



## Unique challenges and outcomes of young women with breast cancers from a tertiary care cancer centre in India

Jyoti Bajpai<sup>a, f, \*</sup>, Pradeep Ventrapati<sup>a, f</sup>, Shalaka Joshi<sup>c, f</sup>, Tabassum Wadasadawala<sup>b, f</sup>, Sushmita Rath<sup>a, f</sup>, Rima Pathak<sup>b, f</sup>, Ravindra Nandhana<sup>a, f</sup>, Samarpita Mohanty<sup>b, f</sup>, Qurratulain Chougale<sup>c, f</sup>, Michelle Engineer<sup>c, f</sup>, Nissie Abraham<sup>a, f</sup>, Jaya Ghosh<sup>a, f</sup>, Nita Nair<sup>c, f</sup>, Seema Gulia<sup>a, f</sup>, Palak Popat<sup>d, f</sup>, Patil A<sup>e, f</sup>, Tanuja Sheth<sup>e, f</sup>, Sangeeta Desai<sup>e, f</sup>, Meenakshi Thakur<sup>e, f</sup>, Venkatesh Rangrajan<sup>e, f</sup>, Vani Parmar<sup>c, f</sup>, R. Sarin<sup>c, f</sup>, S. Gupta<sup>c, f</sup>, R.A. Badwe<sup>c, f</sup>

<sup>a</sup> Department of Medical Oncology, Tata Memorial Centre, Mumbai, India

<sup>b</sup> Department of Radiation Oncology, Tata Memorial Centre, Mumbai, India

<sup>c</sup> Department of Surgical Oncology, Tata Memorial Centre, Mumbai, India

<sup>d</sup> Department of Radiology, Tata Memorial Centre, Mumbai, India

<sup>e</sup> Department of Surgical Pathology, Tata Memorial Centre, Mumbai, India

<sup>f</sup> Homi Bhabha National Institute, India

### ARTICLE INFO

#### Article history:

Received 3 August 2021

Received in revised form

26 September 2021

Accepted 27 September 2021

Available online 6 October 2021

#### Keywords:

Young breast cancer

Chemotherapy

Outcomes

Fertility

Quality of life

### ABSTRACT

**Background:** Young ( $\leq 40$  years) breast cancers (YBC) are uncommon, inadequately represented in trials and have unique concerns and merit studying.

**Methods:** The YBC treated with a curative intent between 2015 and 2016 at our institute were analysed.

**Results:** There were 1228 patients with a median age of 36 (12–40) years; 38 (3.1%) had Stage I, 455 (37.1%) - II, 692 (56.3%) -III, and remaining 43 (3.5%) Stage IV (oligo-metastatic) disease; 927 (75.5%) were node positive; 422 (34.4%) were Triple negatives (TNBC), 331 (27%) were HER-2 positive. There were 549 (48.2%) breast conservations and 591 (51.8%) mastectomies of which 62 (10.4%) underwent breast reconstruction. 1143 women received chemotherapy, 617 (53.9%) received as neoadjuvant and 142 (23.1%) had pathological complete response; 934 (81.9%) received adjuvant radiotherapy. At the median follow-up of 48 (0–131) months, 5-year overall and disease-free survival was 79.6% (76.8–82.5) and 59.1% (55.8–62.6). For stage I, II, III and IV, the 5-year overall-survival was 100%, 86.7% (82.8–90.6), 77.3% (73.4–81.2), 69.7% (52.5–86.9) and disease-free survival was 94% (85.9–100), 65.9% (60.3–71.5), 55% (50.5–59.5), and 29.6% (14–45.2) respectively. On multivariate analysis, TNBC and HER-2+ subgroups had poorer survival ( $p = 0.0035$ ). 25 patients had BRCA mutations with a 5-year DFS of 65.1% (95% CI:43.6–86.6). Fertility preservation was administered in 104 (8.5%) patients; seven women conceived and 5 had live births. Significant postmenopausal symptoms were present in 153 (13%) patients.

**Conclusion:** More than half of the YBC in India were diagnosed at an advanced stage with aggressive features leading to suboptimal outcomes. Awareness via national registry and early diagnosis is highly warranted. Menopausal symptoms and fertility issues are prevalent and demand special focus.

© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

\* Corresponding author. Medical Oncology, Room 1115, HBB, Tata Memorial Centre, Parel, Mumbai, 400012, India.

E-mail addresses: [dr\\_jyotibajpai@yahoo.co.in](mailto:dr_jyotibajpai@yahoo.co.in), [drjyotibajpai25@gmail.com](mailto:drjyotibajpai25@gmail.com) (J. Bajpai).

### 1. Introduction

Young women with breast cancer (YBC) face unique challenges in the management of their cancer. The most widely accepted definition of YBC are women diagnosed with breast cancer at  $\leq 40$  years of age although some consider it to be  $\leq 45$  years [1,2]. Among them is a small population of very young women ( $< 35$

years) with breast cancer (very YBC) [3,4]. These women merit attention to their specific needs pertaining to body image, quality of life (QOL), sexual health and fertility preservation, premature menopause, pregnancy and lactation among others. Research into their poor outcomes has revealed a distinct biology with adverse clinico-pathological risk factors [5].

The National Cancer registry Programme (NCRP) of India has estimated that by the year 2025 there will be 2,30,000 breast cancer patients annually with a significant increase in YBC [6]. Despite their growing numbers there are very few reports on the outcomes and management of these patients from India [6,7]. Our institute is a major tertiary cancer care centre in India and as per the NCRP report of 2012–2016, it has registered the highest number of cancer patients out of all 57 Hospital Based Cancer registries [6]. Therefore, we wanted to study the outcomes of such patients in the real world setting of LMIC.<sup>1</sup>

## 2. Materials and methods

### 2.1. Study population

The study included patients aged ≤40 years with histologically proven invasive breast cancer consecutively, treated with curative intent registered at our institute between January 2015–December 2016. Among these, patients ≤35 years were categorised as very YBC.

### 2.2. Data collection and management

The details of patient demographics and treatment was collected prospectively using the hospital electronic medical records (EMR) system, personal files and further updated by telephonic follow up as required. The AJCC 7th edition was used for staging. The management for all the patients is decided in a multidisciplinary joint clinic as per standard institutional guidelines summarized in [Supplementary table 4](#). To define pCR (pathological complete response), no evidence of invasive residual disease in both the breast and the nodes was required. The data was locked on October 8, 2020 for analysis.

### 2.3. Statistical analysis

Patient, tumour and treatment related characteristics were reported using descriptive statistics. The differences in proportions of categorical variables were calculated using the Chi-square and Fisher's exact test. Univariate analysis was performed on factors affecting the outcomes as shown in [supplementary table 1](#). Factors which were significant on univariate analysis were analysed by the Cox regression model for multivariate analysis. For all results, p-values were two-sided with an alpha error of 0.05. SPSS® (IBM, California) version 25 was used for performing the statistical analysis.

Kaplan Meier method was used for survival analysis and log rank test was used for comparison. Disease free survival (DFS) was defined as the time from diagnosis to the occurrence of any event (local/regional or distant relapse) or death from any cause. Overall survival (OS) was calculated from the date of diagnosis to the date of death due to any cause and those alive were censored at their last follow up. The study was approved by Institutional Ethics Committee and registered to clinical trials registry India (CTRI/2021/01/030325) and conducted as per good clinical practise guidelines.

## 3. Results

### 3.1. Patient characteristics

Of the 8634 breast cancers registered to our centre, 1445 (16.7%) were YBC. Among them 1228 patients aged ≤40 years with a median age of 36 years (IQR:32–38 years) treated with a curative intent were included in this study. There were 217 (15%) upfront metastatic women with YBC and those will be separately reported. Almost half of them (n = 608,49.6%) were aged ≤35 years (very YBC) and 39 (3.2%) patients ≤25 years. Majority had grade-3 (n = 1068, 86.9%) and stage-3 disease (n = 692,53.7%). 422 (34.4%) patients had TNBC and 331 (27%) had HER-2 positive disease. Patient and treatment characteristics are summarized in [Table 1](#).

**Table 1**  
Baseline patient and treatment characteristics.

Age group (n = 1228)	No of Patients (%)
•<25 years	39 (3.2)
•25–29 years	129 (10.5)
•30–35 years	440 (35.8)
•36–40 years	620 (50.4)
Family History of malignancy (n = 1183)	242 (20.4)
Nulliparous (n = 1159)	157 (13.5)
Single live child (n = 1159)	281 (24.2)
Associated with pregnancy	24 (1.9%)
<b>T stage</b>	
•T1	63 (5.1%)
•T2	575 (46.8%)
•T3	298 (24.3%)
•T4	292 (23.8%)
<b>N stage</b>	
•N0	301 (24.5%)
•N1	552 (45%)
•N2	256 (20.8%)
•N3	119 (9.7%)
<b>Clinical Stage</b>	
•I	38 (3.1%)
•II	455 (37.6%)
•III	692 (56.3%)
•IV	43 (3.5%)
<b>Grade</b>	
•I	3 (0.2%)
•II	157 (12.7%)
•III	1068 (86.9%)
<b>Hormone/HER-2 receptor status</b>	
•HR +/HER-2-	475 (38.7%)
•HR+/HER-2+	174 (14.2%)
•HR-/HER-2+	157 (12.8%)
•TNBC	422 (34.4%)
<b>Surgery (n = 1140)</b>	
•Breast conservation surgery	549 (48.2%)
•Modified radical mastectomy	591 (51.8%)
•Breast Reconstruction	62 (10.4%)
<b>Chemotherapy (n = 1143)</b>	
•NACT alone	243 (21.2%)
•ACT alone	526 (46%)
•Both NACT and ACT (sandwich approach)	374 (32.7%)
<b>Neoadjuvant Chemotherapy type</b>	
•Anthracycline + taxane	203 (32.9%)
•Only anthracyclines	371 (60.1%)
•Only taxane w/o anthracyclines	43 (6.9%)
•Platinum based	52 (8.4%)
<b>Trastuzumab use (n = 174)</b>	
•Neoadjuvant	72 (21.7%)
•Adjuvant	102 (30.8%)
•Maintenance	90 (27.1%)
•Short course (3 months)	84 (25.3%)

HR: Hormone receptor; +: positive, -: negative; TNBC: Triple negative breast cancer; BCS: Breast Conservation Surgery; MRM: Modified Radical Mastectomy; NACT: Neoadjuvant Chemotherapy; ACT: Adjuvant chemotherapy; CR: complete response.

<sup>1</sup> LMIC: Low and Middle Income Countries.

## 4. Treatment characteristics

### 4.1. Surgery

549 (48.2%) underwent breast conservation surgery (BCS), 591 (51.8%) underwent modified radical mastectomy (MRM). The option of whole breast reconstruction was discussed with most patients who were not suitable for BCS and needed MRM. However, only 10.4% patients finally received post mastectomy reconstruction due to various reasons including patient reluctance, irrational fears of delay in treatment, additional cost, and other logistic issues. All 62 patients underwent autologous microvascular reconstruction using DIEP (deep inferior epigastric perforator), ALT (Anterolateral thigh), Gracilis and extended LD (Latissimus Dorsi) flaps. Upfront surgery was performed in 359 (72.8%) patients with early breast cancer (EBC: Stage I/II; n = 493) where 216 (60.1%) patients underwent BCS. For those undergoing surgery first and with clinically node negative axilla, axillary staging was done with low axillary sampling (LAS) (n = 406). We previously validated the procedure of LAS to be equivalent to sentinel node biopsy in NO axilla [8]. All patients post-chemotherapy and those with positive lymph nodes either clinically or on intra-operative frozen section analysis had a complete axillary lymph nodal dissection (ALND) (n = 910). Out of the patients who underwent NACT (n = 617), 269 (43.6%) underwent BCS and 299 (48.5%) underwent MRM.

### 4.2. Systemic therapy (ST)

#### 4.2.1. Chemotherapy

A large majority of our patients received chemotherapy (n = 1143, 93.16%): Neoadjuvant [NACT (n = 243, 21.2%)], adjuvant chemotherapy [ACT, n = 526 (46%)] or both NACT and ACT (n = 374, 32.7%). Overall, 889 (77.7%) patients received both anthracyclines and taxanes. In total, 617 patients underwent neoadjuvant chemotherapy of which majority had locally advanced disease with biologically aggressive tumours; 463 (75%) were stage 3, 33 (5.3%) were stage 4, 239 (38.7%) were TNBC, 168 (27.2%) were HER-2 positive.

#### 4.2.2. Targeted therapy

Out of the 331 HER-2+ patients, only 174 (54.5%) patients could receive trastuzumab and among those, 84 (25.3%) received 3 months of trastuzumab (short course); 90 (27.1%) patients received full course of adjuvant trastuzumab for 1 year (Table 1).

#### 4.2.3. Pathological complete response (pCR)

Out of the 617 patients who received NACT, 221 received both anthracyclines and taxanes as NACT and 67 of them (30.3%) achieved a pCR. It was highest in the TNBC subgroup (37.6%, n = 90/239) and lowest in the HR+/HER-2- subgroup (10%, 21/210). Some 21% (48/239) TNBC patients received additional platinum with NACT. In HER-2+ patients, the pCR rate was 32% (24/75) with and 8.4% (8/93) without the addition of Trastuzumab to chemotherapy. (Supplementary table 3).

#### 4.2.4. Toxicity

There were few grade III/IV adverse events: febrile neutropenia (FN) (n = 57, 4.9%), thrombocytopenia (n = 15, 1.3%), peripheral neuropathy (n = 13, 1.1%) and vomiting (n = 8, 0.6%). Three patients, with no comorbidities, died due to treatment related infective complications (2 post-chemotherapy and 1 post-surgery).

### 4.3. Hormone therapy (HT)

All 650 patients with HR + tumours were recommended

adjuvant HT but only 613 (94.3%) received it and 37 (5.7%) defaulted. In HR + patients, tamoxifen was administered as adjuvant HT of which 87 (14.1%) also received ovarian suppression.

### 4.4. Radiotherapy (RT)

Out of 1140 patients who underwent curative surgery, 934 (81.9%) patients also received adjuvant RT (910 with Field-in-field technique, 24 with intensity modulated RT) to a dose of 40Gy in 15 fractions over 3 weeks, additionally tumour bed boost was administered in all patients receiving whole breast irradiation. The supraclavicular nodal region was irradiated in 508 (54.5%) patients, and axillary and internal mammary lymph nodal regions were rarely irradiated (12 patients each) as axilla was adequately addressed surgically. Very few patients developed Grade 3 toxicities, e.g., skin reactions (n = 14, 1.49%).

### 4.5. Postmenopausal symptoms, fertility preservation and pregnancy

Since 1143 (93.5%) received CT and 650 received HT, several of them experienced postmenopausal symptoms (PMS) and fertility issues. The details on the fertility issues and pregnancy were available for 351 patients in the EMR or were gathered during the telephonic follow-up. Among them 341 patients experienced post-chemotherapy amenorrhoea which produced transient symptoms in 148 (43.4%) patients whereas 153 (44.8%) patients experienced significantly distressing PMS like sleep disturbances (n = 72, 47.3%), memory problems and mental exhaustion (n = 57, 37.2%), mood swings (n = 54, 35.2%) followed by hot flushes (n = 37, 24.1%). A very small number of patients reported vaginal dryness (n = 23, 6.7%) or adverse impact on sexual quality of life (n = 12, 3.5%) (Supplementary Table 2).

Majority of the patients received fertility counselling, however there were gaps in communication and documentation and its record was available for 278/341 (81.5%) patients. Only 105 (8.5% of overall population) of those (35 nulliparous and 85 desirous for 2nd child) opted for fertility preservation predominantly with LHRH agonists due to various factors including logistic reasons as well as majority having children already with less motivation. Seven (38.8%) patients conceived post treatment completion, and 5 (27.7%) patients had live births between 2 and 7 years after treatment.

### 4.6. Survival analysis

A total of 407 events and 175 deaths were recorded after a median follow up of 48 (range:0–131; IQR: 25–54) months. The median DFS and OS were 61 (95% CI: 60.1 – NR) months and 94 (95% CI: 80.1–NR) months (Fig. 2a and b) and the 5-year DFS and OS were 59.1% (55.8–62.6) and 79.6% (76.8–82.5) respectively (Table 2).

### 4.7. Prognostic factors

There was a significant difference in the 5 year OS between tumour subtypes which is highest in HR+/HER-2- subgroup and least in the TNBC subgroup [84.3% (95% CI: 80.2–88.4) vs 77.1% (95% CI: 71.8–82.4); p = 0.019]. Although, there was not a significant difference in the DFS among these subtypes. Furthermore, in the HR + group; when compared with stage I/II tumours, Stage III had significantly inferior 5- year DFS [72% (95% CI: 64.9–79.1) vs 54.4% (48.1–60.7); p = 0.0] and OS [88.6% (95% CI: 83.3–93.9) vs 81.8% (95% CI: 76.9–86.7); p = 0.025]. Stagewise survival outcomes are represented in Table 2, Fig. 2c and d. Tumour subtype wise survival

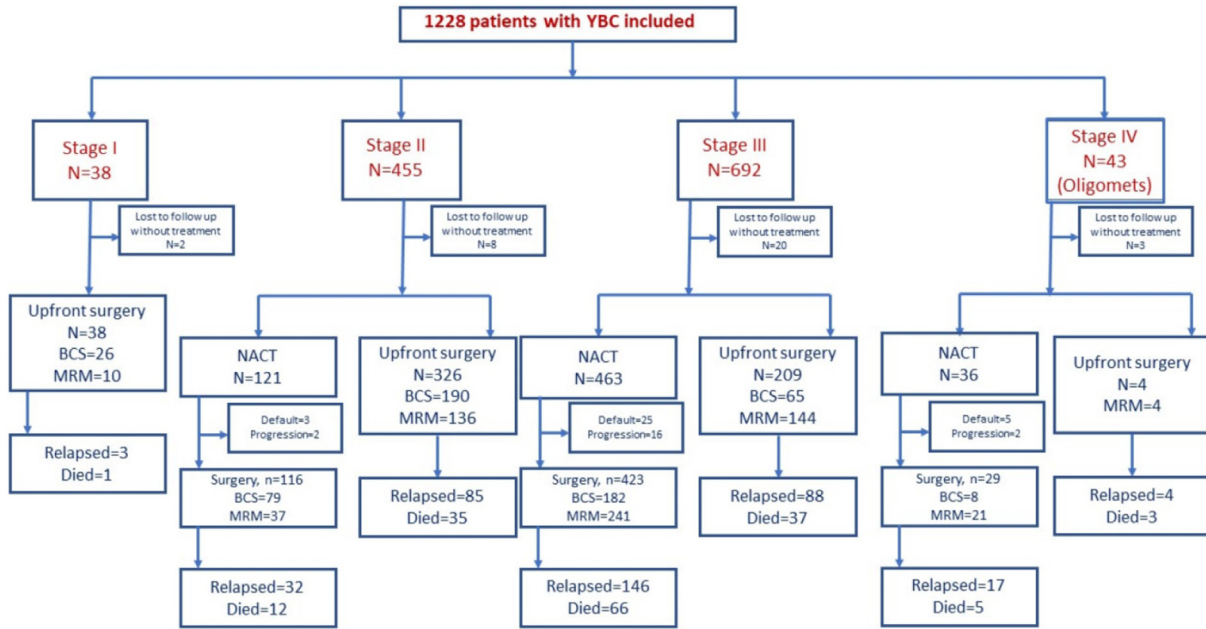


Fig. 1. CONSORT diagram.

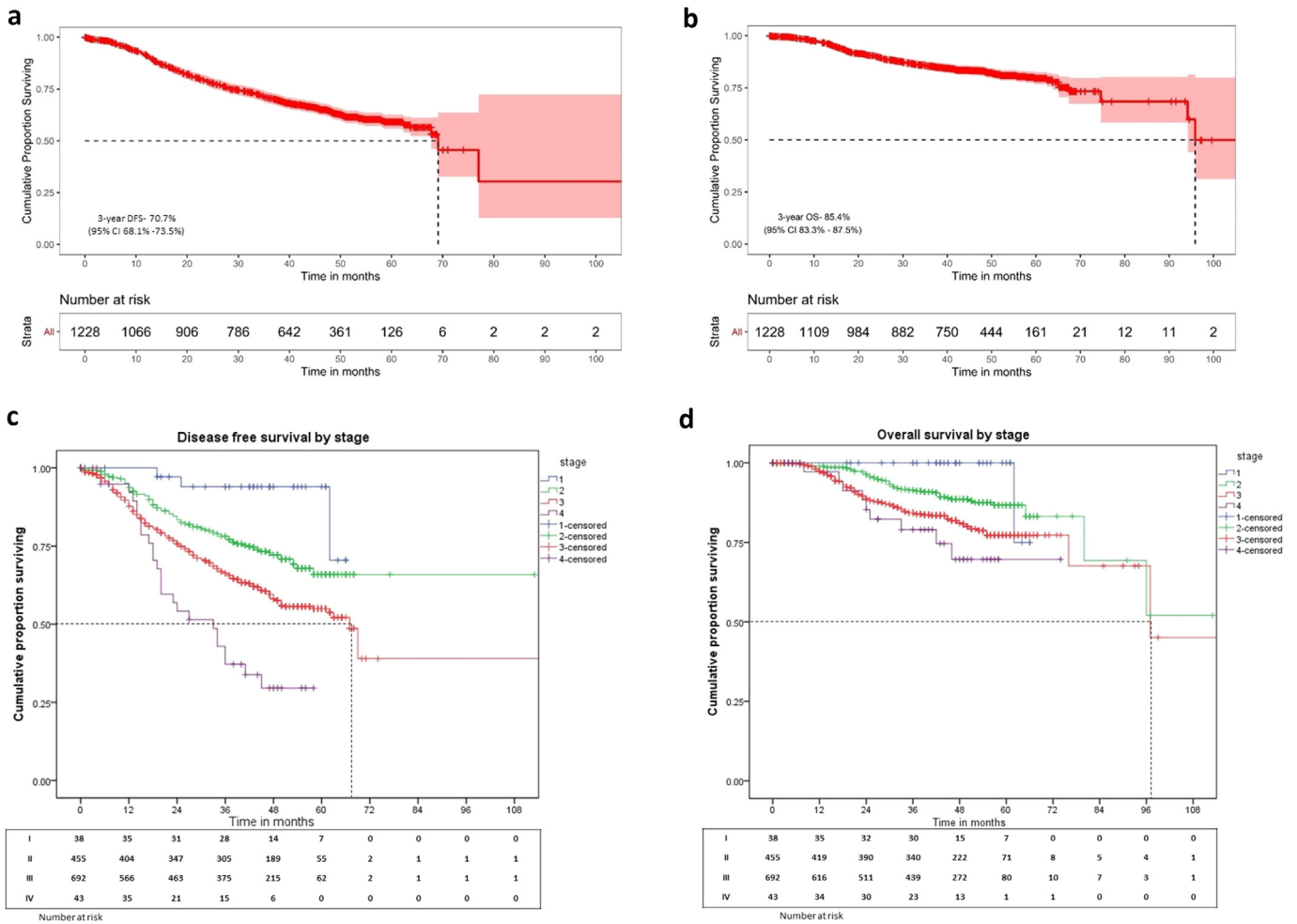


Fig. 2. a: Overall cohort (n = 1228): Disease free survival curve, b: Overall cohort (n = 1228): Overall survival curve, c: Stage wise survival: DFS, d: Stage wise survival: OS.

**Table 2**  
Disease Free Survival and Overall Survival rates.

Time	DFS (95% CI)	OS (95% CI)
2-year	78.8% (76.4–81.2)	90.1% (88.4–91.9)
3-year	70.7% (68.1–73.5)	85.4% (83.3–87.5)
4-year	63.6% (60.6–66.5)	84.2% (81.9–86.5)
5-year	59.1% (55.8–62.6)	79.6% (76.8–82.5)
<b>Stage wise 3 year and 5-year survival rates</b>		
<b>Stage</b>	<b>3-year DFS (95% CI)</b>	<b>3-year OS (95% CI)</b>
I	94.4% (87–100)	100%
II	77.2% (73.4–81.3)	90.4% (87.7–93.3)
III	66.5% (62.8–70.5)	81.9% (78.7–85.1)
IV	43.1% (30.5–60.8)	79.1% (65.1–93)
	<b>5-year DFS (95% CI)</b>	<b>5-year OS (95% CI)</b>
I	94% (85.9–100)	100%
II	65.9% (60.3–71.5)	86.7% (82.8–90.6)
III	55% (50.5–59.5)	77.3% (73.4–81.2)
IV	29.6% (14–45.2)	69.7% (52.5–86.9)

DFS: Disease free survival; OS: Overall Survival; CI: Confidence Interval.

outcomes are represented in [Supplementary Tables 5 and 6](#)

Among the HER-2+ patients, there was a significant difference in the 5 year DFS (73.6% vs 44.6%; HR = 0.42, 95% CI: 0.28–0.63, p = 0.0) and OS (92.1% vs 71.8%; HR = 0.32; 95% CI: 0.16–0.62, p = 0.001) between patients who received trastuzumab and who did not receive respectively. On multivariate analysis ([Table 3](#)), older age, lower T/N-stage, absence of LVI and pCR were associated with superior DFS and OS while HR + status was associated with superior OS alone (p = 0.0035).

#### 4.8. Very young breast cancer

The patient and treatment characteristics of very YBC were compared with the YBC patients in [Table 4](#). A significantly lower PR expression (38.4% vs 44.03%, p = 0.048), higher NACT use (54.6% vs 46.3%, p = 0.009) and LHRH agonists for fertility preservation (13.3% vs 3.7%, p = 0.0) were noted in the very YBC subgroup. Rest of the characteristics were comparable. ([Table 4](#)). There was a significant difference in 5-year DFS of VYBC vs YBC [53.5% (95% CI: 48.4–58.6) vs 65.3% (95% CI: 60.8–69.8), p = 0.002], however, no significant difference was found in 5-year OS [79% (95% CI: 74.9–83.1) vs 83.9% (95% CI: 80.3–87.3), p = 0.145].

#### 4.9. Familial and hereditary cancers

Significant family history was noted in 242 patients (19.7%). A dedicated cancer genetics clinic associated with laboratory at our hospital undertakes genetic testing for research purposes for patients unable to afford genetic testing at a private laboratory. 170 patients were tested in the cancer genetic clinic of which reports were available for 132 patients. 30 patients tested positive for germline mutations of which 25 patients had mutations in BRCA gene (21 pathogenic mutations; 4 variant of uncertain significance). 2 patients had germline mutations in APC gene and 1 each had mutations in FANCD, P53 and MSH-2 genes. Six (30%) and 7 (35%) patients respectively opted for prophylactic contralateral mastectomy and risk reducing bilateral salpingo-oophorectomy. The rest were on intensified follow-up for early detection of breast cancer. The 5-year DFS and OS in patients with germline mutations was 67.2% (95% CI:48.2–86.2) and 96.6% (95% CI:90–100) respectively. The 5-year DFS and OS in patients with BRCA mutations was 65.1% (95% CI:43.6–86.6) and 95.8% (95% CI:87.8–100) respectively.

#### 4.10. Breast cancer during pregnancy (PrBC) or during 1-year postpartum period (PPBC)

There were 24 (1.9%) patients with PrBC(13; 54.1%) or PPBC(11;

**Table 3**  
Multivariate analysis for Disease Free Survival and Overall Survival.

Variables	Disease Free Survival HR (95% CI); p value	Overall Survival HR (95% CI); p value
<b>Age</b>		
<25 years		
25–29 years	0.72 (0.42–1.24); 0.241	0.31 (0.14–0.66); 0.002
30–35 years	0.64 (0.40–1.04); 0.070	0.45 (0.25–0.83); 0.011
36–40 years	0.54 (0.34–0.87); 0.012	0.40 (0.22–0.73); 0.003
<b>T size</b>		
T1	0.32 (0.13–0.75); 0.009	0.39 (0.13–1.15); 0.088
T2	0.56 (0.40–0.80); 0.001	0.41 (0.25–0.67); 0.000
T3	0.96 (0.73–1.27); 0.787	0.77 (0.52–1.14); 0.186
T4		
<b>Node status</b>		
N0	0.33 (0.22–0.50); 0.000	0.39 (0.22–0.69); 0.001
N1	0.35 (0.25–0.48); 0.000	0.36 (0.23–0.58); 0.000
N2	0.76 (0.55–1.05); 0.094	0.78 (0.49–1.24); 0.300
N3		
<b>Receptor subtypes</b>		
TNBC		0.96 (0.63–1.47); 0.862
HR+/HER-2+		0.40 (0.22–0.73); 0.003
HR+/HER-2-		0.62 (0.40–0.95); 0.028
<b>Other pathological features</b>		
<b>LVI</b>		
Negative	0.72 (0.56–0.92); 0.009	0.68 (0.47–0.98); 0.039
Positive		
<b>pCR</b>		
No		
Yes	0.32 (0.20–0.53); 0.000	0.23 (0.10–0.50); 0.000

DFS: Disease free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; T: Tumour; TNBC: Triple negative breast cancer; LVI: lymphovascular invasion; pCR: Pathological complete response.

45.8%) with a median age of 31 years (IQ range: 27–33). Five (38.4%) patients opted to interrupt their pregnancy. The actuarial 5-year DFS and OS in the PABC cohort was 58.5% (95% CI: 23.1%–93.9%) and 81.3% (95% CI:64.3%–98.3%) respectively.

## 5. Discussion

Our comprehensive study represents the largest cohort of YBC patients from India. Biological age can't be measured accurately and thus we used the ESO-ESMO guidelines age cut off as <40 years for YBC to determine our study participants [1]. Furthermore based on the studies by Liukkonen et al. and Fabiano et al. we classified patients aged ≤35 years in the “very young” subgroup (Very YBC) [3,4].

The incidence of YBC varies from 2 to 6% in west to 10–20% in Asia [2,9,10]. It was interesting to note that nearly half of our study patients belonged to the 36–40 years age group and may represent the age structure bias from a relatively younger Indian population. Yet, the scant literature reporting on Indian YBC is ironical. The incidence of YBC in India has been reported as 8% of all breast cancers (7). Contrary to their findings, a SEER data analysis showed a higher frequency of YBC (<40 years) among Asian women compared to the Caucasian women, 16.2% vs 6.23% (p < 0.0001) [11]. In our study, the proportion of YBC was 16.7% which is similar to the SEER data and reflects on the age distribution and possibly poor access to healthcare for older women [12–14].

Only half of the HER-2 positive patients were able to receive trastuzumab (54.5%).This indicates the real world scenarios wherein there is a constraint to offer standard of care targeted therapy even in curative setting and in YBCs [12,15–17]. As expected, the outcomes were significantly better among those who received trastuzumab versus those who could not. Health sector in India receives <2% of India's GDP/national budget allocation and

**Table 4**  
Comparison of patient, tumor and treatment characteristics between Very young (<35 years) and young (36–40 years) subgroups.

	<35 YEARS (n = 608)	36–40 YEARS (n = 620)	p value
<b>Grade</b>			0.505
I	1 (0.001%)	2 (0.003%)	
II	69 (11.3%)	87 (14%)	
III	536 (88.1%)	529 (85.3%)	
<b>PNE</b>	26/605 (4.2%)	37/612 (6%)	0.220
<b>LVI</b>	167/605 (27.6%)	180/612 (29.4%)	0.390
ER+	311/608 (51.1%)	332/620 (53.5%)	0.400
PR+	234/608 (38.4%)	273/620 (44.03%)	<b>0.048</b>
HER-2+	166/608 (27.3%)	165/620 (26.6%)	0.233
<b>Phenotype</b>			0.919
HR+/HER-2-	198/571 (34.6%)	207/568 (37.5%)	
HR+/HER-2+	89/571 (15.5%)	89/568 (15.3%)	
HR-/HER-2+	77/571 (13.4%)	76/568 (13.1%)	
TNBC	207/571 (36.25%)	196/568 (33.9%)	
<b>Positive LN</b>	455/608 (74.8%)	472/620 (76.1%)	0.707
<b>Stage</b>			0.637
I	16/608 (2.6%)	24/620 (3.8%)	
II	242/608 (39.8%)	244/620 (39.3%)	
III	330/608 (54.2%)	329/620 (53%)	
IV	20/608 (3.2%)	23/620 (3.7%)	
<b>Received Neoadjuvant chemotherapy</b>	332/608 (54.6%)	293/620 (47.2%)	<b>0.009</b>
<b>Underwent curative surgery</b>	n = 566	n = 574	0.318
MRM	n = 285 (50.3%)	n = 306 (53.3%)	
BCS	n = 281 (49.7%)	n = 268 (46.7%)	
<b>Pathological Complete Remission rates</b>	79/332 (23.7%)	68/293 (23.2%)	0.919
<b>Received fertility preservation</b>	81/608 (13.3%)	23/620 (3.7%)	<b>0.000</b>

PNE: Perineural extension; LVI: Lymphovascular invasion; ER: Estrogen receptor; PR: Progesterone receptor; '+': positive; '-': negative; HR: Hormone receptor; TNBC: Triple negative Breast cancer LN: Lymph node; NACT: Neoadjuvant chemotherapy; MRM: Modified radical mastectomy; BCS: Breast conservation surgery; pCR: Pathological complete response.

the insurance coverage is negligible especially in the remote areas forcing most patients to spend out of pocket for health care unlike developed countries [18,19]. Our study sheds light on the impact of this disparity and more national and global efforts are required to increase the access of life saving drugs like trastuzumab to the majority.

Though BCS is preferable for YBC patients, mastectomy rates were higher (51.8%) due to the higher proportion of LABCs, multicentricity, poor access to radiation facilities [20,21] and patient preference. Compliance to RT was high possibly reflecting the effect of improved access from adoption of hypofractionated protocol at ours and many other centres across the country.

A greater proportion of our study patients had adverse prognostic factors such as Grade-III tumours (86%), node positivity (75%), HER-2+ (27%) and TNBC phenotype (34%) among others. Similar results have been reported in studies from India [7], Korea and Mexico [5,10,22,23]. When compared to studies from western countries, the proportion of HR+(52%) were lesser whereas, TNBC (34%) were higher. In a study from the California Cancer registry [24], 67% were HR+, 27% were HER-2+ and 10.8% were TNBC. Similar results were reported from the UK POSH study [25], where the proportion of HR+ were 65%, HER-2+ were 24.3% and TNBC were 19.9%.

Nearly half of the population in current study fall under the category of very YBC. The differences in PR expression, NACT use and fertility preservation and similarities in their stage distribution, tumour grade and HR/Her 2 expression are similar to a study from Argentina [3], but contrasting to the studies by Collins [26] and Dubsky [27] who did not find such differences. The reasons for this disparity can be due to geo-ethnic and healthcare access

differences. Though no differences were found in the tumour characteristics, a poorer DFS was noted in very YBC group which suggests the adverse impact of very young age on survival.

Previous studies have reported young age to be a poor prognostic factor for survival. In the metaanalysis by Maajani et al. [28], 776,431 women with breast cancer were analysed and the pooled 5-year OS of 73% was for the overall study population. When developing and developed countries were separately analysed, the 5-year OS was 69% in the developing countries and 76% in the developed countries which was similar to our study. But a recent study [29] of around 1.5 lakh non-metastatic YBC from the SEER database reported a 5 year-OS of 85.6% (95%CI: 84.2–86.8) and 87.9% (95%CI: 87.5–88.3) in the 20–29 and 30–39 year age group which is higher than our study. But it should be noted that the proportion of Stage III at diagnosis was <25% compared to 53% in our study, and additionally we had oligometastatic patients as well. Also, the stage matched outcomes were comparable to ours. Another large Indian multicentric study [30] of all breast cancers treated with curative surgery also reported a higher 5 year-OS of 94.1% (93.25–94.98). In this study, the median age was 53 and only 20% were stage III, which might be the cause for the survival disparity. Since a significantly higher advanced disease appears to be the cause of inferior overall outcomes, it is alarming to note that, even in the current era, more than half of the YBC present at an advanced stage in our country which calls for an urgent need to escalate cancer awareness and screening programmes in this subgroup. Comparable stage matched outcomes (28,29) may be attributed to higher use of effective chemotherapy (93%) including both anthracyclines and taxanes in 77% patients. This multi-drug chemotherapy was well tolerated with grade-III toxicity similar to that reported in major studies despite the high prevalence of malnutrition among multiparous Indian women [31–34]. However, caution must be exercised to avoid intensification of treatment just based on the age as suggested by the international guidelines [1,9]. The outcomes of the small subset of PABC patients in our study were similar to that seen in a larger study of 104 PABC patients published from our institute had showed comparable stage matched OS and DFS with non PABC patients [35].

Due to the small number of patients with germline genetic testing reports, the prevalence of pathogenic variants in this cohort of patients could not be determined and is among the major limitation of our study [36]. We are developing care pathways to improve referral for genetic counselling and provide financial aid for testing along with capacity and infrastructure building to improve the access to genetic testing across the country.

Chemotherapy can accelerate menopause by a decade [37] and there is a 70% lower chance of conception post breast cancer therapy compared to women of the same age [38]. Still, fertility counselling takes a backseat since priority is often given to initiating cancer treatments. We were able to evaluate the outcomes in only a third of our study population due to the retrospective nature of this study and forms a major limitation due to loss of follow-up; however, it was encouraging that 81.5% of these patients received some form of fertility counselling. Even though there were 13% nulliparous and 24% women with single child, only 8.5% of the patients opted for fertility preservation predominantly with LHRH agonists. This could be due to multiple reasons, especially financial (lack of insurance/reimbursement) and logistic issues. Still, 57% of the patients who desired to conceive and received LHRH agonists could do it successfully post treatment (4/7). Marklund et al.[39], reported a 25% improvement in 10-year cumulative childbirth incidence and Vriens et al.[40] reported an improvement in the 5-year live birth rate of 10.4% among those who opted for fertility preservation. This subgroup of patients is small and possibly reflects younger age at child bearing in India leading to most women

being diagnosed with breast cancer after completion of family.

## 6. Conclusion

The proportion of YBC appears to be higher in India and represent a distinct subgroup. It is alarming to note that even in the current era, more than half of the patients present at an advanced stage which calls for an escalation of cancer awareness and screening programmes in this group. The unique problems of the YBC like fertility preservation and QOL issues, need to be addressed appropriately and the data recorded prospectively in future studies.

## Funding source

No funding required.

The study was approved by Institutional Ethics Committee and registered to clinical trials registry India (CTRI/2021/01/030325) and conducted as per good clinical practise guidelines.

## Declaration of competing interest

There are no conflicts of interest relevant to this material for any of the authors.

## Acknowledgements

We are grateful to entire breast disease management group for their active contribution in patients management, Ms Smruti Mokul, for help in statistical analysis and patients and their families for their trust and support.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2021.09.008>.

## Authors contribution statement

Jyoti Bajpai (JB): Conception, design, patient recruitment, management, follow-up, analysis, supervision, administration, first and final manuscript Pradeep Ventrapati (PV)- Patient recruitment, management, data entry, first, final manuscript. Sushmita Rath, Ravindra Nandhana, Samarpita Mohanty, Qurratulain Chogle, Michelle Engineer -Patient recruitment, management, data entry, final manuscript. Tabassum Wadasadawala, Rima Pathak, Shalaka Joshi - Patient recruitment, management, first and final manuscript. Jaya Ghosh, Nita Nair, Seem Gulia, Vani Parmar- Patient recruitment, management, final manuscript. Asawari Patil, Tanuja Sheth, Sangeeta Desai, Meenakshi Thakur, Palak Popat, Venkatesh Rangrajan, - Lab reports interpretation, final manuscript Sudeep Gupta, RA Badwe, Rajiv Sarin - Patient recruitment, management, final manuscript, administration, supervision. Nissie Abraham (NA): recruitment, follow-up, final manuscript All others: recruitment, management, final manuscript.

## References

- [1] Paluch-Shimon S, Cardoso F, Partridge AH, Abulkhair O, Azim HA, Bianchi-Micheli G, et al. ESO-ESMO 4th international consensus guidelines for breast cancer in young women (BCY4). *Ann Oncol* 2020;31(6):674–96.
- [2] Villarreal-Garza C, Platas A, Miaja M, Fonseca A, Mesa-Chavez F, Garcia-Garcia M, et al. Young women with breast cancer in Mexico: results of the Pilot Phase of the Joven & Fuerte prospective cohort. *JCO Glob Oncol* 2020;6:395–406.
- [3] Fabiano V, Mandó P, Rizzo M, Ponce C, Coló F, Loza M, et al. Breast cancer in young women presents with more aggressive pathologic characteristics: retrospective analysis from an Argentine national database. *JCO Glob Oncol*

- 2020 Apr;6:639–46.
- [4] Liukkonen S, Leidenius M, Saarto T, Sjöström-Mattson J. Breast cancer in very young women. *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol* 2011 Dec;37(12):1030–7.
- [5] Azim HA, Partridge AH. Biology of breast cancer in young women. *Breast Cancer Res* 2014;16(4):427.
- [6] Report of national cancer registry programme. 2020 [Internet]. [cited 2021 Feb 14]. Available from: [https://www.ncdirindia.org/All\\_Reports/Report\\_2020/default.aspx](https://www.ncdirindia.org/All_Reports/Report_2020/default.aspx).
- [7] Gogia A, Raina V, Deo SVS, Shukla NK, Mohanti BK. Young breast cancer: a single center experience. *Indian J Cancer* 2014;51(4):604.
- [8] Parmar V, Hawaldar R, Nadkarni MS, Badwe RA. Low axillary sampling in clinically node-negative operable breast cancer. *Natl Med J India* 2009;22(5):234–6.
- [9] Tfyli A, Temraz S, Abou Mrad R, Shamseddine A. Breast cancer in low- and middle-income countries: an emerging and challenging epidemic. *J Oncol* 2010;2010:490631.
- [10] Ryu JM, Yu J, Kim SI, Kim KS, Moon H-G, Choi JE, et al. Different prognosis of young breast cancer patients in their 20s and 30s depending on subtype: a nationwide study from the Korean Breast Cancer Society. *Breast Cancer Res Treat* 2017;166(3):833–42.
- [11] Kakarala M, Rozek L, Cote M, Liyanage S, Brenner DE. Breast cancer histology and receptor status characterization in Asian Indian and Pakistani women in the U.S. - a SEER analysis. *BMC Cancer* 2010;10(1):191.
- [12] Nair N, Shet T, Parmar V, Havaladar R, Gupta S, Budrukkar A, et al. Breast cancer in a tertiary cancer center in India - an audit, with outcome analysis. *Indian J Cancer* 2018;55(1):16–22.
- [13] Bhan N, Madhira P, Muralidharan A, Kulkarni B, Murthy G, Basu S, et al. Health needs, access to healthcare, and perceptions of ageing in an urbanizing community in India: a qualitative study. *BMC Geriatr* 2017;17(1):156.
- [14] Dey S, Nambiar D, Lakshmi JK, Sheikh K, Reddy KS. Health of the elderly in India: challenges of access and affordability [internet]. In: *Ageing in Asia: findings from new and emerging data initiatives*. National Academies Press (US); 2012 [cited 2021 Sep 26]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK109208/>.
- [15] Li J, Wang S, Wang Y, Wang X, Wang H, Feng J, et al. Disparities of trastuzumab use in resource-limited or resource-abundant regions and its survival benefit on HER2 positive breast cancer: a real-world study from China. *Oncol* 2017;22(11):1333–8.
- [16] Adusumilli P, Konatam ML, Gundeti S, Bala S, Maddali LS. Treatment challenges and survival analysis of human epidermal growth factor receptor 2-positive breast cancer in real world. *Indian J Med Paediatr Oncol Off J Indian Soc Med Paediatr Oncol* 2017;38(1):22–7.
- [17] Gupta N, Verma RK, Gupta S, Prinja S. Cost effectiveness of trastuzumab for management of breast cancer in India. *JCO Glob Oncol* 2020;6:205–16.
- [18] Kasthuri A. Challenges to healthcare in India - the five A's. *Indian J Community Med Off Publ Indian Assoc Prev Soc Med* 2018;43(3):141–3.
- [19] Ahlin T, Nichter M, Pillai G. Health insurance in India: what do we know and why is ethnographic research needed. *Anthropol Med* 2016;23(1):102–24.
- [20] Munshi A, Ganesh T, Mohanti BK. Radiotherapy in India: history, current scenario and proposed solutions. *Indian J Cancer* 2019;56(4):359–63.
- [21] Datta NR, Samiei M, Bodis S. Radiation therapy infrastructure and human resources in low- and middle-income countries: present status and projections for 2020. *Int J Radiat Oncol Biol Phys* 2014;89(3):448–57.
- [22] Villarreal-Garza C, Mohar A, Bargallo-Rocha JE, Lasag-Gonsebatt F, Reynoso-Noverón N, Matus-Santos J, et al. Molecular subtypes and prognosis in young Mexican women with breast cancer. *Clin Breast Cancer* 2017;17(3):e95–102.
- [23] Radecka B, Litwiniuk M. Breast cancer in young women. *Ginekol Pol* 2016;87(9):659–63.
- [24] Keegan TH, DeRouen MC, Press DJ, Kurian AW, Clarke CA. Occurrence of breast cancer subtypes in adolescent and young adult women. *Breast Cancer Res* 2012;14(2):R55.
- [25] Copson E, Eccles B, Maishman T, Gerty S, Stanton L, Cutress RI, et al. Prospective observational study of breast cancer treatment outcomes for UK women aged 18–40 years at diagnosis: the POSH study. *J Natl Cancer Inst* 2013;105(13):978–88.
- [26] Collins LC, Marotti JD, Gelber S, Cole K, Ruddy K, Kerekoglow S, et al. Pathologic features and molecular phenotype by patient age in a large cohort of young women with breast cancer. *Breast Cancer Res Treat* 2012;131(3):1061–6.
- [27] Dubsky PC, Gnant MFX, Taucher S, Roka S, Kandioler D, Pichler-Gebhard B, et al. Young age as an independent adverse prognostic factor in premenopausal patients with breast cancer. *Clin Breast Cancer* 2002;3(1):65–72.
- [28] Maajani K, Jalali A, Alipour S, Khodadost M, Tohidinik HR, Yazdani K. The global and regional survival rate of women with breast cancer: a systematic review and meta-analysis. *Clin Breast Cancer* 2019;19(3):165–77.
- [29] Thomas A, Rhoads A, Pinkerton E, Schroeder MC, Conway KM, Hundley WG, et al. Incidence and survival among young women with stage I–III breast cancer: SEER 2000–2015. *JNCI Cancer Spectr* 2019;3(3):pkz040.
- [30] Doval DC, Radhakrishna S, Tripathi R, Kashinath RI, Talwar V, Batra U, et al. A multi-institutional real world data study from India of 3453 non-metastatic breast cancer patients undergoing upfront surgery. *Sci Rep* 2020;10:5886.
- [31] Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla J-P, Weaver C, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005;352(22):2302–13.

- [32] Gianni L, Baselga J, Eiermann W, Porta VG, Semiglazov V, Lluch A, et al. Phase III trial evaluating the addition of Paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or Primary systemic therapy; European cooperative trial in operable breast cancer. *J Clin Oncol* 2009;27(15):2474–81.
- [33] Mamounas EP, Bryant J, Lembersky B, Fehrenbacher L, Sedlacek SM, Fisher B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *J Clin Oncol Off J Am Soc Clin Oncol* 2005;23(16):3686–96.
- [34] Bear HD, Anderson S, Smith RE, Geyer CE, Mamounas EP, Fisher B, et al. Sequential Preoperative or Postoperative docetaxel added to Preoperative doxorubicin plus cyclophosphamide for operable breast cancer: national surgical adjuvant breast and bowel Project protocol B-27. *J Clin Oncol* 2006;24(13):2019–27.
- [35] Bajpai J, Simha V, Shylasree TS, Sarin R, Pathak R, Popat P, et al. Pregnancy associated breast cancer (PABC): report from a gestational cancer registry from a tertiary cancer care centre, India. *Breast Edinb Scotl* 2021;56:88–95.
- [36] Armstrong N, Ryder S, Forbes C, Ross J, Quek RG. A systematic review of the international prevalence of BRCA mutation in breast cancer. *Clin Epidemiol* 2019;11:543–61.
- [37] Wenners A, Grambach J, Koss J, Maass N, Jonat W, Schmutzler A, et al. Reduced ovarian reserve in young early breast cancer patients: preliminary data from a prospective cohort trial. *BMC Cancer* 2017;17(1):632.
- [38] Peccatori FA, Azim HA, Orecchia R, Hoekstra HJ, Pavlidis N, Kesic V, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol Off J Eur Soc Med Oncol* 2013;24(Suppl 6). vi160–170.
- [39] Marklund A, Lundberg FE, Eloranta S, Hedayati E, Pettersson K, Rodriguez-Wallberg KA. Reproductive outcomes after breast cancer in women with vs without fertility preservation. *JAMA Oncol* 2021;7(1):1–6.
- [40] Vriens IJH, Ter Welle-Butalid EM, de Boer M, de Die-Smulders CEM, Derhaag JG, Geurts SME, et al. Preserving fertility in young women undergoing chemotherapy for early breast cancer; the Maastricht experience. *Breast Cancer Res Treat* 2020;181(1):77–86.