

Article Type:

Original Article

Title:**Epidemiological distribution of Breast Cancer Patients in India: A Multi-centric Retrospective Study**

Sarin R¹, Hanitha RNM², Gupta S⁴, Khan E⁴, Bhandari TPS⁵, Prasad SVSS⁵, Reddy VA⁵, Singh M⁶, Thakur R⁶, Anisha R⁶, Jain Jugnu², Chatterjee S²

Author Affiliations:

¹Indraprastha Apollo Hospitals, New Delhi

²Sapien Biosciences Pvt. Ltd.,

³Apollo Speciality Hospital, Chennai, Tamil Nadu

³Apollo Hospital Enterprises

⁴Apollo Gleneagles Hospitals, Kolkata, West Bengal, India

⁵Apollo Hospital Enterprises, Hyderabad, Telangana,

⁶Technology Healthcare Bigdata Analytics, Gurugram, Haryana

Corresponding Author:

Dr. Jugnu Jain

Sapien Biosciences Pvt. Ltd.

Email address: jugnu@sapienbio.com

Word Count:

Abstract: 258

Main Text: 2658

Conflict of Interest: None

Funding Details:

Epidemiological distribution of Breast Cancer Patients in India: A Multi-centric Retrospective Study

ABSTRACT:

Background: A multi-centric hospital-based retrospective study was conducted to understand the epidemiology of breast cancer in terms of demographics and clinical characteristics (staging and hormone receptor status) at the time of diagnosis.

Methods: The data for 5688 female breast cancer patients were collected from the hospital and clinical records of four study centers. All statistical analysis was performed using Microsoft Excel 2016 and R software (Rx 64 version 3.6.2). Survival was estimated by the Kaplan Meier method and compared by the log-rank test. A p-value of <0.05 was considered statistically significant.

Results: The mean and median age of the study population were 52.6 (± 12.4) years and 53.0 (range 51-54 across the 4 centers) years, respectively. About 68% of patients were in the age category of 41-65 years, 17.6% of patients were <40 years in age, and 23.4% of patients also reported positive family history. The majority of the patients (66.3%) were diagnosed at an early stage (Stage I and II). Our study observed a higher 5-year overall survival (OS) and recurrence-free survival (RFS) at 95.2% and 84.3%, respectively. The 3-year OS rate was 100%, 97.5%, 94.1%, and 74.7% for TNM Stages I, II, III, and IV, respectively. The RFS was 95.7%, 95.5%, 84.5%, and 49% for TNM Stages I, II, III, and IV, respectively.

Conclusion: The present study highlights the epidemiological distribution of breast cancer patients across four major cities and private oncology centers in India. It emphasizes the importance of disease awareness among the urban and educated female population as most such patients were diagnosed at an early stage and demonstrated higher OS and RFS.

Keywords: Breast cancer, Epidemiology, Overall survival, Recurrence-free survival

INTRODUCTION

Cancer is the second leading cause of mortality globally (16%) following cardiovascular disease (31%)^{1,2}. The International Agency for Research on Cancer (IARC), September 2018, estimates an increased global cancer burden of 18.1 million new cases and 9.6 million deaths in 2018³. In developed countries, breast and colorectal cancer are two of the most common cancers, while in developing countries, breast and cervical cancer are more frequent female cancers². Globally, the 5-year prevalence of all cancers² is estimated to be 43.8 million. As per GLOBOCAN 2018 database, Asian countries account for nearly half of the global cancer burden and more than half of cancer-related mortality¹.

With an estimated population of 1.33 billion, India is experiencing an alarming increase in cancer incidence and death. The GLOBOCAN 2018, India factsheet estimates about 1.1 million new cases and 0.78 million deaths with a 5-year prevalence of 2.2 million. Both sexes combined, breast cancer is the most frequently observed cancer (14%) and is one of the leading cause of death (11.1%) in India⁴. Earlier detection of breast cancer helps in better treatment outcomes. Compared to western countries, breast cancer is reported more in the younger population in India, with locally advanced or metastatic cancer and a higher proportion of triple-negative hormonal status leading to poor prognosis. Demographic and socio-economic status, time of diagnosis, literacy rate in urban and rural female populations are factors associated with disease outcomes. Literate urban women are less likely to present with an advanced-stage disease than rural and illiterate women⁵. Early detection policies such as preventive screening and quality treatment at the early stage throughout the country without any socio-economic disparities help fight against cancer⁶.

A significant source of information about breast cancer in India is cancer registries such as population-based cancer registries (PBCR) and hospital-based cancer registries (HBCR) established by the government and capture data mainly from health institutions of the public sector. On the other hand, there is a shortage of information from the private healthcare system regarding demographics, clinical profile, management, and survival of breast cancer patients.

The current multicentre hospital-based study helps fill this information gap by analysing the retrospective data collected from four major private oncology super-specialty hospitals, and analyzed for breast cancer epidemiology in terms of demographics and clinical characteristics (staging and hormone receptor status) at the time of diagnosis and its correlation with outcomes.

MATERIALS AND METHODS

Ethics and Data collection:

Institutional Ethics Committee (IEC), approval was obtained prior to collecting retrospective data before the study initiation. Post-IEC approval, data was collected from four sites, Kolkata, Chennai, Delhi and Hyderabad, maintaining confidentiality of patients by deidentifying and masking their personal information.

Study Population:

Data from a total of 5688 females with primary breast cancer, diagnosed and treated at four oncology Apollo hospitals across India; Kolkata (2009 to 2016), Chennai (1997 to 2016), Delhi (2005 to 2016), and Hyderabad (2005 to 2016) were included in the study. We excluded patients with secondary breast cancer or any other cancer from the study. Due to the study's retrospective nature, the data collection period varied based on its availability at the respective study center.

Data was collected and compiled from various oncology departments, medical records department (MRD), hospital information database, and social workers. The data comprised of demographic and clinicopathological details such as age, gender, date of diagnosis, family history wherever available, menopausal status, laterality, tumor stage and grade, metastasis status, hormone receptor (ER, PR, and HER2/neu expression), treatment, and survival information.

Statistical Analysis:

All statistical analysis was performed in Microsoft Excel 2016 and R software (R 64 version 3.6.2). Descriptive statistics of the sample population were expressed in percentage and mean (SD), and median (range). Survival was estimated by the Kaplan Meier method and compared by the log-rank test. The association between independent variables and survival (recurrence-free and overall survival) was assessed using univariate and multivariate Cox's proportional regression analysis. Categorical variables were compared by using the Chi-square test (χ^2). A p-value of <0.05 was considered statistically significant.

RESULTS

The total study sample consisted of 5688 female breast cancer patients, distributed across sites 1 to 4. Nearly 50% of the data was collected from site-1 (49.61%), while the least was collected from site-4 (14.96%). This disparity in sample size is due to data availability at each study site and the different number of patients visiting the respective site.

The mean age of the study population was 52.6 (± 12.4) years, while the median age was 53.0 (51-54) years. About 68% of the patients were in the age category of 41-65 years, while 17.17% of patients belonged to the younger age group (<40 years) across all four sites. About 4.83% (275/5688) patients reported a positive family history, out of which 26.54% patients belonged to the younger age group (<40 years). The demographic details are as shown in Table-1.

The clinicopathological details of the patients are as described in Table-2. Out of the 5688 cases studied, the tumor stage was available for 2376/5688 patients (41.77%). Out of the 2376 patients, 1576 (66.32%) belonged to the early stage (I and II). From the available data, based upon the TNM stages, about 54.17% of patients (1287/2376) were in Stage II, 31.35% of patients in Stage III, 11.41% in Stage I, and 2.3% patients in Stage IV. In addition, a small subset of patients (0.76%) also comprised Stage 0.

With respect to menstruation status, menopause status was available for 64.2% of the patients. Majority (46.36%) of the patients were post-menopausal, 17.9% premenopausal and 0.07% perimenopausal.

Laterality was documented in 78.34% of the breast cancer cases and observed to be equally on the left or right side (Table 2). There were a total of 129 (2.27%) bilateral cases of which **X** were in age group 40 or below and the rest above. Among 35 of the bilateral breast cancer cases in which sequence of occurrence of cancer in the 2nd breast was known, 18 were metachronous and 17 synchronous (based on the time interval between the diagnosis of the primary and secondary tumors).

Metastasis status was available as collected from the physician's medical records. Out of the 2395 patients for whom the metastasis status was known, 95.8% were in the M0 stage, 2.3 % in the M1 stage, and undetermined for the remaining 1.9% cases (Mx stage).

The ER/PR status and HER2/neu receptor status were available for about 60% of the total cases. Of the 3384 cases for which the ER and PR data were available, 63.62% of the cases had positive hormone receptor status. The HER2 status was available for 51.95% of patients (2955/5688), out of which 845 (14.86%) patients were HER-2 positive, 1836 patients were HER-2 negative, and 274 patients were equivocal. About 21.61% of patients (629/2913) were triple-negative (TNBC), while the data was not available for the remaining 2775 patients. Further, the age-wise categorization of TNBC showed 24.1% (152/629) patients belonged to the younger age group (<40 years), while the proportion was 64.38%

(405/629) and 11.44% (72/629), respectively, for 40-65 years and >65 years age category. Table-3 represents the age-wise hormone receptor status of the study population.

Survival Analysis

Of the 2376 patients for which information was available, the survival data were obtained for about 1391 (85.54%) cases. The Kaplan-Meier curve showed a consistent decline in overall survival (OS) and recurrence-free survival (RFS) with advancing stage. The mean OS and RFS pattern in different TNM stages are represented in Figures-1 and 2. Since no event (death) occurred in Stage I patients during the follow-up period, we excluded it from OS calculation in Table-5.

The 5-year OS and RFS were 95.2% and 84.3%, respectively. The mean follow-up period was 3.42 and 3.38 years for overall and recurrence-free survival, respectively. The TNM stage-wise 3-year OS and RFS are as shown in Table-4. The 5-year RFS was 92.1%, 91.6%, and 79.5% for Stage I, II, and III, respectively.

Table-5 depicts the critical factors associated with the survival probability. Stage of the disease (Stage III and Stage IV), negative hormone receptor status (ER and PR), and positive metastasis status significantly reduced both the probable OS and RFS period with a p-value of <0.05. While menopausal status was not associated with RFS (p=1.0) it was associated in the case of OS, where the pre-menopausal patients had higher survival than post-menopausal patients (8.3 years vs. 7.7 years; Table-5) with a p-value <0.05.

DISCUSSION

Breast cancer has emerged as the leading cause of cancer-associated mortality (11%) in India since 2018. It was the most frequently diagnosed form of cancer among Indian women in 2009⁷ and accounted for more than one-fifth of female cancer mortality. Hereditary and genomic factors account for only 5-10% of the breast cancer cases¹. A New York-based study reported associations of various risk factors with elevated incidence rates. These include early age menstruation, later age at menopause, later age at first childbirth (>30 years), fewer or no children (nulliparity), use of oral contraceptives, hormone replacement therapy, alcohol intake, and sedentary lifestyle, while breastfeeding and physical activity acting as potential protective factors⁸. Timely diagnosis of breast cancer gives a higher chance of survival; hence regular self-examination should be encouraged for early detection⁹.

The present study provides insights into the breast cancer prevalence and diagnostic patterns across four major cities in India: Chennai, Delhi, Kolkata, and Hyderabad. The study significantly updates the number of cases and outcomes data from our previous study in 2015 on breast cancer patients from the

same centers conducted by Khandrika et al., 2016¹⁰. In the present study, data for 5688 cases were collected and collated until the year 2016. About 17.2% of the breast cancer patients were aged less than 40 years, similar to a previous report by the breast cancer India statistics, stating a higher number (20%) of patients were diagnosed with breast cancer at a young age (thirties and forties)¹¹. In another multicenter retrospective study conducted by Agarwal et al. (2007), at three major Asian breast cancer centers (India, Malaysia, and Hong Kong), 26% patients at the Indian center were younger than 35 years of age (based on 544 breast cancer patients managed at SGPGIMS Lucknow, India)¹². Whereas in the USA, as per the American Cancer Society (ACS), only 6.6% of all breast cancer cases were diagnosed before 40 years of age as reported in 2008¹³.

Accurate staging at the time of diagnosis is essential for optimizing therapy. The TNM is the most widely used staging system and assesses cancer growth and invasion. In our study, 33.7% of the 2376 patients presented at an advanced stage (28-40% across the four centers), which is relatively less than that reported by a hospital-based (Tata Memorial Hospital, Mumbai) study in India comprising 1210 cases wherein 54% of the patients were diagnosed at an advanced stage-)⁵. Another New Delhi-based cross-sectional study involving 569 breast cancer cases diagnosed during 1989-2003 reported that 70.2% of the cases presented with advanced stage at the time of diagnosis¹⁴. Health, literacy, socio-economic status and urban background have been associated with lower odds of late diagnosis^{15,16}. Hence, fewer patients presenting at the advanced stage (33.7%) in our study could be attributed to differences in education levels, health literacy, and economic affordability between the patients treated at public versus private hospitals.

Familial cancer or cancer inherited from a genetic mutation is a critical risk factor, constituting approximately 20% of breast cancers. In a US-based study comprising 1,135,977 patients, about 13-19% of females affected with breast cancer reported having an affected first-degree relative¹⁷. Another retrospective study on 570 Moroccan patients with breast cancer reported a higher incidence of high-grade tumor and lymph node involvement in younger patients (predominantly pre-menopausal), with familial breast cancer¹⁸. Although 23.4% of the patients reported positive for family history in our study, with 26.54% of them belonging to a younger age group, it was not significantly associated with OS and RFS.

[In this study, average age of menopause was observed to be XX, similar to a meta-analysis of multiple studies from India with minimal publication bias, reported as 46.6 years \(95% CI: 44.83, 48.44; Prasad et al 2021\). This age is significantly lower than the age reported in some developed countries ~52...](#)

Hormone receptor status has a major role in deciding the management of breast cancer and also has prognostic significance. In our study, the hormone receptor status was available for 3384 cases. The hormone receptor positivity (ER or PR positivity) was 63.62%, with 59.2% ER-positive, 54.3% PR-positive, and 30% ER/PR double-positive patients. A retrospective study in South India on 5436 breast cancer patients, collected during a similar period (January 2010- December 2016), had reported a lower incidence (48%) of hormone receptor (HR) positive patients.¹⁹ In a review of 11,780 breast cancer cases spanning seven years at a tertiary cancer center in India, the percentage of hormone receptor expression varied from 52 to 57% (Shet et al., 2009), closer to the numbers observed in our study here.²⁰

The Her2/neu testing in India started only after 2012, post the approval and availability of Her2 targeting drugs. In our study, 28.6%, 9.3%, and 62.1% of patients were Her-2 positive, equivocal, and negative, respectively, while data was unavailable for 48% of patients. A retrospective study on 5436 breast cancer patients in South India estimated an incidence of 37% Her-2 positivity, slightly higher than observed in our study.¹⁹

About 21.61% of the total 2681 cases were triple-negative (TNBC), which is remarkably similar to the 20.8% reported previously by us in 2016 (based on 1240 cases with complete ER, PR, Her2/neu data). TNBC percentage in the present study varied across the four sites, ranging from 16.6% in Delhi to a higher 23.7-24.8% at Hyderabad and Chennai hospitals, again similar to our previous 2016 published data¹⁰. The retrospective South Indian study¹⁹ reported 15% TNBC cases, similar to our percentage from Delhi. However, in another systematic review and meta-analysis²¹ study on an Indian population, which included 17 studies and 7237 patients, the prevalence of TNBC was reported to be as high as 31% (95% CI: 27% - 35%).

Overall survival is expressed as the percentage of people alive at a time duration (usually 5-years) following the cancer diagnosis. In addition to differences in the prevalence of screening/early detection services, global disparities in cancer survival rates are influenced by the types of cancer, stage at the time of diagnosis, and treatment facilities availability.

The OS and RFS in Indian breast cancer patients vary from study to study. According to a Kerala-based study comprising 449 cases²², 5-year survival rates were 90% for Stage I, 65% for Stage II, 33% for Stage III, and 6% for Stage IV. A population-based registry in Bangalore with 1514 patients²³ reported overall 5-year survival as 42.3% and 5-year relative survival as 46.8%. Survival was significantly associated with age at diagnosis, marital status, education, and clinical extent of the disease. A Chandigarh-based study (North India), conducted between 1995 and 2000 on 688 patients with carcinoma breast, reported 5-year overall survival of 81% and disease-free survival of 69%²⁴. Another tertiary care center in North India (Delhi) involving 128 locally advanced breast cancer (LABC) reported 5-year OS and RFS survival 58% and 41%, respectively²⁵. According to a study during 2000-2014 from 322 population-based registries in

71 countries on global trends in cancer survival (CONCORD-3), the 5-year overall survival in breast cancer was just 66.1% in India, while in Australia and the USA, it was 89.5% and 90.2% respectively. In our study, the 5-year OS and RFS were 95.2% and 84.3%, respectively²⁶, closer to the ~90% OS reported in global studies and much higher than the Indian studies cited above. The 3-year OS rate was 100%, 97.5%, 94.1%, and 74.7% for TNM stages I, II, III, and IV, respectively, while RFS was 95.7%, 95.5%, 84.5%, and 49% for TNM stages I, II, III, and IV respectively. The higher survival outcomes in our study may be partially due to the higher socio-economic and literacy status, which may have further contributed towards earlier detection and timely treatment. The better treatment and patient care provided at these private centers may also act as positive modulators.

LIMITATION:

One of the limitations of our study being retrospective in nature was incomplete data from out-patient visits of the patient and lack of follow-up information for many cases, as also likely under-representation of stage IV patients detected by PET/CT etc that did not undergo any treatment at the hospital. Hence, further follow-ups and filling in of missing data (e.g., ER, PR, Her2) will help fill this gap and draw more profound conclusions about improving OS and RFS in breast cancer patients. Similarly, gathering more information on family history can help understand the role of familial risk factors in breast cancer in India.

CONCLUSION:

The study outcome improves our understanding of epidemiological, clinical, and prognostic characteristics of breast cancer patients in private health care settings in India. The study assessed the impact of these characteristics with patients' overall and recurrence-free survival. In addition, the study emphasizes the importance of an increased disease awareness among the urban and educated female population as most patients were diagnosed at an early stage and had significantly better OS and RFS outcomes than their late stage counterparts.

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