RESEARCH ARTICLE

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# Prospective Study of Incidence and Impact of Comorbidities on Breast Cancer Survival from India

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## Abstract

**Purpose:** To report comorbidity burden in newly-diagnosed treatment-naïve breast cancer patients and its effect on survival. **Methods:** Prospective observational study in which demographic, comorbidity and outcome data from a consecutive cohort of patients diagnosed and treated between September 2019 to September 2021 were collected. Charlson Comorbidity Index (CCI) score was calculated for all and proportion of each comorbidity was determined at diagnosis (baseline), at conclusion and six-months post-treatment. Univariate and multivariate analysis was done for impact of various demographic and disease-related factors on the incidence of comorbidities as well as on progression free survival (PFS) and overall survival (OS). **Results:** Out of five hundred patients who consented for the study, 416 patients completed planned treatment and only 206 patients had physical follow-up due to COVID-19 pandemic. Incidence of comorbidity at the three time-points was 24%, 32% and 26% respectively. The difference was significant compared to baseline at both the time-points ($p<0.05$). Hypertension and diabetes were the most common types (incidence 15%-21% and 12-18% respectively) of comorbidities. Advancing age, post-menopauusal status and not being married were significant factors for presence of comorbidities. Median follow-up was 27 months (95% CI 26.25-28.55 months). Presence of multiple comorbidities was a poor prognostic factor for both PFS (2-yr PFS 85% vs 77%) and OS (2-yr OS 89% vs 79%) (both $p=0.04$) but no such correlation for CCI score. **Conclusion:** Breast cancer treatment impacted incidence of comorbidities. Presence of multiple comorbidities had an adverse impact on survival. Hence, further research on treatment optimization is required in patients with substantial comorbidities.

**Keywords:** Incidence of comorbidities- charlson comorbidity index- survival- breast cancer

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## Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide. Approximately 60% of women with breast cancer are aged 65 years and above (Lacey et al., 2002). With increasing age, the risk of developing cancer increases and so is the risk of other comorbid illnesses. Comorbidity is defined as simultaneous presence of medical conditions other than disease of interest. It may have been present before or diagnosed at the time of present illness (Last, 2001).

Breast cancer is a multifactorial disease, common risk factors being hyper estrogen state- early menarche, late menopause, delayed age of first pregnancy, previous histories of breast biopsies (atypical hyperplasia), family history of breast/ovarian cancers (Momenimovahed and Salehiniya, 2019). Incidence of breast cancer in India is on a rising trend, owing to lifestyle changes which can also impact the prevalence of comorbidities like obesity, hypertension, diabetes mellitus and cardiac illnesses (Mehrotra and Yadav, 2022). However, comorbidity pattern in India is still different from western countries where metabolic syndrome is predominant. India still faces problems of socioeconomic deprivation and thus a greater burden of comorbidities like chronic obstructive pulmonary disease (COPD)/asthma, cardiovascular and chronic kidney diseases, besides hypertension/diabetes (Singh and Misra, 2020).

Treatment of cancer is decided based on age, performance status (ability to carry out activities of daily living without/with assistance), presence of comorbidities and stage of the disease. Presence of comorbidities impairs the performance status of a patient and negatively impacts survival of cancer patients. This is primarily due

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to poor tolerability, or treatment related toxicity resulting in reduced intensity of treatment (Cronin-Fenton et al., 2007). There is lack of randomized data in this regard as patients with high burden of comorbidities are often excluded from clinical trial participation.

The aim of this study is to describe the incidence of comorbidities in a prospective cohort of patients diagnosed with breast cancer in a tertiary care oncology center in India and to study its impact on survival.

## Materials and Methods

Histologically confirmed new cases of breast cancer prospectively evaluated in the breast clinic at Tata Memorial Hospital (TMH) from September 2019 to September 2021 were included in the study. This manuscript reports one of the secondary endpoints of a larger study that primarily collected data on expenditure for breast cancer treatment. This prospective observational study was approved from the Institutional Review Board (IRB) at TMH and was also registered in clinical trial registry of India [CTRI/2019/07/020142].

All patients underwent clinical assessment and radiological studies were done at baseline as per stage of cancer at presentation. Clinical staging and stage grouping were done using tumor node metastasis (TNM) [Union for International Cancer Control-American Joint Committee on Cancer (UICC-AJCC) staging] 8th edition classification. All patients underwent cancer-directed therapy as per stage along with management of comorbidities. Patients received multimodality treatment comprising surgery +/-chemotherapy +/-radiotherapy with endocrine or targeted therapy as per stage and institutional protocols. For patients with oligo-metastatic disease, curative treatment was delivered if all the metastatic sites could be safely treated. Surgery entailed either breast conserving surgery (BCS) or mastectomy. Chemotherapy drugs used were a combination of adriamycin, cyclophosphamide, 5-flourouracil, methotheraxte and/or taxanes. Radiotherapy was given using a hypofractionated regimen with appropriate portals covering the whole breast/chest wall and regional nodal regions (supraclavicular +/- internal mammary nodes).

Prior history (before diagnosis of cancer) of comorbidities were ascertained from all patients and/or caregivers at the time of initial evaluation, at treatment conclusion and at first follow up (6 months post conclusion). Comorbidity scores were calculated using the Charlson Comorbidity Index (CCI) for all the three time points (Hall et al., 2004). A total of 500 patients were accrued in whom all baseline information was captured. However, 84 patients (16.8%) were excluded as they defaulted within 4-6 weeks of presentation majorly due to COVID pandemic. Hence, the treatment conclusion data is available for 416 patients (83%) and the first follow-up data were available for 206 patients (41%) who reported physically to the institute for clinical evaluation. The high drop out at first follow up was also primarily due to COVID pandemic as patients were discouraged to come for hospital visit and avail teleconsultation facility.

*Statistical analysis*

Patient demographics, disease characteristics and treatment profiles were represented as frequencies and percentages. Types of comorbidities were grouped into cardio-vascular, metabolic, neurological, pulmonary, gastro-intestinal, renal, hematological (malignant/ non-malignant), other solid tumours, psychological issues, musculoskeletal/ connective diseases and/or AIDS as specified in the CCI score. Distributions of comorbidities at baseline, at treatment completion and at 6-month follow-up was analyzed. Univariate and multivariate analysis for factors such as age, menopausal status, marital status, education, financial dependency, type of family was done to study the association with the presence of comorbidities and CCI score. Logistic regression analysis was used to examine predictors associated with the presence of comorbidity or CCI >=1.

Progression free survival (PFS) and overall survival (OS) was calculated using Kaplan Meier method. Events considered for PFS were any local/locoregional/ distant recurrence or contralateral/second primary whereas for OS events considered was death from any cause. Univariate and multivariate analysis was done for factors associated with worse PFS and OS using the time to event analysis in SPSS version 24.

## Results

Five hundred consecutive patients diagnosed with non-metastatic or oligo-metastatic breast cancer over two years from September 2019 to September 2021 and treated at our center were included in the study. The median age of patients was 46 years (IQR 39- 55 years). An equal number of women were premenopausal and peri/postmenopausal. One quarter of patients were illiterate and half of them were educated only up to secondary level. Overwhelming majority (85%) of the women were financially dependent and currently married (84%) The demographic details of patients are described in detail in Table 1. Sixty one percent of patients were diagnosed with stage III disease (61%) followed by stage II (34%). Majority of patients (79%) had grade 3 invasive breast carcinoma, 56% were hormonal positive and 34% patients were Her2 neu positive. Of the total, 274 (53%) of patients had an MRM while 147 (30%) had BCS as primary surgery. Disease and treatment characteristics are detailed in Table 2.

Regarding the distribution of comorbidities, 378/500 (76%) patients had no comorbidities at baseline, while 122 (24%) had 1 or more comorbidities. At the time of conclusion of treatment, out of 416 patients who completed treatment, 133 (32%) were found to have 1 or more comorbidities. Of the 206 patients who came for physical follow up after 6 months, 153 (74%) had no comorbidities and 53 (26%) patients had 1 or more comorbidities. The incidence of comorbidities is described in Table 3a. The temporal difference compared to baseline for both the time points was statistically significant. Diabetes mellitus (DM) and hypertension (HT) were the most prevalent comorbidities seen at all-time points, followed asthma and neurological/psychiatric ailments. Patterns of comorbidities at the three time-points seen

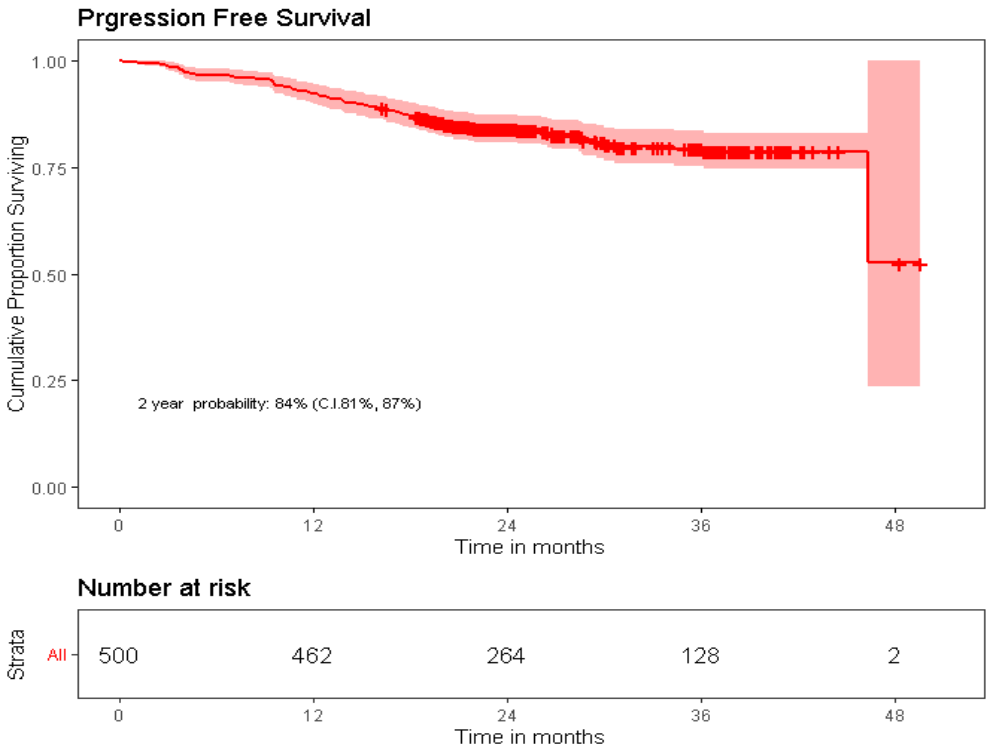


Figure 1. Progression Free Survival (PFS) in whole Cohort of Patients

Table 1. Demographic Details of Patients

| Characteristics | Frequency | Percentages |
|---|---|---|
| Age | Median 46 years | |
| Menopausal status | | |
| Premenopausal | 254 | 50.8 |
| Peri-menopausal | 23 | 4.6 |
| Postmenopausal | 215 | 43.0 |
| Not known | 8 | 1.6 |
| Education level | | |
| Illiterate | 133 | 26.6 |
| Primary/ Secondary | 233 | 46.6 |
| Higher Secondary | 54 | 10.8 |
| Graduate | 61 | 12.2 |
| Post-Graduate | 19 | 3.8 |
| Financial dependency | | |
| Yes | 425 | 85.0 |
| No | 75 | 15.0 |
| Marital status | | |
| Never married | 13 | 2.6 |
| Currently married | 421 | 84.2 |
| Widow | 61 | 12.2 |
| Divorced/ Separated | 5 | 1.0 |
| Type of Family | | |
| Living alone | 8 | 1.6 |
| Spouse only | 15 | 3.0 |
| Spouse & children | 245 | 49.0 |
| Children only | 20 | 4.0 |
| Extended | 212 | 42.4 |

among patients are described in detail in Table 3b. The incidence of both HT and DM increased at conclusion as well as at 6 months and the difference was statistically

Table 2. Disease Characteristics of Patients

| Variables | Frequency | Percentages |
|---|---|---|
| Stage | | |
| I-II | 168 | 34.0 |
| III | 304 | 61.0 |
| IV | 28 | 5.0 |
| Grade | | |
| 1-2 | 25 | 5.0 |
| 3 | 395 | 79.0 |
| Not known | 80 | 16.0 |
| Hormonal status | | |
| Positive | 280 | 56.0 |
| Negative | 220 | 44.0 |
| Her 2 neu status | | |
| Positive | 170 | 34.0 |
| Negative | 330 | 66.0 |
| Type of surgery | | |
| BCS | 150 | 30.0 |
| MRM | 266 | 53.2 |
| Not available (NA) | 84 | 16.8 |
| Type of chemotherapy | | |
| Anthracyclines | 292 | 58.4 |
| Taxanes | 110 | 22.0 |
| Both | 6 | 1.2 |
| Others | 8 | 1.6 |
| NA | 84 | 16.8 |
| Radiotherapy | | |
| Yes | 373 | 74.6 |
| No | 43 | 8.6 |
| NA | 84 | 16.8 |

BCS, Breast conserving surgery; MRM, Modified radical mastectomy

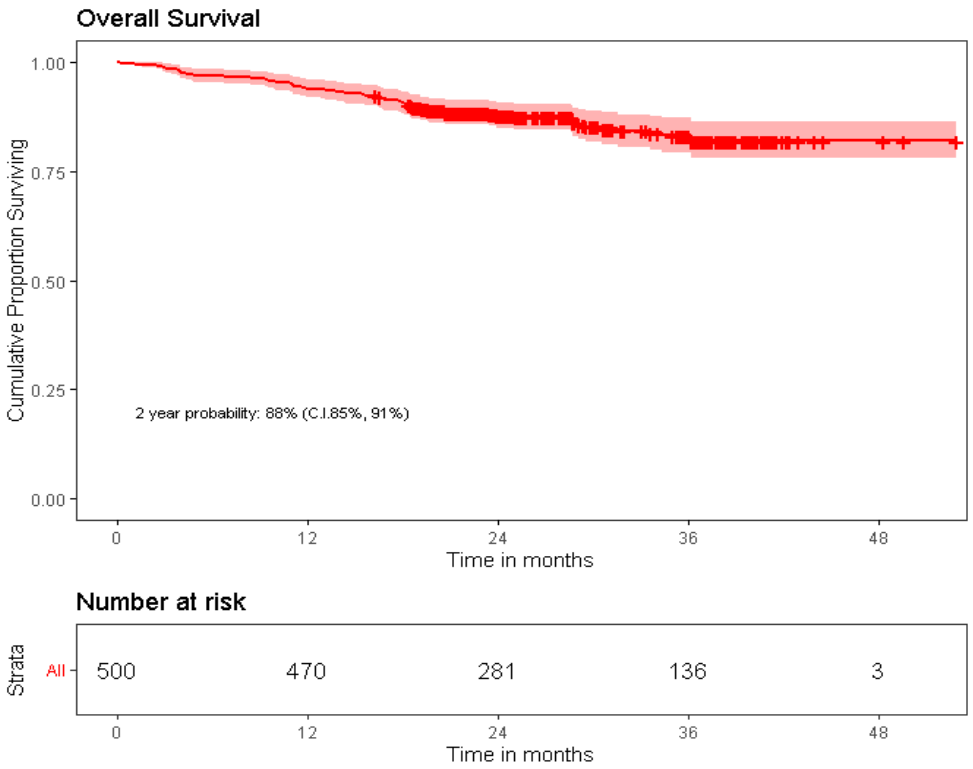


Figure 2. PFS in Patients with <2 and >=2 Comorbidities

Table 3a. Incidence of Comorbidities and Presence of Multiple Comorbidities at Different Time Points

| Comorbidities present | At baseline (N=500) | At conclusion of treatment (N=416)P<0.001 | | At 6th month follow up (N=206)P=0.017 | |
|---|---|---|---|---|---|
| Nil | 378 (75.6) | 283 (68) | | 153 (74) | |
| Present | 122 (24.4) | 133 (32) * | [p=0.02] | 53 (26) * | [p=0.01] |
| One | 83 (17) | 94 (23) | | 37 (18) | |
| Two | 37 (7.4) | 38 (9.1) | | 16 (7.8) | |
| Three | 1 (0.2) | 1 (0.2) | | 0 (0) | |
| > Three | 1 (0.2) | 0 (0) | | 0 (0) | |

*P value <0.05 (compared to baseline); number in parenthesis denotes percentages out of total patients mentioned N in each column.

significant. The proportion of patients with different CCI scores is shown in Supplementary Table 1. The median CCI score was 1 (range 0-5) at all time points.

Of the 122 patients with comorbidities at diagnosis, all had an indication for adjuvant chemotherapy. However, 25 patients (20.4%) were not offered standard chemotherapy due to anticipation of poor tolerability and toxicity (13 patients' anthracycline was omitted due to cardiac ailments, in 4 taxanes was omitted due to uncontrolled diabetes and neuropathy and remaining 8 patients both were omitted). Such variations in surgery and radiotherapy was not observed.

On univariate analysis, age above 60 years, postmenopausal and marital (widow/separated) status were significantly associated with presence of any comorbidities at baseline (Table 4a). For CCI score of 1 or more than 1, postmenopausal status, marital (widow/separated) status and higher education were significant factors on univariate analysis (Table 4b). On multivariate analysis, only postmenopausal and marital (widow/separated) status were statistically significant for both the variables (Table 5a and 5b). At a median follow-up of 27

Table 3b. Patterns of Different Types of Comorbidities Present at Baseline, Conclusion and 6 Months

| Type of comorbidities | At baseline (N=122) | At conclusion (N=133) | | At 6th month (N=53) | |
|---|---|---|---|---|---|
| Hypertension | 66 (54.1) | 75 (56.4) * | p=0.04 | 30 (56.6) * | p=0.04 |
| Diabetes | 33 (27.1) | 49 (36.8) * | p=0.02 | 21(39.6) * | p=0.02 |
| Asthma | 7 (5.7) | 1 (0.8) | | 1 (1.9) | |
| Neurological/psychiatric problems | 6 (5.0) | 2(1.5) | | 0 (0.0) | |
| Hypercholesteremia | 3 (2.5) | 6 (4.5) | | 1 (1.9) | |
| Stroke | 2 (1.6) | 0 (0.0) | | 0 (0.0) | |
| Arthritis | 5 (4.0) | 0 (0.0) | | 0 (0.0) | |

* P value <0.05 (compared to baseline)

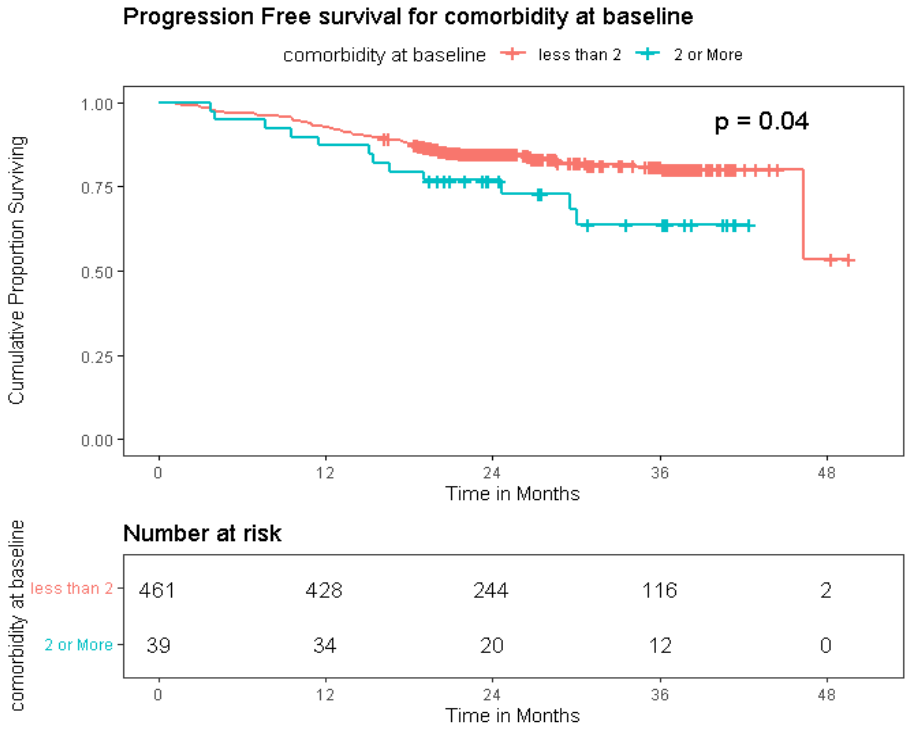


Figure 3. Overall Survival (OS) in whole Cohort of Patients

months (95% CI 26.25- 28.55 months), 91/416 (21.8%) patients had progression. Table 6 shows the details of the patterns of progression. Majority of the patients (81%) failed distantly, leading to cancer-related deaths in 67 patients. Another four patients died due to other causes.

On univariate analysis as well as on multivariate analysis; factors like advanced T stage (T3-T4), nodal stage (N2-N3), metastatic stage and presence of two or more comorbidities were significantly associated with worse PFS as well as OS (Supplementary Table 2a and 2b and Table 3a and 3b). Adjusting for age, even in patients aged <60 years, presence of >/=2 comorbidities were associated with worse OS; p=0.03 (Supplementary Figure 1). The 2-and 3-year progression free and overall survival for the entire cohort was 83.8%, 78.8% and 87.9% and 82.1% respectively (Figures 1 and 2). The 3-yr PFS and OS in patients with >/=2 comorbidities were (68.3% and 69.6%) compared to those with <2 comorbidities

Table 4a: Univariate Analysis for Presence of Any Comorbidities at Baseline

| Characteristic | N | Events | OR1 | 95% CI1 | p-value |
|---|---|---|---|---|---|
| Marital Status | | | | | |
| Currently Married | 421 | 89 | — | — | |
| Never Married | 13 | 1 | 0.31 | 0.02, 1.61 | 0.264 |
| Widow/Divorced/Separated | 66 | 32 | 3.51 | 2.05, 6.01 | <0.001 |
| Educational Level | | | | | |
| Illiterate | 132 | 36 | — | — | |
| Primary-Higher Secondary | 287 | 73 | 0.91 | 0.57, 1.46 | 0.691 |
| Graduate/Post Graduate | 80 | 13 | 0.52 | 0.25, 1.03 | 0.068 |
| Type of Family | | | | | |
| Alone/Spouse only | 22 | 9 | — | — | |
| Spouse and children | 245 | 56 | 0.43 | 0.18, 1.09 | 0.065 |
| Extended family or non-nuclear family | 212 | 50 | 0.45 | 0.18, 1.14 | 0.081 |
| Children/Others | 21 | 7 | 0.72 | 0.20, 2.50 | 0.608 |
| Menopausal Status | | | | | |
| Pre/Peri Menopausal | 277 | 40 | — | — | |
| Postmenopausal | 215 | 81 | 3.58 | 2.33, 5.57 | <0.001 |
| Age | | | | | |
| <60 | 449 | 95 | — | — | |
| >=60 | 51 | 27 | 4.19 | 2.31, 7.64 | <0.001 |

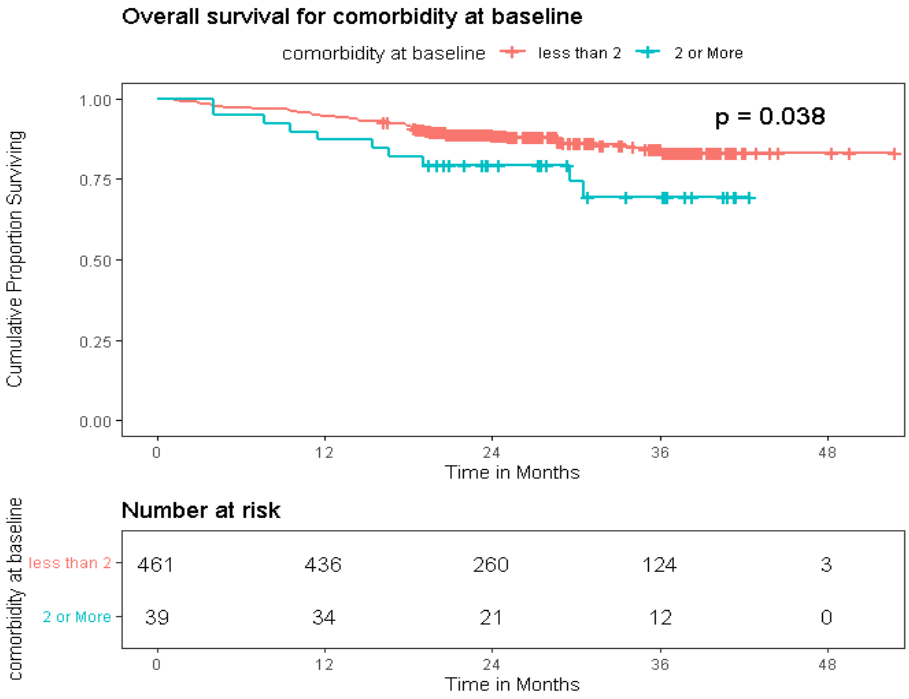


Figure 4. OS in Patients with <2 and >=2 Comorbidities

(80.2% and 83.2%), p 0.04 respectively (Figures 3, 4, 5).

## Discussion

Life expectancy in India has been on an increasing trend and so is cancer incidence with increasing age. Likewise, comorbidity increases with advancing age. Presence of comorbidities affects cancer treatment owing to decreased tolerability of treatment and increased risk of treatment related side effects. All these factors contribute to inferior survival among cancer patients with comorbidities (Søgaard et al., 2013). Moreover-a, breast cancer patients with comorbidities have less social support and more unmet needs thereby leading to poorer health related quality of life (Fu et al., 2015; Ho et al., 2018).

The most common comorbidity noted in our cohort

Table 4b. Factors Contributing to CCI>=1 at Time Point Baseline based on Univariable Model

| Characteristic | N | Event N | OR1 | 95% CI1 | p-value |
|---|---|---|---|---|---|
| Marital Status | | | | | |
| Currently Married | 421 | 172 | — | — | |
| Never Married | 13 | 8 | 2.32 | 0.76, 7.78 | 0.147 |
| Widow/Divorced/Separated | 66 | 53 | 5.90 | 3.21, 11.6 | <0.001 |
| Educational Level | | | | | |
| Illiterate | 132 | 84 | — | — | |
| Primary-Higher Secondary | 287 | 125 | 0.44 | 0.29, 0.67 | <0.001 |
| Graduate/Post Graduate | 80 | 24 | 0.24 | 0.13, 0.44 | <0.001 |
| Type of Family | | | | | |
| Alone/Spouse only | 22 | 16 | — | — | |
| Spouse and children | 245 | 98 | 0.25 | 0.09, 0.63 | 0.005 |
| Extended family or non-nuclear family | 212 | 106 | 0.38 | 0.13, 0.95 | 0.049 |
| Children/Others | 21 | 13 | 0.61 | 0.16, 2.19 | 0.451 |
| Menopausal Status | | | | | |
| Pre/Peri Menopausal | 277 | 55 | — | — | |
| Postmenopausal | 215 | 173 | 16.6 | 10.7, 26.3 | <0.001 |
| Age | | | | | |
| <60 | 449 | 182 | — | — | |
| >=60 | 51 | 51 | 62,414,642 | inf | 0.974 |

OR, Odds Ratio; CI, Confidence Interval

Table 5a. Factor Affecting Presence of any co-morbidity among Breast Cancer Patients at Baseline based on Multivariable Model

| Characteristic | N | Event N | OR1 | 95% CI1 | p- value |
|---|---|---|---|---|---|
| Marital Status | | | | | |
| Currently Married | 416 | 88 | — | — | |
| Never Married | 12 | 1 | 0.28 | 0.02, 1.56 | 0.238 |
| Widow/Divorced/Separated | 64 | 32 | 2.35 | 1.30, 4.21 | 0.004 |
| Menopausal Status | | | | | |
| Pre/Peri Menopausal | 277 | 40 | — | — | |
| Postmenopausal | 215 | 81 | 2.59 | 1.62, 4.19 | 0.000 |
| Age60 | | | | | |
| <60 | 443 | 94 | — | — | 0.019 |
| >=60 | 49 | 27 | 2.23 | 1.14,4.37 | |

OR, Odds Ratio; CI, Confidence Interval

Table 5b. Factors Correlating with Baseline CCI>=1 among Breast Cancer Patients at Baseline based on Multivariable Model

| Characteristic | N | Event N | OR1 | 95% CI1 | p-value |
|---|---|---|---|---|---|
| Marital Status | | | | | |
| Currently Married | 415 | 170 | — | — | |
| Never Married | 12 | 7 | 2.05 | 0.49, 8.77 | 0.328 |
| Widow/Divorced/Separated | 64 | 51 | 3.08 | 1.46, 6.81 | 0.004 |
| Educational Level | | | | | |
| Illiterate | 130 | 82 | — | — | |
| Primary-Higher Secondary | 282 | 122 | 0.62 | 0.36, 1.06 | 0.078 |
| Graduate/Post Graduate | 79 | 24 | 0.59 | 0.28, 1.23 | 0.165 |
| Menopausal Status | | | | | |
| Pre/Peri Menopausal | 276 | 55 | — | — | |
| Postmenopausal | 215 | 173 | 13.9 | 8.85, 22.3 | 0.000 |

OR, Odds Ratio; CI, Confidence Interval

were hypertension and diabetes (approximately 15-20%) which is in concurrence with other studies from India that report an incidence of around 20-25% (Sankranti et al., 2018; Sharma et al., 2016). Prevalence of comorbidities and compliance to treatment was analyzed in a cohort of breast cancer patients suffering from comorbidities (Sharma et al, 2016). Lower treatment compliance (88.5%) and planning of standard multimodality treatment (44.2%) was seen in patients with comorbidities. However, such a finding was not observed in our study as approximately one-fifth of the patients with and without comorbidity did not receive standard chemotherapy. They also reported a higher prevalence of COPD (20%) and rheumatologic disease (18.6%) besides hypertension/ diabetes mellitus. In our study, these were infrequently reported.

Table 6. Patterns of Progression- Total 91 Patients had Progression

| Patterns of progression | Frequency | Percentages |
|---|---|---|
| Distant metastasis alone | 74 | 81.3 |
| Locoregional+distant metastasis | 7 | 7.7 |
| Local site- I/L breast/CW | 2 | 2.2 |
| Locoregional | 2 | 2.2 |
| C/L breast/CW | 2 | 2.2 |
| Second primary cancer | 2 | 2.2 |
| C/L nodal region | 1 | 1.1 |
| Regional node+distant metastasis | 1 | 1.1 |

I/L, Ipsilateral; C/L, Contralateral; CW, Chest wall

The study from South India, assessed the incidence of HT, DM and dyslipidemia which was documented in 26%, 20.6% and 13.5% of breast cancer patients respectively (Sankranthi et al, 2018). In their cohort of 257 patients, 50% patients presented with operable breast cancer, 37% with locally advanced stage and 8% with de-novo metastatic disease. In our study, majority (61%) had locally advanced stage and a minority (5%) had presented with de-novo metastatic disease. The incidence of HT (15%), DM (12%) and dyslipidemia (0.6%) was also lower at baseline which increased to 21%, 18% and 1.4% respectively. Dyslipidemia is generally infrequently reported as it was not routine to ask for lipid profile for all patients at the time of initial evaluation. The above mentioned study did not analyze the impact of cancer treatment on the incidence of comorbidity nor did they show correlational analysis with survival. Another study from Tamil Nadu reported 37.3% incidence of HT, 22.6% tuberculosis, and 14.7% DM in a mix cancer cohort comprising predominantly of gastrointestinal tract cancer (19.3%), breast cancer

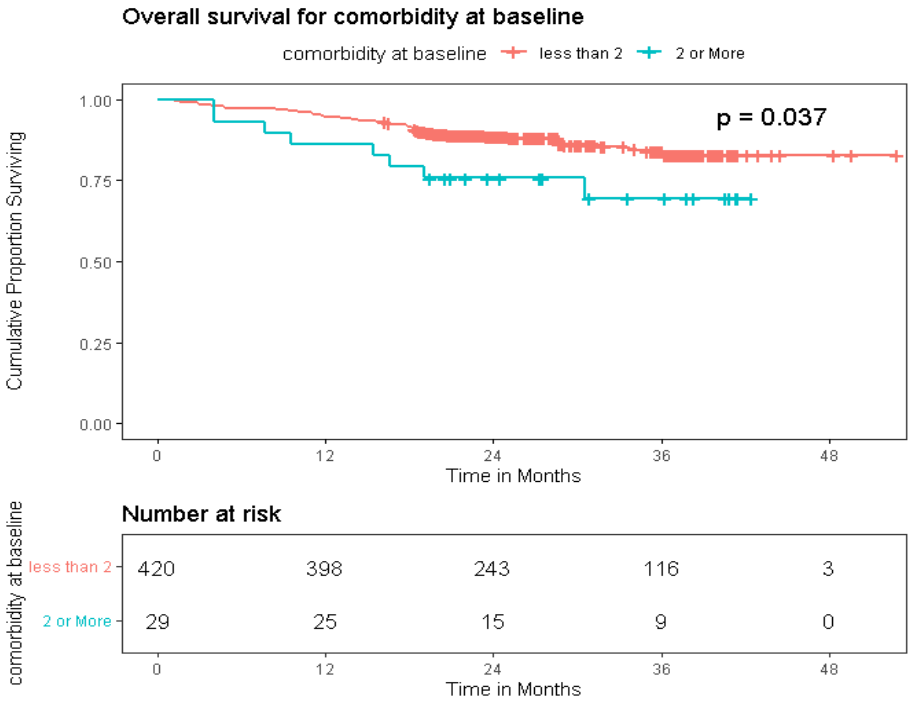


Figure 5. OS in Patients Aged <60 Years with Presence of <2 and >=2 Comorbidities

(18.6%), and head and neck cancer (14.6%). However, the results were not reported separately for breast cancer due to very small sample size of the breast cancer cohort (Rathi et al., 2020).

Advanced age, stage, hormone negative status are known predictors for detrimental outcomes among breast cancer patients (Nguyen et al, 2020). In this study, advanced tumor stage, nodal stage, presence of metastasis and multiple comorbidities was associated with worse PFS and OS (both on univariate and multivariate analysis) while molecular subtype, CCI score and elderly age did not predict outcome. On the contrary, our data showed that though age >60 years was associated with increased probability of developing comorbidities as well as reduced survival, higher comorbidity burden had inferior survival even in age group younger than 60 years when compared to those without comorbidities.

There is no current guideline on the choice of comorbidity score that can be used in clinical practice for tailoring of treatment for breast cancer. Scores such as CCI has been used to commonly to score comorbidities in both non-cancer and cancer patients. It has been validated in various cancer sites. Studies have shown that CCI is a strong predictor of long term survival in breast cancer patients after adjusting for age and stage (Salas et al., 2021). Likewise, in the present study, presence of multiple comorbidities was associated with worse PFS as well as OS, though such association was not evident for CCI score. This could be explained by the complex interaction between comorbidities and survival outcome that limits the predictive power of the comorbidity indices. The relation of CCI scores with receipt of guideline-adherent treatment has been studied in a German breast cancer cohort and it was found that increasing CCI score was linked to lesser use of adjuvant chemotherapy and radiotherapy and had higher rates of mastectomy (Wollschläger et al, 2018). An adverse impact of concurrent comorbidity on breast cancer mortality was also observed in a small cohort of patients with triple negative breast cancer (Parise et al., 2020). Moreover, presence of DM has been reported to have an independent fatal effect in breast cancer patients. A meta-analysis reported a pooled hazard ratio of 1.51 (95% CI 1.34–1.70) for overall mortality for diabetics with breast cancer compared to non-diabetics (Zhao and Ren, 2016). Diabetes mellitus and/or glucose intolerance has been associated with increased risk of recurrent metastatic breast cancer (Anwar et al., 2021).

Various other comorbidity indices have been used for scoring in cancer patients, example Haematopoietic Cell Transplantation Comorbidity Index (HCT-CI) majorly being used for haematological malignancies (Sorror et al., 2005), Cumulative Illness Rating Scale (Linn et al., 1968), Elixhauser Comorbidity Index and Adult Comorbidity Evaluation (ACE-27) derived from Kaplan-Feinstein Comorbidity Index (Decompensation et al., 2003). ACE-27 is scored from 0-3; taking into account both number of comorbidities and grade of severity of each. It is a chart-based cancer-specific tool as against CCI that is a general comorbidity assessment tool. Kimmick et al studied association of ACE-27 with guideline concordance which ranged from 70% for patients without comorbidity to 43% with severe comorbidity (Kimmick et al., 2014).

*Strength and Limitations*

A large cohort of breast cancer patients treated in a single tertiary care center have been studied prospectively. Data on comorbidities at all-time points were obtained through the same questionnaire thus uniform detailed information was available. We have also studied correlation with survival which has not been reported from in earlier studies from India. Sharma et al only calculated

an estimated survival based on CCI score alone (Ho et al., 2018). Temporal trend also gives valuable information that cancer treatment does significantly increase the burden of comorbidity.

The main limitation of the study was high dropout rate as half of the patients defaulted after treatment completion due to study period being at time of COVID pandemic. The follow up time is short to conclusively provide effects of comorbidities on long-term survival but the cohort will be followed up for a longer period. Nonetheless, the impact of comorbidities was clearly seen even at this shorter follow up time irrespective of age. We did not analyze the impact of individual comorbidity on the survival outcome.

In conclusion, This study highlights the comorbidity burden of breast cancer diagnosed in a tertiary care center in India and association with worse outcomes in patients. Comorbidity profile of a patient is a critical deciding factor for treatment and requires an individualistic approach as these patients are often under-represented in clinical trials.

## Author Contribution Statement

Authorship contributions TW and SKM conceptualized the study, research design, drafted and edited the manuscript. NP collected the data DD analyzed the data and drafted the manuscript.. PR contributed to data analysis and statistical review. RS, VP and SG critically reviewed the manuscript.

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*Ethical statement*

This study reports one of the secondary endpoints of a larger study that primarily collected data on expenditure for breast cancer treatment. It was approved from the Institutional Ethics Committee -I (IEC-I and project no 3279) at TMH and was also registered in clinical trial registry of India [CTRI/2019/07/020142].

The authors affirm the accuracy and completion of the data. This project was not a student thesis.

*Conflict of Interest*

All authors declare no conflict of interests.

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