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Oncology

PROGNOSTIC FACTORS IN TRIPLE NEGATIVE BREAST CANCERS

Dr Amitabh Pandagle	M.D., Assitant Professor, Department Of Radiotherapy And Clinical Oncology, Cama And Albless Hospital, Mumbai.
Dr Priyanka Bhoj*	M.D., Assitant Professor, Department Of Radiotherapy And Clinical Oncology, Cama And Albless Hospital, Mumbai. *Corresponding Author
Dr Pranjil Mandloi	Senior Resident (Academic),DNB SS Medical Oncology, Artemis Hospital, Gurgaon.
Dr Aradhna Tripathi	M.D. Radiation Oncology, Jabalpur.

ABSTRACT

Background- The study was conducted to assess the mortality rate and factors associated with mortality in triple negative breast cancer patients. **Methodology-** The study was conducted as a retrospective record based study at Cama and albless hospital Mumbai on cases with TNBC. Mortality rate and factors associated with poor mortality were observed. **Results-** In present study, out of 444 cases, 135 (30.4%) succumbed to death. Odds of mortality was significantly higher in TNBC with MRBS score >7 on univariate analysis and advanced stage, presence of PNE, LVI and PNI (p<0.01) on both univariate and multivariate analysis. **Conclusion-** Triple negative breast cancer constitute significant proportions of breast cancer and are aggressive tumors. The risk of recurrence and mortality is high in such cases. Factors associated with high risk of mortality in triple negative cancers include advanced stage, high MRBS score, presence of Perinodal extension (PNE), Lymphovascular invasion (LVI) and Perineural invasion (PNI).

INTRODUCTION

Breast cancer is one of the most common cancer in India. According to Population based cancer registry, breast cancer followed by cancer cervix are the most common cancer in females in India.[1] According to GLOBOCAN 2018 data, the incidence of breast cancer is reported to be 14% and had approximately 50% mortality.[2] Breast cancer is a heterogeneous disease with variable biological behavior, and response to treatment and prognosis may also vary.[3,4] Breast cancer can be classified into four molecular subtypes based upon estrogen receptor (ER), progesterone receptor (PR) and HER 2 receptor expression i.e. Triple positive (with expression of all three receptor), ER/PR positive subtype, HER-2 positive subtype and Triple negative (absence of ER, PR and HER2 receptor expression).[5]

The management modality as well as prognosis depend upon receptor expression. Targeted therapy is useful in management of breast cancer patients with ER/PR or HER2 receptor expression whereas TNBC cases require systemic chemotherapy drugs for their management. TNBC are considered as most malignant subtypes. These cancer are associated with aggressive features such as increased tumor size, increased risk of recurrence and lymph node invasion. Thus, patients with triple negative breast cancer has aggressive course, and risk of recurrence is high.[6]

As TNBC is associated with worst prognosis, certain prognostic factors may help in determining the risk of mortality and predict survival in these cases. The present study was therefore conducted to assess the mortality and factors associated with mortality in triple negative breast cancer patients.

METHODOLOGY

The present study was conducted as a retrospective record based study on a total of 444 patients with TNBC managed during the study period of 5 years i.e. from 1st March 2016 to 28th February 2021 at Cama and albless hospital Mumbai.

After obtaining ethical clearance from Institute's ethical committee, the records of all the cases diagnosed with breast cancer during the study period at our institute was retrieved from the MRD department. The records were thoroughly analysed and triple negative breast cancer patients whose outcome was known were included whereas records of patients with ER/PR or HER 2 or both receptor expression were excluded from the study. Detailed data regarding sociodemographic variables such as age, menopausal status, place of residence, grade and stage of tumor etc. was noted and entered in questionnaire. Also, the Modified Richardson bloom score (MRBS), Perinodal extension (PNE), Lymphovascular invasion (LVI) and Perineural invasion (PNI) was retrieved from the records.

Statistical methods

Outcome in the form of death or alive was noted. Msexcel was used form compilation of data and IBM SPSS software version was used for data analysis. Numerical data was expressed as mean and SD while categorical data was expressed as frequency and proportions. Multivariate analysis was done to assess the risk of mortality. P value less than 0.05 was considered statistically significant.

RESULTS

We obtained 2198 records from MRD department and of them 598 cases were TNBC. Among them 444 cases fulfilled the inclusion criteria and thus data of these patients was analysed.

Figure 1- Mortality rate in TNBC cases
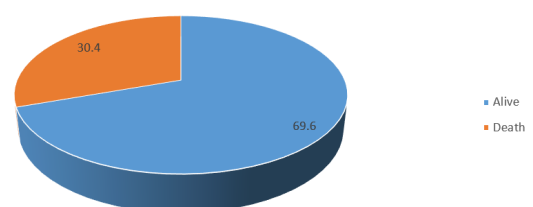
In present study, out of 444 cases, 135 (30.4%) succumbed to death whereas 69.6% cases were alive.

Table 1- Association of outcome with various factors

		Alive (n=309)	Death (n=135)	P value
Age (years)	≤25	5 (1.6)	2 (1.5)	0.09
	26-35	42 (13.6)	25 (18.5)	
	36-45	111 (35.9)	45 (33.3)	
	46-55	104 (33.7)	31 (23)	
	56-65	37 (12)	23 (17)	
	>65	10 (3.2)	9 (6.7)	
Menopause	Attained	166 (53.7)	69 (51.1)	0.78
	Not attained	143 (46.3)	66 (48.9)	
Grade	1	8 (2.6)	7 (5.2)	0.28
	2	49 (15.9)	17 (12.6)	
	3	252 (81.6)	111 (82.2)	
MRBS	5	50 (16.2)	11 (8.1)	0.001
	6	63 (20.4)	14 (10.4)	
	7	32 (10.4)	12 (8.9)	
	8	96 (31.1)	46 (34.1)	
	9	68 (22)	52 (38.5)	
Stage	1-3B	307 (99.4)	53 (39.3)	0.001
	>3B	2 (0.6)	82 (60.7)	
PNE	Positive	24 (7.8)	89 (65.9)	0.001
	Negative	285 (92.2)	46 (34.1)	
LVI	Positive	63 (20.4)	102 (75.6)	0.001
	Negative	246 (79.6)	33 (24.4)	
PNI	Positive	10 (3.2)	84 (62.2)	0.001
	Negative	299 (96.8)	51 (37.8)	

Mean age of patients with TNBC was 46.2 ± 10.8 years. Table 1 reveal that higher MRBS score, advanced stage, Perinodal extension (PNE), Lymphovascular invasion (LVI) and Perineural invasion (PNI) were significantly associated with mortality (p<0.05).

Table 2- Univariate and multivariate analysis for predictors of mortality

		Univariate		Multivariate	
		OR (95%CI)	P value	OR (95%CI)	P value
Age (years)	>65	1.59 (0.97-2.6)	0.10	3.6 (0.71-18.1)	0.12
Menopause	Attained	0.56 (0.07-1.2)	0.18	1.6 (0.6-2.6)	0.22
Grade	>2	1.03 (0.7-1.5)	0.87	0.98 (0.36-2.7)	0.97
MRBS	>7	1.84 (1.3-2.6)	0.001	1.84 (0.79-4.2)	0.15
Stage	>3B	6.63 (5.2-8.5)	0.001	7.4 (1.8-18.1)	0.001
PNE	Positive	5.67 (4.3-7.5)	0.001	6.6 (1.4-15.96)	0.001
LVI	Positive	5.23 (3.7-7.4)	0.001	5.98 (1.88-16.5)	0.09
PNI	Positive	6.13 (4.7-7.9)	0.001	7.15 (1.72-15.8)	0.001

In present study, univariate and multivariate analysis was done to assess the risk of mortality in presence of certain risk factors. Odds of mortality was significantly higher in TNBC with MRBS score >7 [OR-1.84 (95% CI-1.3-2.6), p<0.01)], stage >3B [OR-6.63 (5.2-8.5), p<0.01)], PNE [OR-5.67 (4.3-7.5), p<0.01)], LVI (OR-5.23 (3.7-7.4), p<0.01) and PNI (OR-6.13 (4.7-7.9), p<0.01)] on univariate analysis. Similarly, on multivariate analysis, odds of mortality was higher in advanced stage, presence of PNE, LVI and PNI (p<0.01).

DISCUSSIONS

Triple negative breast cancer characterized by non-expression of ER/PR or HER 2 receptor has been associated with poor prognosis as compared to breast cancers with hormonal receptor expression, These tumors have aggressive

phenotype and may relapse early following diagnosis.[6] This cancer has characteristic pattern of recurrence and maximum deaths are reported within 5 years following the initiation of treatment.[7] As TNBC is known to have aggressive course and poor clinical outcome, various morphological and biological features which may be of prognostic significance, are associated with uncertainty and controversy. The present study is an attempt to assess the mortality rate and factors associated with mortality in triple negative breast cancer patients.

In this retrospective analysis, we included relatively large sample of patients (444) with the median follow-up of approximately 4-5 years. Literature suggest that patients with Triple negative breast cancer is associated with increased risk of distant metastasis, recurrence and mortality. Mortality was observed in 30.4% cases in our study. According to American cancer society, mortality rate in TNBC may vary depending upon SEER stage. The 5 year survival rate in localized cancer has been documented as 91% whereas breast cancer with regional and distant metastasis is associated with poor prognosis.[8]

In present study, we documented no significant association of age and menopausal status with mortality. However, on univariate and multivariate analysis risk of mortality was significantly higher in patients with advanced stage of cancer, presence of Perinodal extension (PNE), Lymphovascular invasion (LVI) and Perineural invasion (PNI) (p<0.01). Our study findings were supported by findings of Ryu et al in which LVI and perineural invasion was associated with significant mortality risk and poor prognosis. Although the mechanism of LVI has not been clearly proven, LVI could reflect a surrounding tumor microenvironment that predicts underlying aggressive tumor and worse prognosis.[9] The authors documented LVI to be an independent prognostic factor in patients with negative lymphnode on adjuvant chemotherapy.[9] However, LVI can be graded as nil, minimal, moderate and marked according to Uematsu et al[10] and higher the degree of LVI, poor was the prognosis (p<0.05).[10]

Perinodal extension and perineural invasion was associated with higher risk of mortality on both univariate as well as multivariate analysis. These findings were supported by previous studies. Literature suggest that positive axillary node is associated with increased risk of local as well as distant recurrence and thus mortality. Overall, survival rates have been documented upto 40% in node-positive patients as compared to patients with node negative breast cancer.[11-13] Our study findings were also supported by findings of Singh et al, where authors observed significantly higher risk of recurrence with pathological stage, perineural invasion (PNI) as well as number of positive lymph nodes (p= < 0.001).[14]

On univariate analysis, MRBS score >7 was associated with significant risk of mortality but the risk was statistically significant on multivariate analysis in our study. Similar findings were observed in a study by Kwon et al in which higher grade of MRBS score was significantly associated with reduced survival on univariate analysis (p<0.05).[15] However, Chollet et al. documented that MRBS score rather than Scarff-Bloom-Richardson (SBR) system has significantly higher prognostic value.[16]

CONCLUSION

Triple negative breast cancer constitute significant proportions of breast cancer and are aggressive tumors. Patients with TNBC usually present in locally advanced stage. The risk of recurrence and mortality is high in such cases. Factors associated with high risk of mortality in triple negative cancers include advanced stage, high MRBS score, presence of Perinodal extension (PNE), Lymphovascular invasion (LVI) and Perineural invasion (PNI).

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