Prognostic Factors and Survival Analysis of Patients with Triple Negative Breast Cancer - A Retrospective Study from a Tertiary Care Teaching Hospital in Kerala

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ABSTRACT

BACKGROUND

Breast cancer is now the most common cancer in Indian women, having recently surpassed cervical cancer in incidence. Triple negative breast cancer (TNBC), which accounts for 15 % of all the breast cancers is an aggressive type seen in younger women with early signs of metastasis, has a poor prognosis due to systemic recurrence and its refractoriness to conventional adjuvant therapy. The purpose of this study was to look into the various prognostic factors associated with 5 years disease-free survival (DFS) and overall survival (OS) in TNBC.

METHODS

This retrospective study included 67 patients with complete treatment and follow-up (median 57 months) presented and treated in the Department of Radiotherapy, Kottayam, between January 2011 and December 2012. The Kaplan-Meier approach was used to analyse survival. Using the log-rank test, univariate analysis of prognostic factors was completed. Using the Cox regression process, multivariate analysis was performed on IBM SPSS version 20.

RESULTS

The average age was 51.36 ± 11.393 (median, 51.36 years; range 30.0 – 80.0 years), with a median of 50 months, the five-year OS was 65.7 % and DFS was found to be 59.7 % with a median of 45 months, suggesting aggressive nature and poor TNBC survival. Univariate analysis of prognostic factor, clinical stage (cN) and positive nodes (pN) status, clinical tumour size, lympho-vascular invasion (LVI), grade, and nodal density were found to have a significant impact on DFS. Except tumour grade and LVI all were found to be associated with OS. Multivariate analysis, clinical tumour size and pathological nodal status had a significant impact on OS and DFS.

CONCLUSIONS

TNBC is an aggressive subtype of breast cancer in younger patients with a high risk of metastasis to visceral organs with inherent molecular subtypes and immunological heterogeneity. For treatment of TNBC, targeted estimated glomerular filtration rate (EGFR), fibroblast growth factor receptor 2 (FGFR2), vascular endothelial growth factor (VEGF), and mechanistic target of rapamycin (mTOR) receptor based initial treatment setting will improve the outcome dramatically and will fill the unmet clinical needs.

KEYWORDS

TNBC, Recurrence, OS, DFS, Nodal Density

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DOI: 10.18410/jebmh/2021/246

How to Cite This Article:
Thomas BT, Vasanthakumary P, Joseph A. Prognostic factors and survival analysis of patients with triple negative breast cancer - a retrospective study from a tertiary care teaching hospital in Kerala. J Evid Based Med Healthc 2021;8(18):1287-1292. DOI: 10.18410/jebmh/2021/246

Submission 24-12-2020,
Peer Review 30-12-2020,
Acceptance 19-03-2021,
Published 03-05-2021.

BACKGROUND

Breast cancer accounts for the highest number of cases of all the cancers in females worldwide including India where it has an increasing trend of 27. 7 % with 162,468 newly detected cases and 87,090 deaths (11.1 % of the total cancer-related deaths) in India as per Global cancer statistics (GLOBOCAN) 2018[1,2] The triple-negative breast cancers (TNBC) are considered as the most malignant subtypes with a multitude of distinctive hostile clinicopathological characteristics, like the age of onset and large size of the tumour, higher tumour grade, the early peak of recurrence, and a worse 5-year overall survival rate.[3,4,5,6] TNBC comprises of about 15 - 20 % of total breast cancers in Indian females, The mean age of presentation is less than 50 years, which is lower than invasive breast cancers in Western populations[7] often diagnosed in late-stage with a majority (about 70 %) at an advanced clinical stage at the time of diagnosis.[7] This study describes the clinicopathological characteristics and intends to analyse prevalence, recurrence rate and survival of TNBC patient cohort treated in a single cancer institution tertiary care centre at Kerala, India.

Objectives

The study's purpose was to look into the clinical behaviour and poor prognosis of triple negative breast cancer patients in Kerala, as well as how different prognostic factors can aid in focused treatment planning. The analysis of the effect of prognostic factors on triple negative breast cancer was secondary objective. There have been many such studies published in the Western world, but very few have been recorded from India, and this will be the first from Kerala.

METHODS

This single-institution retrospective study included a TNBC patient cohort determined as per histopathological guideline according to WHO classification[8] and histological grade of tumours based on Nottingham histological score which was treated in the Department of Radiotherapy, Kottayam between January 2011 and December 2012. All the patients were classified according to the American Joint Committee on Cancer (AJCC TNM) 7th edition. A total of 325 breast cancer cases were reported during that period, of which 67 patients were TNBC. The data retrieved included: patients' characteristics (age at diagnosis, menopausal status, and family history), tumour characteristics (grade, size, nodal involvement and metastases at presentation), composite and pathological stage, number of involved lymph nodes, node density, and treatment received (surgery, chemotherapy, and radiotherapy) and recurrence data (type, size, and date). Disease-free survival was defined from the start of primary therapy to the date of disease recurrence, or last follow-up. Overall survival was defined as the time from the date of the start of primary therapy to the date of death or the last follow-up.

Statistical Analysis

Statistical evaluation was done using IBM SPSS version 20. Data were described in terms of mean ± standard deviation (SD) or frequencies and percentage when appropriate.
The 5-year disease-free survival and overall survival were estimated using the Kaplan-Meier method. P-value < 0.05 was considered statistically significant. Univariate analysis of prognostic factors was done by log-rank test and multivariate analysis by Cox regression model.

RESULTS

	Variable	N (%)
Age (yrs)	≤ 50	37 (55.2 %)
	> 50	30 (44.8 %)
Family history	Yes	4 (6 %)
	No	63 (94 %)
Menopausal status	Premenopausal	36 (53.7 %)
	Postmenopausal	31 (46.3 %)

Table 1. Patients' Characteristics (N = 67)

		Frequency	%
Clinical tumour stage	T 1	2	3 %
	T 2	36	53.7 %
	T 3	21	31.3 %
	T 4	8	11.9 %
Clinical nodal stage	N 0	23	34.3 %
	N 1	34	50.7 %
	N 2	9	13.4 %
	N 3	1	1.5 %
Composite stage	1	2	3.0 %
	2	41	61.2 %
	3	24	35.8 %
Pathological tumour stage	P T 1	2	3 %
	P T 2	45	45 %
	P T 3	17	17 %
	P T 4	3	3 %
Pathological nodal stage	P N 0	36	53.7 %
	P N 1	16	23.9 %
	P N 2	12	17.9 %
	P N 3	3	4.5 %
Grade	1	4	6 %
	2	33	49.3 %
	3	30	44.8 %
Lymphovascular invasion	Present	15	22.4 %
	Absent	52	77.6 %
Margin	Negative	59	88.1 %
	Positive	8	11.9 %
Histology	Ductal	62	92.5 %
	Medullary	2	3.0 %
	Metaplastic	3	4.5 %
Pathological complete response	Present	6	25 %
	Absent	18	75 %
Nodal density	≤ 0.05	44	65.7 %
	> 0.05	23	34.3 %
Postoperative radiation	Yes	41	61.2 %
	No	26	38.8%
Surgery	MRM	61	91.0 %
	BCS	6	9.0 %
Chemotherapy	Neoadjuvant	24	35.8 %
	Adjuvant	43	64.2 %
Chemo protocol	Anthracycline	6	9.0 %
	Anthracycline taxane sequential	51	76.1 %
	Anthracycline and taxane concurrent	10	14.9 %
Local recurrence	Yes	4	6.0 %
	No	63	94.0 %
Metastasis	No metastasis	41	61.2 %
	Bone	2	3.0 %
	Lung	11	16.4 %
	Liver	2	3.0 %
	Brain	6	9.0 %
	Multiple sites	5	7.5 %

Table 2. Tumour Characteristics, Treatment Lines and Patterns of Failure

67 patients were eligible for this study as non-metastatic TNBC. Of the total 325 cases of breast cancer cases reported in the study period, non-metastatic TBNC came around 20 % (67 cases). The median age at diagnosis was 51. 36 ± 11.393 (range, 30.0 – 80.0 years). Patient characteristics are

shown in Table 1. Only 6 % had a family history of breast cancer. The majority of the patients were premenopausal (53.75 %). Most of the patients had ductal carcinoma (92. 5 %) followed by metaplastic (4.5 %) and medullary carcinoma (3.0 %). Clinically, majority of the patients were of T2 stage (41.9 %) and N1 stage (59.6 %). Composite clinical stage2 dominated (49.5 %) followed by stage 3 (46.3 %) and stage 1 (4.2 %). 62.8 % were of p T2 stage and 36 % idiopathic neutropenia (inp) N0 stage which constitutes major portion. Pathological nodal positivity was seen in 46.3 %. Clinically and pathologically tumour stage and the nodal stage was proportionate on cross tab analysis. Nodal density ≤ 0.05 was present in 65.7 % of the patients, whereas 34.3 % of patients had nodal density ≥ 0.05. Lymphovascular invasion was positive in 22.4 % (N = 15) and was absent in 77.6 % of the patients. Margin positivity was present in 8 patients (11.9 %).

Modified radical mastectomy was done in 91. 0 % (N = 61), and 6 (9 %) patients underwent breast conservation surgery. Adjuvant chemotherapy was given to 43 patients (64.2 %), while among 24 (35.8 %) patients who received neoadjuvant chemotherapy (NACT)) pathological complete response (pCR) was seen in 6 (25.0 %) patients. Post mastectomy radiation therapy, as part of adjuvant treatment, was given to 41 (61.2 %) patients. Chemotherapy regimen mostly consisted of anthracycline in 6 patients (9.0 %), anthracycline along with taxane as sequential therapy was considered in 51 patients (76.1 %) whereas remaining 10 patients (10.9 %) were treated with anthracycline taxane concurrent regimen. At a median follow up of 45 months, 23 patients (34.32 %) showed metastatic disease of which lung was found to be the most common site of recurrence (16.4 %), followed by brain (9 %) multiple sites (7.5 %) liver (3 %) and bone (3 %). Local recurrence occurred in 4 cases of which 2 cases recurred in chest wall and 2 as supraclavicular nodal recurrence.

On univariate analysis, clinical and pathological nodal status, clinical size of the tumour, LVI, grade, and nodal density were found to have a significant impact on DFS whereas all these parameters except grade and LVI were found significantly associated with OS. Clinical tumour stage as advanced from T1 to T4 DFS showed a decline from 100 % (T1) to 12. 5 % (T4), OS came down from 100 % (T1) to 25 % (T4). Clinical nodal stage showed a fall of DFS from 78.3 % (N0) to 0 % (N3) and OS from 82.6 % (N0) to 0 % (N3). Likewise, p Nodal stage made DFS to fall from 83.3 % (pN0) to 0 % (pN 3) and OS dropped from 83.3 % (pN0) to 0 % (pN 3). Nodal density < 0.05 had higher DFS (72. 7 %) compared to LND more than 0.05 (34.8 %). All these factors showed statistically significant association to DFS and OS. Grade and presence of LVI showed significant impact on DFS but those factors were not significantly associated with OS.

On multivariate analysis, c tumour stage and p nodal stage were found to have a significant impact on DFS and OS. c Tumour stage showed a HR of 3.79 and p nodal stage a HR of 5.30 for DFS. Both were found to have statistically significant association to DFS. With regard to OS c tumour stage had a HR of 3.03 and pNodal stage a HR of 4.45 both of which were significant statistically. The five-year overall survival (OS) was 65.7 % with a median of 50 months and disease-free survival (DFS) was 59.7 % with a median of 45 months.

Variable		Disease Free Survival		Overall Survival	
		%	P-Value	%	P-Value
Age	≤ 50 years	54.1 %	0.395	56.8 %	0.11
	> 50 years	66.7 %		76.7 %	
Menopausal status	Premenopausal	55.6 %	0.592	58.3 %	0.211
	Postmenopausal	64.5 %		74.2 %	
Grade	1	100 %	0.02*	100 %	0.112
	2	69.7 %		72.7 %	
	3	43.3 %		53.3 %	
Clinical tumour stage	T 1	100 %	< 0.0001*	100 %	< 0.0001 *
	T 2	77.8 %		83.3 %	
	T 3	42.9 %		47.6 %	
	T 4	12.5 %		25.0 %	
Clinical nodal stage	N 0	78.3 %	< 0.0001*	82.6 %	< 0.0001*
	N 1	58.6 %		67.6 %	
	N 2	22.2 %		22.2 %	
	N 3	0 %		0 %	
Pathological tumour stage	P T 1	100 %	0.192	100 %	0.211
	P T 2	64.4 %		71.1 %	
	P T 3	47.1 %		47.1 %	
	P T 4	33.3 %		66.7 %	
Pathological nodal stage	P N 0	83.3 %	< 0.0001*	83.3 %	< 0.0001*
	P N 1	56.3 %		81.3 %	
	P N 2	8.3 %		8.3 %	
	P N 3	0.0 %		0 %	
Lymphovascular invasion	Yes	33.3 %	0.012*	46.7 %	0.052
	No	67.3 %		71.2 %	
Nodal density	≤ 0.05	72.7 %	0.001*	75.0 %	0.01*
	> 0.05	34.8 %		47.8 %	
Pathological complete response (neoadjuvant cases only)	Yes	66.7 %	0.1	83.3 %	0.088
	No	27.8 %		38.9 %	

Table 3. Univariate Survival Analysis

* indicates statistically significant difference among survival distributions at 5 % level of significance (P < 0.05)

Variable	Disease Free Survival		Overall Survival	
	HR (CI)	P Value	HR (CI)	P Value
Age	1.04 (0.96 - 1.12)	0.340	1.02 (0.94 - 1.12)	0.673
Menopausal status	0.64 (0.12 - 3.43)	0.603	0.3 (0.05 - 1.94)	0.205
Grade	1.38 (0.55 - 3.44)	0.495	0.97 (0.34 - 2.80)	0.960
Clinical tumour stage	3.79 (1.89 - 7.60)	< 0.0001*	3.03 (1.40 - 6.56)	0.005*
Clinical nodal stage	0.67 (0.27 - 1.68)	0.396	1.74 (0.73 - 4.17)	0.211
Pathological tumour stage	0.66 (0.30 - 1.44)	0.292	0.57 (0.23 - 1.38)	0.21
Pathological nodal stage	5.30 (2.22 - 12.63)	< 0.0001*	4.45 (1.85 - 10.67)	0.001*
Lymphovascular invasion	1.21 (0.42 - 3.5)	0.727	1.17 (0.41 - 3.38)	0.767
Nodal density	0.537 (0.186 - 1.55)	0.25	0.44 (0.13 - 1.41)	0.166

Table 4. Multivariate Survival Analysis

HR - Hazard Ratio; CI - Confidence Interval. * indicates statistically significant difference among survival distributions at 5 % level of significance (P < 0.05); HR > 1 indicates predictor increases the risk of the outcome

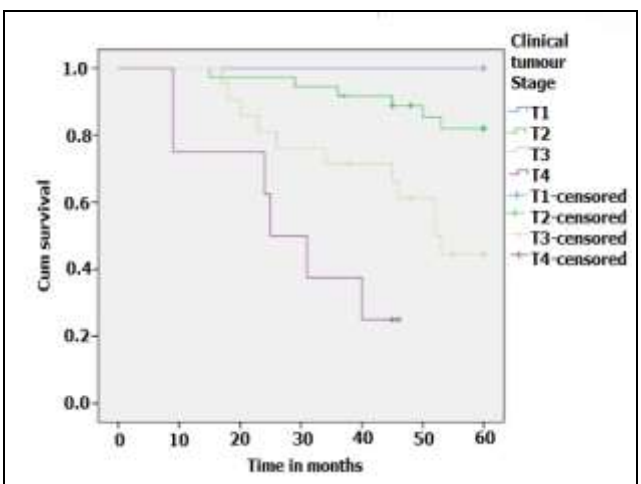

Figure 1. Kaplan-Meier Survival Curve for the Overall Survival of Clinical Tumour Stage

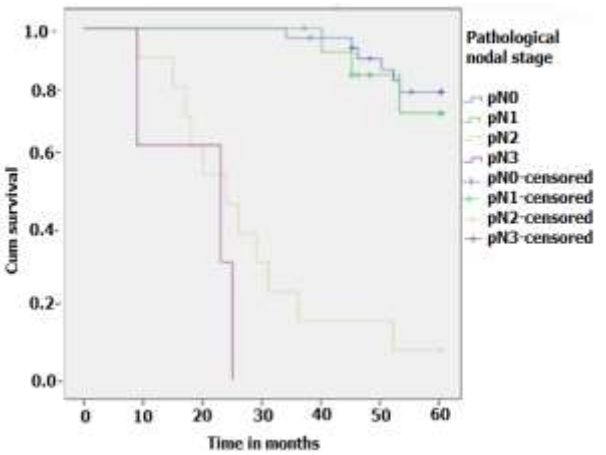

Figure 2. Kaplan-Meier Survival Curve for the Overall Survival of Pathological Nodal Stage

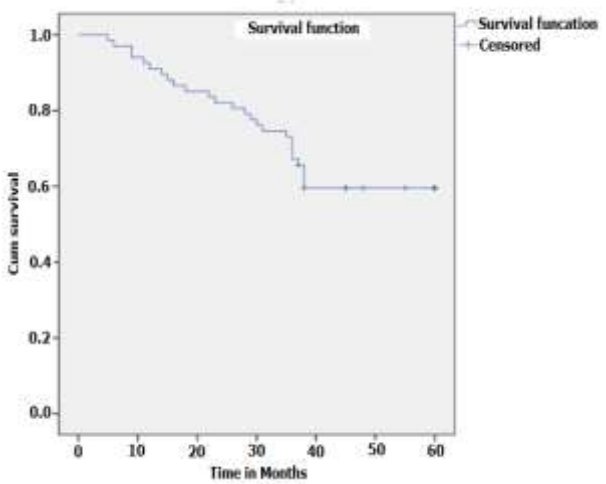

Figure 3. Kaplan-Meier Survival Curve for Disease Free Survival

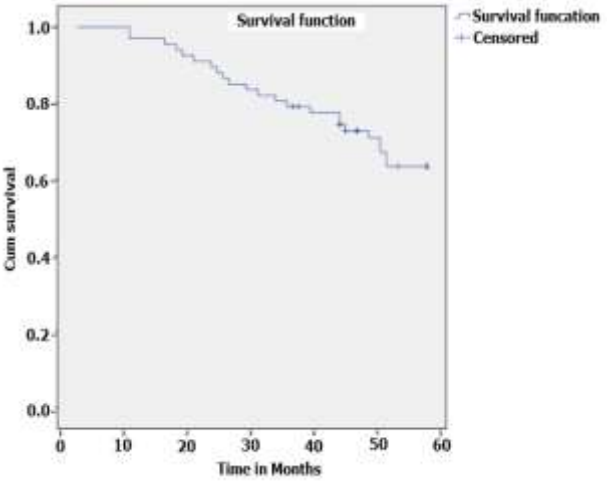

Figure 4. Kaplan-Meier Survival Curve for Overall Survival

DISCUSSION

TNBC, particularly in Indian women, has a frightening increase in incidence, and remains a challenge and scourge for clinicians to obtain treatment. TNBC has not only characteristic of aggressive clinical behaviour and insensitivity for endocrine and HER-2 targeted therapeutic strategies but also has the tendency for rapid metastasis and early relapses.[9,10,11]

More in-depth studies have now separated TNBC into various subtypes based on their molecular characteristics in the modern period. Lehman et al discovered six distinct subtypes of androgen receptors in TNBC by studying their gene expression profiles: basal-like 1 and 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptors.[12] Burstein et al. proposed a new classification for TNBC, dividing it into four subtypes: luminal androgen receptor, mesenchymal, basal-like immune-suppressed, and basal-like immune-activated. The basal-like immune-activated subtype was found to be associated with a positive prognosis in the same study.[13] TNBC with its heterogeneous nature and theses several subtypes which have different natural histories and may react to different treatment Approach based on chemotherapy, targeted therapy and immunotherapy. Based the approach to TNBC care remains challenging primarily because of its other high proliferative activity and grade, absence of infiltrative margin, focal necrosis, absence of gland formation, central scar / fibrotic foci, and existence of predominant lymphoplasmacytic infiltrates, rendering surgery and chemotherapy the only available treatment choices in combination or individually. Various studies from India and the western world have estimated TNBC in between 27 % to 35 % in literature and is estimated to be around 31 % as reported by Sandhu, et al. Lakshmaiah et al. Suresh et al.[14,15,16] The mean age of TNBC in our study was 51.6 years which was almost similar to our studies to that described in various studies in Western literature from the Indian perspective Chintalapani et al. Doval et al. and Verma et al have reported mean age of 50, 51.3 and 53 years for patients reported respectively[17,18,19] pCR rate of 25 % observed in this study was similar to Chintalapani, et al. study though it didn't show any significant prognostic value.[18] One major observation in this study that came as rare was, cT and cN were proportionate as well as pT and pN and documented rarely. Major studies in TNBC documented have higher stages of lymph node positivity for small tumours due to the aggressive nature of the tumour. In study by Wang et al. has reported similar results in our study majority presented as early breast cancer (64.2 %). pT2 stage was more common in our study (45 %) which is similar to Lakshmiah et al. (35.7 %),[16] Hakim et al. (31.4 %)[20] and Doval et al. (62.1 %).[17] Pathological lymph node positivity was found to be 46.3 % in our study. Lakshmiah et al.[16] and other Indian studies show pathological lymph node positivity around 50 % to 74 % whereas Doval et al.[17] study shows 36.8 %. Majority of grade II (49.3 %) followed by grade III (44.8 %) Most recurrences were systemic with only a few local recurrences. Lung was the major site of metastatic involvement similar to a study by Rathi et al.[21] The aggressiveness of the disease can be understood by an earlier onset of metastases and local recurrences which happened around 26 to 39 months of follow-up. The five-year DFS and OS were 59.7 % and 65.7 % respectively which were very low compared to other subtypes of breast cancer. The data corresponds to survival data from a few

other studies. As the various international studies have reported OS and DFS in between 72 - 79 % like Chinese studies reported DFS and OS 77.8 % and 79.9 %[22] and another study from Brazil by Goncalves et al. achieved a survival rate of 62 %.[23] The study by Liedtke et al showed 62 % 5 yr. OS.[24] The low survival rate in our study could be attributed to the aggressive nature of tumour in the reported set of patients. Very few patients received aggressive protocols in which anthracycline and taxane combined which might have resulted in low survival.

The univariate analysis of prognostic factors showed a significant association between disease-free survival and Clinical T stage (cT), Clinical Stage N (cN), Positive nodes (pN stage), LVI, grade, and lymph node density. Overall survival is significantly associated with cT, cN, pN, and lymph node density. In multivariate analysis only clinical-stage T and pathological node (pN) showed significant association with survival. This is the second such study from Kerala where advanced T and N stage was significantly associated with recurrence and survival which was matching with the similar study of Beena Kunheri et al.[25]

Lymph node density (LND) has been shown to play a predictive role after surgery for pancreatic, gastric, colon, oral cavity, and thyroid cancers.[19,26] But there is rare reporting of LND as prognostic significance in triple-negative breast cancers. This is the first case reported from Kerala where LND has been having a major statistical significance, affecting OS and DFS. Based on this single-institution study we can say LND can play a predictor of outcome and an important prognostic marker for both independent factors and as a useful adjunct to the current eighth edition TNM staging system. It can also identify the patients with LND having high risks of death in triple-negative breast cancer.

This study is retrospective in nature and the last 5 years, a lot of treatment advances have come in triple-negative breast cancer. In the cancer treatment scenario in India, a lot of major decisions are still affected by cost as the majority of cancer patients are non-insured which plays a major constraint in selecting the optimal treatment strategies. TNBC is a heterogeneous group. To develop treatment strategies with the current menu of chemotherapy choices and potential combinations of targeted therapies, molecular biomarkers to predict response to specific treatment setting must be identified.[27] Which can be based on molecular staging and targeted therapy like BRCA 1, EGFR mutation and angiogenesis-based treatment strategies. Many clinical trials are currently evaluating a number of new promising treatment options. Androgen receptor inhibitors, antibody–drug conjugates (e.g., sacituzumab govitecan), and Akt inhibitors are among the most promising.

CONCLUSIONS

Triple-negative breast cancer is a heterogeneous disease and poses a major challenge and uphill task during treatment as these tenacious tumours have aggressive tumour biology. In the absence of biomarker-based therapeutic methods, targeted treatments neglect one significant desired outcome aimed at minimising recurrences and improving survival in this patient population. There are many developments in treatments for metastatic triple-negative breast cancer, such as poly-ADP ribose polymerase (PARP) inhibitors, EGFR targeted therapies and tailor-made therapies but in non-metastatic breast cancer there is a dearth of adequacy in available therapeutics as treatment is still heavily dependent on available chemotherapeutic regimens. For improved survival and positive clinical outcomes, we can look for the use of predictive biomarkers which are indispensable and can help in designing a targeted treatment approach currently being used in metastatic triple-negative breast cancer treatment. In current era of immunotherapy, novel biomarkers that can predict immunotherapeutic response must be identified and implemented as soon as possible for better outcomes. In Indian clinical setup and especially centres like Kottayam will be heavily benefitted with this enforcement and appurtenances with superior targeted therapies to address a challenging disease like TNBC. The identification of predictive biomarkers, as well as a comprehensive understanding of their clinical and molecular diversity, are critical for future therapeutic changes. It will aid in the advancement of TNBC care by implementing a new receptor based targeted approach in the adjuvant and neo adjuvant stages rather than the metastatic stage for more selective and effective disease therapy and better outcome.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

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