

Patient-Reported Shoulder Morbidity and Fatigue among the Breast Cancer Survivors: An Insight from a Tertiary Care Cancer Hospital

Abstract

Context: Breast cancer is the most common cancer in Indian women with an annual mortality of around 87,000. Treatment for breast carcinoma may lead to swelling of the ipsilateral arm and shoulder stiffness and arm pain and cancer-related fatigue. Very few centers in India have reported the arm and shoulder morbidity treated in their hospital. **Aims:** The study aims to evaluate the predictive factors of arm and shoulder morbidity and fatigue among the survivors. **Settings and Design:** Retrospective analysis from a prospectively maintained database. **Materials and Methods:** Early and locally advanced cases of breast cancer patients were screened for the study during 2015–2018. Eligible participants were invited to fill up the predetermined questionnaire and their demographic and treatment-related information was accrued from a file archive. Follow-up period was estimated from the date of tissue diagnosis to last contact/time of interview. **Statistical Analysis Used:** Predictive factors of shoulder morbidity and fatigue were analyzed by independent sample *t*-test and univariate analysis. Significant predictive factors were selected for further validation in the multivariate cox regression model. A $P \leq 0.05$ was considered significant. **Results:** Shoulder stiffness was the most common complaint followed by arm numbness. Obesity and diabetes played a crucial role in most of the morbidities and fatigue. The median fatigue score was 34 and the median time of appearance of lymphedema was 13 months. Modified radical mastectomy, and radiotherapy to axilla were significantly associated with greater shoulder stiffness and arm swelling. **Conclusions:** Obesity, diabetes, type of surgery, the extent of axillary dissection, and radiation plan are the major predictive factors of arm and shoulder morbidity. Further prospective validation is necessary for future breast cancer survivorship programs.

Keywords: Breast cancer, patient-reported outcome, shoulder morbidity, survivorship

Introduction

Breast cancer is the most frequently diagnosed cancer in women across the globe. India has registered a staggering number of 1,62,468 new cases with an annual mortality of 12.11% in 2018.^[1] The multimodality treatment approach in the form of surgery, chemotherapy, and radiotherapy revolves around the core management of early to locally advanced breast carcinoma. Although these treatments have improved clinical outcomes, they have been associated with substantial adverse effects. These treatment strategies are associated with many short and long term complications such as shoulder pain, decreased range of motion, lymphedema, numbness, and fatigue.^[2-4] Shoulder morbidities can appear at varied times after surgery and may persist in the long run.^[5,6] Lymphedema, a sequela of breast

cancer disease as well as its management, changes patient's functional abilities, and psychosocial health as a constant reminder of the suffering. Breast cancer-related lymphedema occurs as a consequence of various risk factors such as the number of axillary lymph node excised, regional nodal irradiation, obesity, decreased compliance to physiotherapy and exercise but a clear consensus on its exact etiology is still lacking and likely to be multifactorial.^[7] Although the incidence of lymphedema has decreased from 63% to 16% in the last three decades, it continues to be a major complication even with the most advanced treatments.^[8,9] Various population-based registries have documented their findings regarding breast cancer-related lymphedema; most of them are retrospective in design with contradictory findings. In general, lymphedema appears within the first 2 years of treatment (surgery and

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**Bidyut Mandal,
Annesha Sen,
Shinjini
Chakrabarty,
Bhukya Swetha,
Janmenjoy Mondal,
Abhishek Basu,
Debjit Ghosh,
Subhendu
Gangopadhyay**

Department of Radiotherapy,
Medical College & Hospital
Kolkata, Kolkata, West Bengal,
India

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Address for correspondence:
Dr. Debjit Ghosh,
Medical College & Hospital
Kolkata, Kolkata, West Bengal,
India.
E-mail: debjitghosh15@gmail.
com

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adjuvant radiotherapy) with an average duration of 14 months.^[10]

Cancer-related fatigue, on the other hand is frequently experienced by the survivors in the form of weakness, insomnia, and depression thus posing a major threat to the quality of life.^[11] The remarkable survival benefit in the past few years has also thrown a pertinent question regarding the quality of life among breast cancer survivors. Indian data on shoulder morbidity among breast cancer survivors are not very encouraging. This study aimed to elucidate the predictive factors of shoulder morbidity and fatigue and its association with the clinical outcome in a tertiary academic cancer hospital in India.

Materials and Methods

Breast cancer survivors, attending their routine follow-up visits at radiotherapy outpatient department (OPD) of our hospital were requested to be included in this study. Participants were selected as per predefined inclusion and exclusion criteria (see below) between January 2015 and December 2018 and traced till December 2019. Informed consent was taken in all cases before the collection of data after a thorough explanation of the study. Personal information was de-identified and each participant was allotted a study number.

Inclusion criteria

- Patients with histologically proven carcinoma breast of early and locally advanced stage based on AJCC 8th staging
- Female patients age between 18 and 65 years
- Adequate performance status (Karnofsky performance status >60)
- Provision of informed consent.

Exclusion criteria

- Known case of rheumatoid arthritis, cervical spondylitis, or any previous history of shoulder injury or pathology
- Prior chemotherapy, radiotherapy, or surgery for this or any other malignancy
- Current or previous history of reconstructed breast surgery.

Participants were asked to complete the predetermined questionnaire in their language. Patient's caregivers aided them if needed and a nonmedical staff was kept in standby. The questionnaire focused on symptoms of shoulder morbidity such as pain, numbness, and decreased range of motion in simple terms in three languages (English, Hindi, and Bengali). The questionnaire was inspired by the Australian Breast Cancer Family Study^[11] and fatigue was assessed by interviewing with the FACIT Fatigue Scale (Version 4).^[12] Symptoms appeared with in the first 6 months from surgery were excluded to avoid confounding and to gauge the long term burden. The assessment of arm swelling/edema was also examined

by careful visual inspection of both hands, forearms, and upper arms with the arms down, abducted 90° and elevated above the head.

Baseline demographic characteristics and treatment-related data including tumor size, TNM stage (AJCC 8th), tumor grade, type of surgery, status of axillary clearance, nodal yield (ratio of number of positive nodes to total no of nodes removed), status of neo-adjuvant and/or adjuvant chemotherapy, and field, as well as dose fractionation schedules of radiotherapy, were retrospectively collected from a prospectively maintained database. Patients of breast cancer were encouraged to pursue physical exercises and physiotherapy through thorough referral to Physical Medicine and Rehabilitation (PMR) department as a routine institutional protocol and their compliance to such advices were also noted from file archives. Follow-up period was defined from the date of histopathologic diagnosis to the date of last contact or death. Response assessment was done as per RECIST criteria (version 1.1) based on the data from the file archives.

Statistical considerations and data analysis

Five hundred and sixty consecutive patients of breast cancer, registered during the study period were screened and only 364 patients were invited based on inclusion/exclusion criteria. Fourteen patients turned down the invitation and eight responses were incomplete, so finally 342 patients' self-reported responses were accrued for final analysis. Demographic and clinical data were analyzed by descriptive statistics, where categorical variables were reported in frequencies and percentages and numerical variables were described by the mean and standard deviation. Predictive factors of shoulder morbidity and fatigue were analyzed by independent sample *t*-test and Univariate analysis. Significant predictive factors were selected for further validation in the Multivariate cox regression model. In the Cox regression analysis, hazard ratios (HR) and 95% confidence intervals were calculated to summarize the effect of each factor on fatigue and disability outcomes. Cox regression model is a method for investigating the effect of several variables upon the time a specified event takes to happen. If the HR is < 1, the factor is protective; if it is more than 1 then the factor is associated with increased risk or decreased survival. Age, body mass index (BMI), and treatment related factors (like type of surgery, radiation field etc.) were adjusted covariates because they were fixed for a patient, not changed over time. Outcome variables like shoulder stiffness, arm pain/swelling, numbness and fatigue were time dependent variable. Participants who did not develop the symptoms under study at the end of their follow up were censored. Survival analysis was done by the Kaplan–Meier test along with a log-rank test for comparison between groups. A *P* < 0.05 was considered statistically significant. All the statistical analysis was done using IBM SPSS Statistics for Windows, Version 23.0. (2015, Armonk, NY: IBM Corp.).

Results

With a median follow-up of 37 months, the median age of the participants was 47 years. Stage II and III cases predominated as per inclusion criteria; other baseline demographic and clinical characteristics were comparable in the participants [Table 1]. The median diagnostic delay (appearance of symptoms to tissue diagnosis) was 8 months. We observed that 9.2% of patients underwent wide local excision, 33.2% BCS (breast-conserving surgery + axillary clearance) and 57.6% modified radical mastectomy (MRM) [Table 2]. Adequate axillary dissection (more than 10 lymph node removed) was noted in 53.5% cases while 1% of them were associated with extra capsular extension. The study also revealed that 85.4% and 81.9% of patients received chemotherapy and radiotherapy respectively. The median external beam radiotherapy dose was 50 Gy and the majority of the cases (92%) were treated with two-dimensional radiotherapy by a Telecobalt machine (780C Theratron). Only 15.5% of patients received tumor boost radiation as per indication. Association of shoulder morbidity and fatigue with the predictive factors is depicted in Tables 2 and 3. We have noticed that 91.35% survivors attended PMR OPD for consultation, among them 76.27% had revisited after initial referral and 27.45% participants required assisted physiotherapy for more arm swelling, arm, and shoulder pain.

Shoulder stiffness

Two hundred and eighteen (63.7%) participants reported shoulder stiffness anytime during 6 months after diagnosis till the time of evaluation. Among them 117 (34.2%) patients reported stiffness during radiotherapy and 93 (27.2%) patients reported severe stiffness in any of the period. On physical examination, 60 (18.4%) patients had a noticeable decrease in range of motion and still complained of shoulder stiffness even after the best possible exercise on the treated side. We noticed that high BMI ($P = 0.01$), diabetes ($P = 0.01$), and patients who underwent MRM ($P < 0.01$) and axillary radiation (10% more) were more prone to develop the ipsilateral shoulder stiffness [Table 2]. There was no significant association with radiotherapy dose fractionation and extent of axillary clearance.

Arm swelling

The assessment of arm swelling/edema was examined by careful visual inspection of hands, forearms, and upper arms with the arms down, abducted 90°, and elevated above the head. This study found that 144 (42.1%) patients reported arm swelling (ipsilateral) anytime during 6 months after diagnosis till now. The median time of development of lymphedema was 13 months. We noted that 11% of the sufferers had reported severe disability while 64.5% of patients had very little impact on carrying out the daily

Table 1: Participant's demographic and clinical characteristics

Variable	Number of participants	Percentage (median)
Age (years)		
<40	167	48.83 (47 years)
>40	175	51.17
Residence (urban/semi-urban/rural)	133/143/66	38.9/41.8/19.30
Education (primary/secondary/hs/graduate)	171/80/54/37	50/23.4/15.8/10.8
Comorbidity		
Diabetes mellitus	87	25.4
Hypertension	129	37.7
Missing	126	36.9
Parity (nulliparous/parous)	46/296	13.45/86.54
BMI (kg/m ²)		
<18.5	47	13.74 (26.50)
18.5- 24.9	85	24.85
25- 29.9	97	28.36
≥30	110	32.16
Affected side		
Right	158	46.2
Left	184	53.8
Tumor Grade (1/2/3)	32/198/112	9.4/57.9/32.7
Stage (I/II/III)	31/115/196	9.0/33.6/57.3
Molecular subtype (luminal A/luminal B/Her2+/TNBC)	124/98/75/45	36.3/27.7/23.8/12.2
Nodal status at diagnosis (clinicopathological)		
Node positive	286	83.62
Node negative	50	14.61
Missing value	6	1.75

BMI: Body mass index

Table 2: Prognostic factors of arm and shoulder morbidity among survivors

Variables (percentage of case) (n=342)	Count (P)			
	Shoulder stiffness	Arm swelling	Arm numbness	Arm pain
Age group (years)				
<40 (48.8)	112 (P=0.3)	68 (P=0.7)	94 (P=0.4)	68 (P=0.6)
>40 (51.2)	106	76	114	70
Time of appearance				
6 months- 1 year	35	56	26	22
1- 2 year	82	79	72	60
>2 year	101 (P=0.4)	9 (P=0.6)	110 (P=0.7)	56 (P=0.2)
Diabetes mellitus (25.4) n=86	67 (P<0.05)	34 (P<0.05)	80 (P<0.05)	28 (P<0.05)
BMI				
18.5- 24.9	90	69	100	77
25 or more	128 (P=0.04)	75 (P=0.06)	108 (P=0.7)	61 (P=0.4)
Type of surgery				
WLE (9.2)	21	12	23	8
BCS + ALND (33.2)	89	48	68	63
MRM (57.6)	108 (P=0.04)	84 (P=0.01)	117 (P=0.05)	67 (P=0.04)
Radiotherapy fields				
2 (CW) (33.6)	78	34	96	64
3 (CW + SCV + Axilla) (48.3)	140 (P=0.01)	110 (P=0.01)	112 (P=0.05)	74 (P=0.06)
Radiotherapy dose fractionation				
Conventional (52.3)	149	74	128	70
Hypo fractionation (29.6)	69 (P=0.02)	70 (P=0.06)	80 (P=0.08)	68 (P=0.06)
Chemotherapy				
Neo-adjuvant (36.4)	101	66	86	77
Adjuvant* (72.2)	117 (P=0.6)	78 (P=0.3)	122 (P=0.3)	61 (P=0.4)
Missing value (14.6)				
Additional adjuvant therapy				
Hormone (64)	166	83	148	84
Trastuzumab (20.1)	52 (P=0.03)	61 (P=0.06)	60 (P=0.07)	54 (P=0.08)

*Adjuvant cases also include some cases who received neo-adjuvant chemo also. Univariate analysis test was used. CW: Chest wall, SCV: Supraclavicular, WLE: Wide local excision, BCS: Breast conservation surgery, ALND: Axillary nodal dissection, MRM: Modified radical mastectomy, BMI: Body mass index

activity [Table 4]. MRM ($P = 0.03$), axillary radiation ($P = 0.01$), and a greater number of nodal dissection ($P = 0.01$) were associated with significant lymphedema [Tables 2 and 3].

Numbness of arm

Two hundred and eight (60.8%) patients reported numbness anytime during 6 months after diagnosis till now. Among them 126 (60.57%) patients reported numbness during radiotherapy and 82 (39.42%) patients still complained of numbness. Only 15.5% of the sufferers had complained about significant disability [Table 4]. Diabetes mellitus ($P = 0.02$) and type of surgery (0.01) were noted predictive factors of arm numbness.

Pain/ache in arm

One hundred and thirty-eight participants had reported pain in arm and 27.7% of them complained moderate to severe pain. The majority of them have developed the symptoms at least a year after the diagnosis. Diabetes mellitus and type of surgery had registered increasing risk for developing the morbidity

($P < 0.05$). Hypo-fractionated radiotherapy was associated with a 36% lower risk of developing pain in arm but was not statistically significant [Table 3]. Multivariate analysis turned down such correlations barring diabetes mellitus.

Fatigue

Assessed by FACIT Fatigue Scale (Version 4). It was assessed by one to one interview basis. Score lies b/w 0–52 theoretically. The median fatigue score is 34 (14–42 in our study). Independent sample *t*-test revealed that fatigue in survivors was correlated with high BMI, diabetes, and multiple lines of adjuvant therapy. On multivariate cox regression analysis, there was trend of high fatigue score was with high BMI, diabetes, and type of surgery but none was statistically significant.

Tumor stage, tumor grade, molecular subtype, diagnostic delay, age and laterality (right/left) were neither associated with shoulder morbidity nor fatigue in our study population.

Kaplan–Meier survival analysis had shown that the study population had a 3-year disease-free survival (DFS) of

Table 3: Cox regression analysis of the covariates

Variables	HR (95% CI)				
	Shoulder Stiffness	Arm swelling	Arm numbness	Pain in arm	Fatigue
BMI	1.42 (1.6- 2.4)	0.81 (0.5- 2.2)	0.88 (0.5- 2.1)	0.92 (0.4- 1.6)	1.52 (0.4- 2.1)
Diabetes mellitus	1.14 (1.2- 2.7)	0.91 (0.5- 2.6)	1.70 (1.3- 3.2)	1.19 (1.3- 2.5)	1.81 (0.9- 2.2)
Type of Surgery	1.8 (1.1- 3.4)	1.31 (1.8- 3.3)	1.24 (1.6- 3.7)	0.78 (0.6- 1.5)	1.21 (0.4- 1.7)
Radiotherapy dose fractionation	0.91 (0.4- 1.8)	1.0 (0.4- 2.1)	0.81 (0.4- 2.1)	0.64 (0.5- 1.1)	1.02 (0.4- 1.3)
Field of radiotherapy	1.1 (1.5- 2.6)	1.27 (1.3- 2.1)	0.64 (0.4- 1.9)	1.17 (0.6- 1.8)	0.97 (0.6- 1.5)
Additional adjuvant therapy	0.97 (0.4- 2.1)	0.91 (0.5- 1.9)	0.89 (0.6- 1.3)	0.79 (0.5- 1.1)	0.92 (0.6- 1.1)
>10 ALND	1.21 (0.4- 3.3)	1.95 (1.2- 3.8)	1.21 (0.5- 1.9)	1.25 (0.6- 1.8)	0.99 (0.5- 1.3)

HR: Hazard ratio, ALND: Axillary nodal dissection, CI: Confidence interval, BMI: Body mass index

Table 4: Prevalence of severity of symptoms (%) among the participants

	Not at all/very little	Quite a lot	A great deal
Shoulder stiffness (n=218)	72.8	20	7.2
Arm swelling (n=144)	64.5	24.5	11
Arm numbness (n=208)	84.5	10.8	4.7
Arm pain (n=138)	72.3	21.3	6.4

78%. The median DFS has not achieved yet, stage III cases had the lowest DFS of 72.4% as compared to stage II (83.1%) and stage I (100%) [Figure 1].

Discussion

This study reports on breast cancer survivors in a state-sponsored tertiary cancer hospital in eastern India. We observed that shoulder morbidity was the most common reported complaint followed by arm numbness and arm swelling and pain. We noted that obesity and diabetes mellitus were significantly associated with shoulder morbidity, arm pain, and numbness and fatigue. This observation was well supported by the published literature.^[11,13] Although it was not clear whether obesity *per se* or its associated co-morbidities (diabetes, hypertension) reflected such association. This study found that lymphedema (a surrogate for arm swelling) was slightly on the higher side than the previously reported European studies.^[14,15] This discrepancy can be explained in terms of racial heterogeneity, compliance to physical exercise, and level of documentation in the patient records. Moreover, the degree of disability and time of appearance was varied among the survivors. Type of surgery, the extent of nodal dissection and axillary radiation were significant covariates of arm swelling in our study. It should be kept in mind that we also incorporated the data from the patient's file with self-reported outcomes and thus avoided the inconsistent reports regarding the predictive factors of lymphedema.^[11,13,16] It is noteworthy that a patient can't understand the field of radiotherapy or the type of

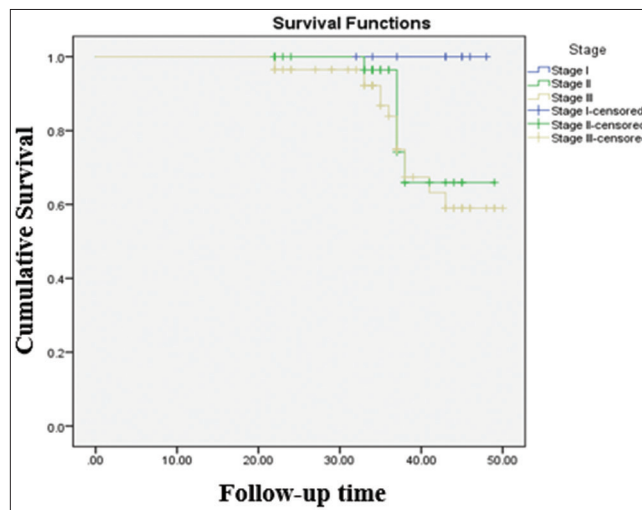


Figure 1: Disease-free survival (stage wise) of the survivors. Log rank value $P = 0.14$

surgery, hence over-reliance on self-reported outcomes could lead us to a confusing conclusion.

Age was not associated with shoulder and arm morbidity though there is some evidence that older age is more prone to reduced shoulder movement,^[17,18] Arm numbness was the second most commonly reported outcome (60.5%) and the majority of the survivors have experienced it during or after radiotherapy. Pain in the arm also followed a similar trend. Compromise of the intercostobrachial nerve during axillary dissection and nociceptive role of radiotherapy could explain the trend in accord with the evidences.^[19,20] Although whether radiotherapy could cause neurogenic pain is debatable and still under considerable doubt. Consistent with the previous reports pain in the arm was correlated with axillary nodal dissection, a greater number of lymph nodes dissected, and radiotherapy to the axilla.^[21,22] However, it is important to note that Kudel *et al.*, 2007^[23] and Miaskowski *et al.*, 2012^[24] have suggested that persistent pain in arm or shoulder is associated with preoperative breast pain. We did not explore this point at the time of evaluation; hence we could not share our thoughts on it. There has been data to suggest that lesser education and lower economic background considerably impact chronic pain.^[25,26] Our

data could not establish such association and was in the line of evidence suggested by Kudel *et al.*, in 2007 and Poleshuck *et al.*, in 2006.^[27] State-sponsored medication (free of cost) and other economic packages could explain such results in our study cohort.

Laterality (side affected) was not a significant factor of pain in our study unlike others,^[28] where it has been hypothesized that the right hemisphere is dominant in processing emotional experience, suggesting a possible link between the right hemisphere and the emotional component of pain processing.

The impact of physical exercise on pain management could not be analyzed as a majority of the participants did not document their response regarding it. However, from the data (physician's note in file archive) in hand, we conclude that the participation and compliance to physical exercise is satisfactory. A prospective evaluation could have avoided this scenario. It is also noteworthy that we didn't have a conclusive idea on pain management of the survivors and their association with peripheral inserted central catheter or central venous port.

The majority of the patients have received taxane-based chemotherapy and it was noted that subsequent lines of chemotherapy (in cases of recurrences) aggravated arm pain. Multiple intravenous cannulation, repeated biopsy, and anxiety could explain this, but the association was not significant ($P = 0.06$) hence was not included in the primary analysis. We admit that a better study design could nullify such errors and we will keep this in mind. Along with obesity and diabetes, shoulder stiffness, pain in arm, and type of surgery were significantly associated with fatigue.

Several study limitations need to be acknowledged. Though the sample size was representative of the Indian scenario, retrospective design was a noted caveat. Participants had to recall their symptoms so a possibility of bias could not be negated. The assessment of preoperative breast pain, number of breast biopsies, compliance to physiotherapy and physical exercise could not be explored in detail even with our best efforts. We did not measure arm circumference and had to rely on the patient's perception of arm swelling. Having that said we believe that our data is robust and possibly the only one which reports shoulder morbidity along with fatigue in the breast cancer survivors from India in recent times. This observation is important as it gauges the nuances of the treatment approach and its impact on quality of life among women of different socioeconomic backgrounds.

Conclusion

We conclude that obesity, diabetes, type of surgery, the extent of axillary dissection, and radiation plan are the major predictive factors of arm and shoulder morbidity. Further prospective validation is necessary for future breast cancer survivorship programs.

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Conflicts of interest

There are no conflicts of interest.

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