, 70)	71 (69, 74)

Abbreviations: BCS, Breast Conservation Surgery; luminal contains both luminal A and luminal B; Luminal with HER2, luminal with HER2 enriched; NACT, Neoadjuvant Chemotherapy; PCR, Pathological Complete Response; PR, Pathological Response.

Table 3. Univariate Analysis Conducted for Patients having Breast Cancer Based on Different Categories. The hazard ratio is reported by taking one category as the reference group. Hazard ration greater than 1 indicates higher event rate and vice-versa.

Category	Comparison	DFS: HR (CI) p	DDFS: HR (CI) p	OS: HR (CI) p
Age	per year	1.02 (1.01, 1.02) <0.01	1.01 (1.00, 1.02) <0.01	1.01 (1.00, 1.02) <0.01
Menopausal Status	Premenopausal vs Postmenopausal	0.78 (0.58, 1.04) 0.09	0.92 (0.73, 1.15) 0.46	0.89 (0.70, 1.13) 0.34
Type of surgery	BCS vs Mastectomy	0.67 (0.46, 0.97) 0.03	0.65 (0.49, 0.87) <0.01	0.54 (0.39, 0.75) <0.01
Tumor stage	T2 vs T1	1.34 (1.02, 1.76) 0.04	1.12 (0.90, 1.38) 0.31	1.30 (1.03, 1.66) 0.03
	T3 vs T1	2.34 (1.68, 3.25) <0.01	1.80 (1.38, 2.36) <0.01	2.23 (1.67, 2.99) <0.01
	T4 vs T1	5.29 (3.82, 7.32) <0.01	4.20 (3.21, 5.50) <0.01	5.37 (4.02, 7.17) <0.01
Nodal stage	N1 vs N0	1.84 (1.49, 2.27) <0.01	1.63 (1.37, 1.94) <0.01	1.86 (1.54, 2.25) <0.01
	N2 vs N0	2.65 (2.05, 3.42) <0.01	2.44 (1.97, 3.03) <0.01	2.84 (2.26, 3.57) <0.01
	N3 vs N0	4.48 (3.48, 5.77) <0.01	4.34 (3.50, 5.38) <0.01	5.10 (4.08, 6.39) <0.01
Grade	G2 vs G1	1.40 (1.01, 1.92) 0.04	1.30 (0.99, 1.70) 0.06	1.31 (0.99, 1.73) 0.06
	G3 vs G1	1.52 (1.09, 2.12) 0.01	1.48 (1.12, 1.95) 0.01	1.44 (1.07, 1.93) 0.01
Molecular profile	TNBC vs Luminal	1.35 (1.11, 1.64) <0.01	1.18 (0.99, 1.39) 0.06	1.19 (1.00, 1.42) 0.05
	HER2 Enriched vs Luminal	1.17 (0.89, 1.54) 0.25	1.19 (0.95, 1.49) 0.14	1.12 (0.88, 1.43) 0.35
	Luminal with HER2 vs Luminal	0.94 (0.68, 1.31) 0.71	1.04 (0.80, 1.35) 0.77	0.99 (0.75, 1.31) 0.94
Ki67 index	More than 20% vs Less than 20%	1.28 (0.94, 1.73) 0.12	1.31 (1.02, 1.66) 0.03	1.35 (1.05, 1.74) 0.02
TNM Stage	II vs I	1.33 (1.06, 1.67) 0.01	1.15 (0.95, 1.39) 0.15	1.21 (0.98, 1.48) 0.07
	III vs I	2.61 (2.08, 3.27) <0.01	2.16 (1.78, 2.61) <0.01	2.48 (2.03, 3.04) <0.01
	IV vs I	13.29 (10.44, 16.92) <0.01	574.45 (373.70, 883.04) <0.01	269.18 (199.15, 363.84) <0.01
Pathological response	No PCR vs PCR	1.61 (0.71, 3.65) 0.25	2.47 (1.27, 4.82) 0.01	2.23 (1.14, 4.37) 0.02
Histotype	lobular vs ductal	0.75 (0.38, 1.47) 0.41	0.91 (0.56, 1.48) 0.70	0.89 (0.53, 1.51) 0.68
	mucinous vs ductal	1.44 (0.64, 3.25) 0.38	1.78 (1.00, 3.18) 0.05	1.63 (0.87, 3.08) 0.13
	others vs ductal	1.23 (0.76, 1.98) 0.40	0.84 (0.54, 1.31) 0.43	0.91 (0.58, 1.44) 0.70
ER Receptor	Positive vs Negative	0.77 (0.65, 0.91) <0.01	0.84 (0.72, 0.96) 0.01	0.84 (0.72, 0.97) 0.02
PR Receptor	Positive vs Negative	0.83 (0.71, 0.98) 0.03	0.88 (0.76, 1.01) 0.07	0.87 (0.75, 1.01) 0.06
HER2 Receptor	Positive vs Negative	1.02 (0.83, 1.26) 0.83	1.09 (0.91, 1.30) 0.35	1.06 (0.88, 1.28) 0.54
Year of Diagnosis	patients from 2004-'10 vs 2011-'20	2.22 (1.83, 2.69) <0.01	1.61 (1.38, 1.87) <0.01	1.72 (1.47, 2.02) <0.01

Note: Hazard Ratios are reported with corresponding Confidence Intervals and p-values. Abbreviation: BCS, Breast Conservation Surgery; HR, Hazard Ratio ; CI, Confidence Interval; p, p-value; PCR, Pathological Complete Response; luminal, both luminal A and luminal B; Luminal with HER2, luminal with HER2 enriched.

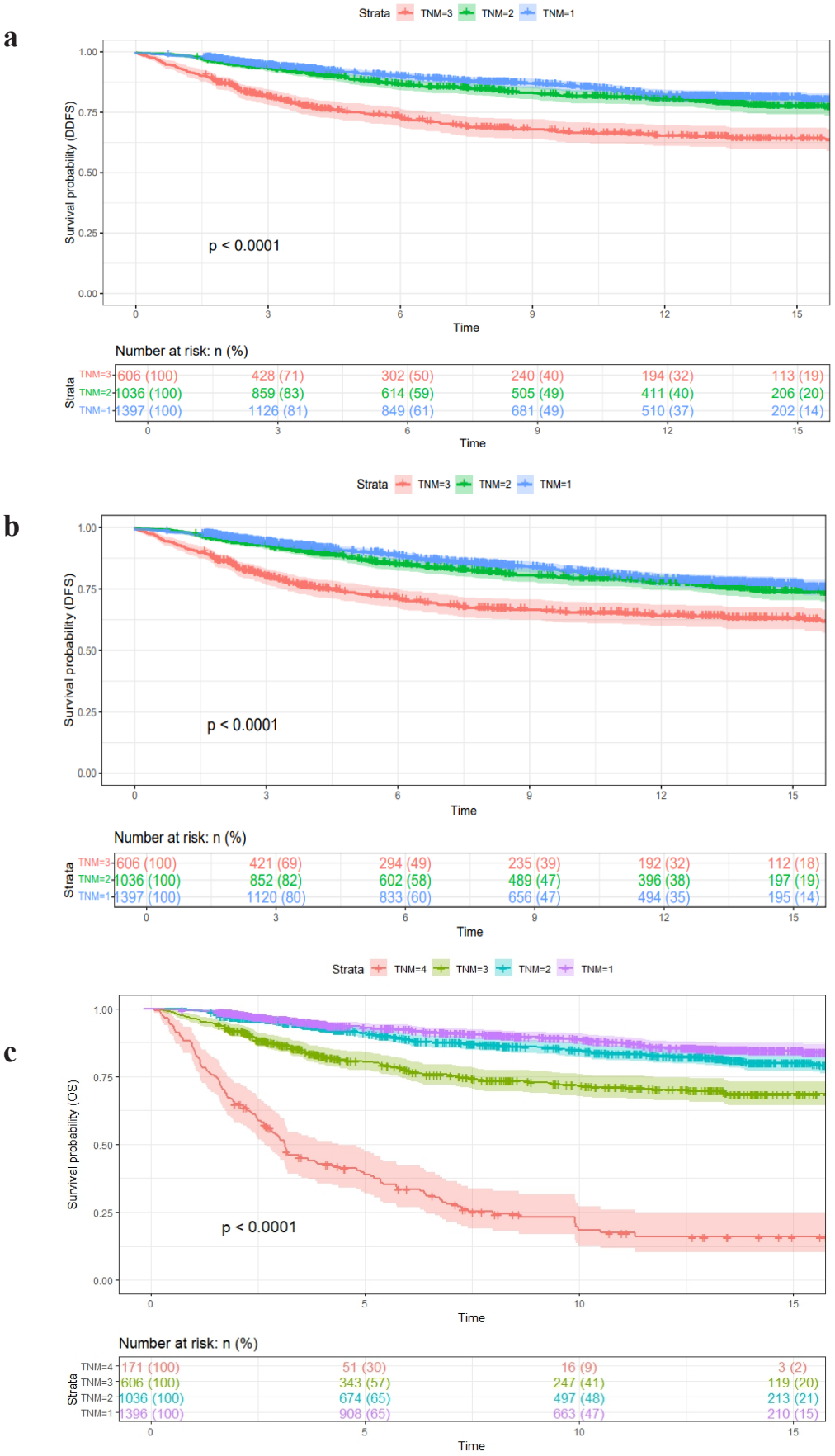

Figure 2. Kaplan - Meier Curves for the Patients based on TNM Classification. The horizontal axis(x-axis) represents the time in years, and the vertical axis(y-axis) shows the probability of surviving people. The lines represent the survival curves of the groups. A vertical drop in the curves indicates an event. The vertical tick mark on the curves means that a patient was censored at this time. At time zero, the survival probability is 1(100% of the participants are alive). (a): Disease Free Survival Curve for TNM Classification. (b): Distant Disease Free Survival curve for TNM Classification. (c): Overall Survival curve for TNM Classification.

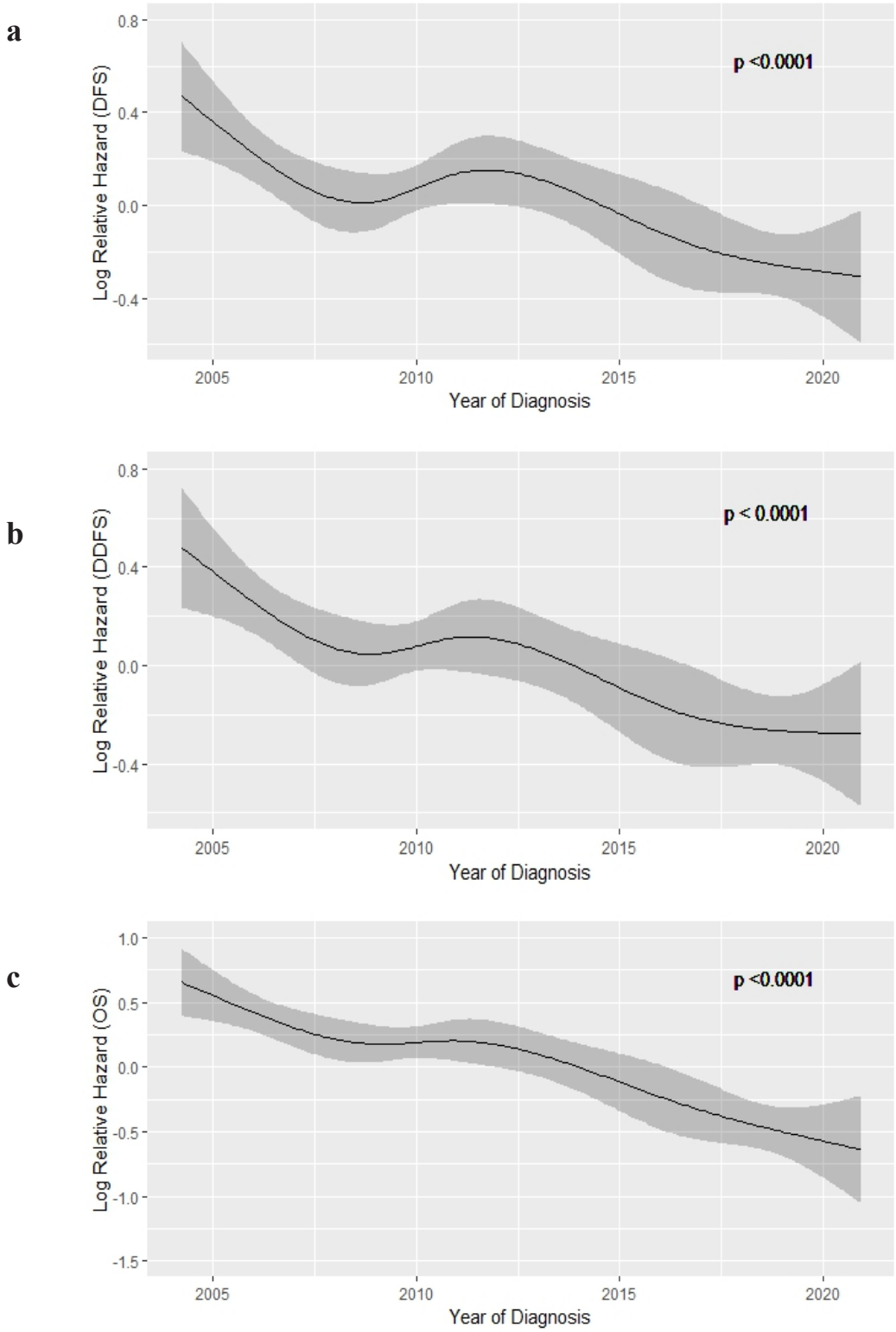

Figure 3. Trends in the hazard ratio among the patients yearwise is shown using Regression Plot. Log relative hazard is plotted on y-axis and year of diagnosis on x-axis. (a): Trend in Hazard Ratio for Disease Free Survival over years. (b): Trend in Hazard Ratio for Distant Disease Free Survival over years. (c): Trend in Hazard Ratio for Overall Survival over years.

population [9], but a lower rate compared to developing countries [18]. This encouraging trend could be attributed to the enhanced knowledge and awareness regarding breast cancer as well as the availability of resources for early detection in Kerala, a state in South India. The proportion of patients presenting with metastatic disease in our cohort (5.6%) was comparable to the Western population (3 – 6%) [13] and other studies from India (5 – 10%). Consistent with other studies, our study showed differences in overall survival rates based on different stages. Notably, the recurrence rate differed depending on the tumor and nodal status of breast cancer patients.

Fabiana Tonellotto et al. [26] conducted a study on breast cancer patients with positive lymph nodes and found that five-year breast cancer recurrence was higher for pN2 and pN3 compared to pN1 patients [27], which aligns with our own findings.

While the distribution of the clinicopathological characteristics of the patients in the cohort did not change significantly over the last decade, the survival rates have continuously improved, from 80% in the 5-year survival of the 2004-2010 cohort to 90% after 2010 and are now comparable to developed countries. This can be seen from a pooled analysis of survival rates from 52 countries, where the 5-year survival rate was 80-85% in developed countries and 65-75% in developing countries [15,28]. Similarly, a study conducted by Ademuyiwa FO et al reported an overall 5-year survival rate of 89% for breast cancer in the Western population [26]. In contrast, studies from developing countries like India, China and Iran reported lower 5-year survival rates of 51%, 59%, and 72% respectively. However, in the current study, the survival rate is more comparable to the survival rate of 86.9% in Western populations [29-31].

Retrospective studies in many developing countries encounter several challenges, including inadequate documentation, difficulties in data retrieval, noncompliance with treatment and loss to follow-up [7]. These difficulties are not present for the Amrita Breast Cancer Cohort, since this is a single-center study and the diagnosis and the treatment procedures were consistent for all patients during the study period. It is worth mentioning that patients from outside India were excluded from the analysis and that the study had a very comprehensive follow-up with only 12.6% of patients lost to follow-up. Some limitations of the current study should be mentioned. Detailed information on the patients lost to follow-up is not available. It might for example be the case that those who were lost to follow-up on average had high staging as compared to those not lost. This has to be acknowledged as a potential source of bias. The inclusion of cases from a single center may raise concerns about the generalizability of the findings to the broader population, as they may not be fully representative of the general population. Furthermore, in the first 6 years, some patient characteristics were not digitally recorded, and in this subset, only stage, tumour characteristics and follow-up data were included.

Lower survival outcomes in developing countries could be attributed to poor public awareness, social and cultural stigma, and limitations in accessible and affordable healthcare centers [12, 18]. As a society, the state of Kerala has higher literacy rates (Over 90% for over 2 decades) and higher mean income compared to the rest of India. This translates to increased awareness, access and affordability to healthcare amongst the general public, and this could be the reason why the survival rates of our cohort is comparable to several developed nations. This also highlights the importance of education and financial stability, which should be the key focus of all policies in health care drafted by developing countries including India. Uplifting and educating the women in each community, and dispelling myths about breast cancer treatment can encourage more women to seek help at the earliest.

Author Contribution Statement

Conception and design: Dhanya Mary Louis, Lakshmi Malavika Nair, Dehannathparambil Kottarathil Vijayakumar, Keechilat Pavithran. Collection and assembly of data: Dhanya Mary Louis, Lakshmi Malavika Nair. Data analysis and interpretation: Merin Mathew, Georg Gutjahr. Manuscript writing: all authors. Final approval of manuscript: all authors

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Ethical Clearence

Ethical approval was granted by Amrita Institute of Medical Sciences Institutional Ethics Committee with approval number IEC-AIMS-2022-PHARM-178.

Availability of data

Patient-level data can not be shared due to regulations.

Conflict of interest

The authors have no conflict of interest to declare

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