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A Simple Risk Scoring System for Predicting Recurrence in Women with Locally Advanced Breast Cancer (LABC) Treated with Neoadjuvant Chemotherapy (NACT)

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Authors' contributions

This work was carried out in collaboration among all authors. Author SA designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Author PM managed the analyses of the study. Author SA managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Breast cancer commonly presents in locally advanced stage (LABC) in developing countries, for which NACT followed by surgery and radiotherapy is the standard of care. There is a need for a simple tool to risk categorise patients in the clinic, so that treatment intensification can be offered to women with high risk of recurrence.
Materials and Methods: Data of prospectively maintained database of LABC (between January 2007 - December 2012), who received NACT followed by surgery, radiotherapy and endocrine therapy was retrospectively analysed for clinico-pathological factors associated with disease

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recurrences. A recurrence risk scoring model was developed on the basis of regression coefficient of identified independent risk factors.
Results: In the data set of 206 patients, the median follow-up was 48 months (range: 6-156 months) and mean and median disease-free survival (DFS) were 87.41 and 85 months. The 1, 5, 10 years DFS was 95%, 54% and 41%. The independent risk factors (on modified p value <0.40) for recurrence were Tumour stage, Nodes stage, grade, age groups, pathologic complete response, intrinsic subtype, and type of surgery. Risk score prepared by regression coefficient (β), was in the range of 1-8 with median score of 5. ROC curve showed that area under ROC Curve of the score was 71.8% (95% CI: 64.8%-78.8%, p<0.001). To detect recurrences, a risk score ≥3 had at least 93.1% sensitivity and 31.9% specificity whereas score ≥4 had at least 73.5% sensitivity and 59.6% specificity. Based on cluster analysis, score 1-4 was identified as low risk whereas 5-6 as moderate risk group and ≥7 identified as high-risk group and their mean/median disease free survival time were 107.86/ NR, 66.99/30 months and 58.34/20 months respectively.
Conclusions: The significant difference in DFS among three risk groups, indicates goodness of the fit of our risk score model. The risk scoring model developed by us is simple, easy to use in clinic and can be used for selecting high risk patients who benefit from treatment intensification.

Keywords: recurrence risk score, neoadjuvant therapy, locally advanced, breast cancer.

1. INTRODUCTION

The incidence of locally advanced breast cancer (LABC) represents only 2% to 5% of all breast cancers in western countries but its incidence is higher in developing countries (80%) [1]. This is because in developing countries young women more often present with advanced disease with high risk features, and report late to practitioners due to their tendency to hide their disease and their ignorance about the nature of disease [2]. 25% patients in such countries are of young age (< 40 yrs.) and 45% are premenopausal in these countries. 80% of young women present as LABC and 90% of them have node positive disease [3]. Long-term survival in such cases has been greatly improved with aggressive tri-modality treatment [4]. A combination of Anthracycline- and taxane-based chemotherapy regimen is the standard NACT regimen with trastuzumab in Her-2 neu positive LABC. The vast majority of patients will have clinical response to therapy, and 15% to 25% will experience a pathological complete response (pCR) [3]. It has been reported that complete pathologic response is associated with superior outcomes among women with LABC [4]. The other advantage of NACT is down-staging of disease to allow breast conservation (BCS) in large tumours and higher feasibility of resection of a previously inoperable disease. The 5 year overall survival after NACT, mastectomy and radiotherapy has been reported as 90% in pathologically node negative (ypN0) and 75% in pathologically node positive disease (ypN+) in developed countries, while in developing countries, the 5 year OS is 40% in such patients. There is clearly a need for intensifying therapy for high risk patients to improve outcomes. Risk stratification of such patients at presentation would help in identifying those at highest risk of relapse, in whom treatment intensification would be beneficial.

The primary aim of the present study was to develop a recurrence risk scoring system according to the risk factors that were identified among clinic-pathological and treatment related factors in patients of LABC treated in our department from 2007 to 2012. The secondary aim was to internally validate the risk scoring model developed by us so that it can be routinely used in clinical practice.

2. METHODS

The data of consecutive patients of LABC (non-inflammatory) registered between January 2007 to December 2012 in the department of Radiotherapy, who underwent NACT (taxane and or anthracyclines based) followed by definitive surgery, radiotherapy and endocrine therapy were extracted from a prospectively maintained database. Patients were staged according to the American Joint Committee on Cancer (AJCC), 7th edition staging system. Data for age, comorbidities, disease and treatment related characteristics, pathological response rates, and outcome were collected. The choice of NACT was as per the physician's choice which was either sequential four cycles of 3 weekly FEC / CAF (5-FU 600 mg/m², epirubicin 90 mg/m² / Adriamycin 60mg/m2, cyclophosphamide 600 mg/ m²) followed by four cycles of 3 weekly docetaxel (docetaxel 85 mg/m2, 3 weekly) or 6

cycles of CAF (cyclophosphamide 600 mg/ m², Adriamycin 60 mg/m2, 5-FU 600 mg/m²). Since trastuzumab was not widely available at that time or was costly, we had not started using trastuzumab as a part of NACT during this period. Patients were then subjected to either modified radical mastectomy (MRM) or breast conserving surgery (BCS) depending on extent of down-staging and suitability for breast conservation. All patients underwent axillary dissection up to level II axillary nodes. Thereafter all patients received postoperative radiotherapy (PORT) to chest wall and supraclavicular lymph-nodes (in MRM cases) and intact breast radiotherapy and supraclavicular lymph-node irradiation (in BCS cases). The dose of radiotherapy was 50 Gy in 25 fractions in 5 weeks (from January 2007- September 2011) and 40 Gy in 15 fractions in 3 weeks (after October 2011, when hypo-fractionated radiotherapy was adopted for routine use in the department). Radiotherapy was delivered by 3-D conformal technique. All patients with BCS also received boost of 10 Gy in 5 fractions in 1 week. Patients with hormone receptor positive were started on hormone therapy at least for 5 years. Overall pCR was considered according to FDA definition i.e. ypT0 ypN0 (i.e., absence of invasive cancer and in-situ in tumour as well as axillary lymph nodes).The data on intrinsic subtypes of breast cancer (Luminal type A, B, Her-2 neu enriched and triple negative) was obtained from the immunohistochemistry report.

2.1 Outcome Measures

Disease free survival (DFS) was calculated as the interval from successful treatment to the earliest occurrence of loco-regional recurrence or distant metastases. Follow-up data was updated up to March 2019. Patients alive without an event of interest (recurrences) or loss of follow up or death with unrelated causes were considered as censored. Overall survival was not evaluated for this modelling because our intent was to develop a risk score model to assess the recurrences in breast cancer patients.

2.1.1 Identification of clinico-pathological and treatment related factors affecting recurrence

To estimate the factors affecting the recurrence of the disease, age, grade of the disease, tumour stage, Nodal stage, Type of Surgery, Histological grade (Intrinsic subtype), pathological response to NACT in tumour as well as axillary nodes [complete response (pCR), partial response and stable disease were categorised as pPR] was ascertained from the histopathology report were evaluated. Age was categorised as less than and more than or equal to forty years, grade of tumour was categorised into two groups: low risk group (well differentiated) and high-risk group (moderate to poorly differentiated). These variables were included in analysis for final independent factors.

2.2 Statistical Analysis and Risk Scoring Model

Continuous variables are presented in mean ± standard deviation or median (range) whereas categorical variables in frequency (%). Univariate cox regression analysis was performed to evaluate the relationship between Disease free survival (DFS) and identified demographic and clinical variables. All the significant factors on univariate analysis (with p value < 0.40, modified cut-off value was taken because some clinically proven variables like tumour stage etc were not significant ie $p<0.05$) were considered to be included in multivariate analysis. In the final model, all the variables within range of modified p value have been considered as independent factors for disease recurrences. The score of each risk factor was weighted according to the regression coefficient in the final model obtained from the multivariate cox regression analysis. All the observed regression coefficient was multiplied by 2 and then rounded off to get the nearest integers (complete number) to produce a risk score. The total score for each patient represented the sum of scores for independent risk factor. Mann Whitney U test was used to compare the scores between recurrence and non-recurrence patients. The predictive performance of the observed score was assessed by Area under ROC Curve and estimated cut-off value of the observed score with corresponding sensitivity and specificity. Bootstrapping model (at 1000 bootstrap samples) was used to validate the confidence interval. Cluster analysis was used to categorize the total risk score of recurrence into 3 groups (using the predicted probabilities estimated from the total score using binary logistic regression analysis). All the statistical analyses were performed using Statistical Package for the Social Sciences, version 23 (SPSS-23, IBM, Chicago, IL, USA).

3. RESULTS

In this study, 206 patients were included in the final analysis. Pre-treatment patient

characteristics are mentioned in Table 1. Median age of the breast cancer patients was 47 years. 53.4% women were postmenopausal. Most of the patients (70%) were age group of 40 years or more. T3 and T4 stage together comprised 84% patients and 92% patients had node positive disease. The proportion of various intrinsic subtypes in our population were Luminal A (26%), Luminal B (11%), Her-2 type (23%) and triple negative (40%). 58% patients received a combination of anthracyclines and taxanes and 30% could undergo breast conservation (BCS). 87% patients were in stage III whereas 53%, 43% and 4% were in the grade of III, II and I respectively. (Table 1).

At a median follow-up of 48 months (IQR 19-92 months, range 6-156 months) and 87 months for those alive (IQR 57-102 months) the 1, 5, 10 years DFS was 95%, 54% and 41%. No event was reported after 10 years. In Table 2, Kaplan Meier method showed that median DFS was higher in older women > 40 years (36 vs 105 months). Similarly, median follow-up time of the other variables are also given in Table 2.

Table 1. Pre-treatment characteristics of Breast Cancer Patients (N=206)

Variable´s	Number (%)
Age in years (median)	47
<40 (years)	61 (30%)
≥40 (years)	145 (70%)
Menopausal status	
Premenopausal	46.6%
Postmenopausal	53.4%
Laterality	
Right	88 (42.7%)
Left	118 (57.3%)
T status	
T2	33 (16%)
T3	80 (39%)
T4	93 (45%)
N status	
N0	17 (8%)
N1	86 (42%)
N2	83 (40%)
N3	20 (10%)
Intrinsic subtype	
Luminal A	54 (26%)
Luminal B	26 (11%)
Her 2 type	48 (23%)
Triple negative	78 (40%)
Type of NACT	
Adriamycin based	86 (41.8%)
Combination of Adriamycin, Texan based	120 (58.2%)
Type of surgery	
Modified Radical mastectomy	143 (70 %)
Breast conservation surgery	63 (30 %)
Pathology	
Pathological CR	46 (22.3%)
Pathological PR+SD	170 (77.7%)
Stage group	
Stage II	25 (13%)
Stage III	181 (87%)
Grade	
1	9 (4.4%)
2	88 (42.7%)
3	109 (52.9%)

Table 2. Factors affecting disease recurrences in Breast Cancer Patients (N=206)

Variable´s	Univariate Analysis		Multivariate Analysis	
	Median DFS #	P value$	Hazard rate (95% CI) €	P Value
Age group				
< 40 (n=127)	36	0.104	1.59 (1.04-2.42)	0.032
> 40 (n=79)	105			
N status				
N0 (n=18)	85			
N1 (n=86)	120	0.054	0.97(0.40-2.35)	0.260
N2 (n=83)	46		1.37(0.56-3.38)	
N3 (n=19)	24		1.81(0.64-5.06)	
T status				
T2	NR			
T3	115	0.176	1.34(0.70-2.56)	0.348
T4	48		1.60(0.83-3.07)	
Intrinsic Subtype				0.002
Luminal A	120			
Luminal B	NR	0.049	1.05(0.50-2.20)	
Her-2 enriched	NR		1.16(0.62-2.16)	
Triple negative	45		2.40(1.42-4.08)	
Grade of Tumours				0.208
Well differentiated (n=19)	NR	0.120		
Poorly differentiated (n=187)	80		1.73(0.74-4.04)	
Type of NACT				--
Adriamycin (n=86)	85	0.990	-	
Adriamycin +Taxanes (n=120)	80			
Pathological CR (n=46)	NR			0.109
Pathological PR+SD (n=170)	72	0.046	1.60(0.90-2.82)	
Type of Surgery				0.048
BCS (n=63)	NR	0.015	1.67(1.00-2.78)	
MRM (n=143)	105			

#Kaplan Meier method used to compute median Disease-free survival (DFS) time and $p value by Univariate cox regression analysis. €Multivariate Cox regression analysis performed to compute Hazard ratio (HR) and corresponding 95% confidence interval (CI). NR: Median could not compute as disease free probability not reached to 50%. P<0.05 significant

3.1 Factors Affecting Recurrence

To estimate the factors affecting the recurrence of the disease, Age group, N status, T status, Intrinsic Subtype, Type of NACT, Pathological responses and Type of Surgery were tested in univariate analysis. Out of these variables, Intrinsic Subtype, pathological responses, and type of surgery were significant whereas age, N status, T status and Grade of the disease were statistically insignificant. To include the variables in multivariate analysis, modified cut-off p value ($p<0.4$) was taken. Result showed that; age group (<40 years), Intrinsic Subtype and type of surgery were statistically significant (each $p<0.05$) whereas Nodes status, tumour stages, Grade of disease and pathological CR were statistical insignificant (each $p>0.05$). Although based on modified criteria ($p<0.40$), except Type of NACT, rest other variables were considered independent factors affecting disease recurrences. (Table 2).

3.2 Risk Scoring for DFS

Based on the Regression coefficient, risk score observed for the various groups came out in the range of 0 to 2. When variable was divided into more than two groups, reference group score was observed zero. (Table 3). Total score of the individual patients was varying between 1 to 8 with median of 5 where larger score showing higher risk. (Table 4).

3.2.1 Predicted probability and stratification of the risk score

Predicted probability of the risk score was estimated using binary logistic regression

analysis. Result showed that patient with one risk score had 9% chances of the recurrences whereas risk with 8 risk score had 90% chances of the recurrences. (Table 4, Fig. 1). Based on cluster analysis, score 1-4 was identified as low risk whereas 5-6 as moderate risk group and ≥7 identified as high-risk group. Based on this risk grouping stratification, the mean/median disease free survival time were 66.99/30 months, 58.34/20 months and 107.86/ NR of the low risk group (Score : 1-4), moderate risk group (Score : 5-6) and high risk group (Score ≥7) respectively. (Fig. 2).

3.2.2 Diagnostic accuracy of the risk score

Diagnostic accuracy and Cut off value of the Risk Score were estimated using Receiver operating characteristics (ROC) curve. Result showed that area under ROC Curve of the score was 71.8% (95% CI: 64.8%-78.8%, p<0.001). To detect recurrences, a risk score ≥3 had at least 93.1% sensitivity and 31.9% specificity whereas score ≥ 4 had at least 73.5% sensitivity and 59.6% specificity to detect recurrence. (Fig. 3).

Table 3. Development of a risk scoring model to predict recurrence in LABC (N=206)

Variable´s	Regression Coefficient [β, 95% CI]	Final Score
Age		
<40	0.463 (0.025, 0.999)	1
>40	-0.463 (-973, -0.025)	0
Grade		
Well differentiated	-0.546 (-1.70, -0.298)	0
moderately and Poor	0.546 (0.297, 1.706)	1
T status		
T2		0
T3	0.289 (-3.81, 1.076))	1
T4	0.470 (-0.173, 1.235)	1
N status		
N0		0
N1	-0.036 (-0.966, 0.998)	0
N2	0.316 (-0.512, 1.341)	1
N3	0.591 (-0.543, 1.855)	1
Histological subtype		
Luminal A		0
Luminal B	0.046 (-0.863, 0.934)	0
Her 2 enriched	0.150 (-0.553, 0.825)	0
Triple negative	0.877 (0.379, 1.514)	2
Pathological response		
pCR	-0.467 (-1.15, 0.035)	0
pPR+SD	0.467 (-0.025, 1.143)	1
Type of surgery		
BCS	-0.512 (-1.11 to -0.043)	0
MRM	0.512 (0.032, 1.125)	1

95% Confidence Interval (CI) of the Regression coefficient (β) was measured on 1000 bootstrap samples. Regression coefficient was insignificant (p>0.05) when 0 fallen within lower and upper limit.

Table 4. Predicted probability of the risk scores (N=206)

Total Score	Predicted Probability of reoccurrence (%)
1	9
2	15
3	25
4	38
5	53
6	68
7	80
8	90

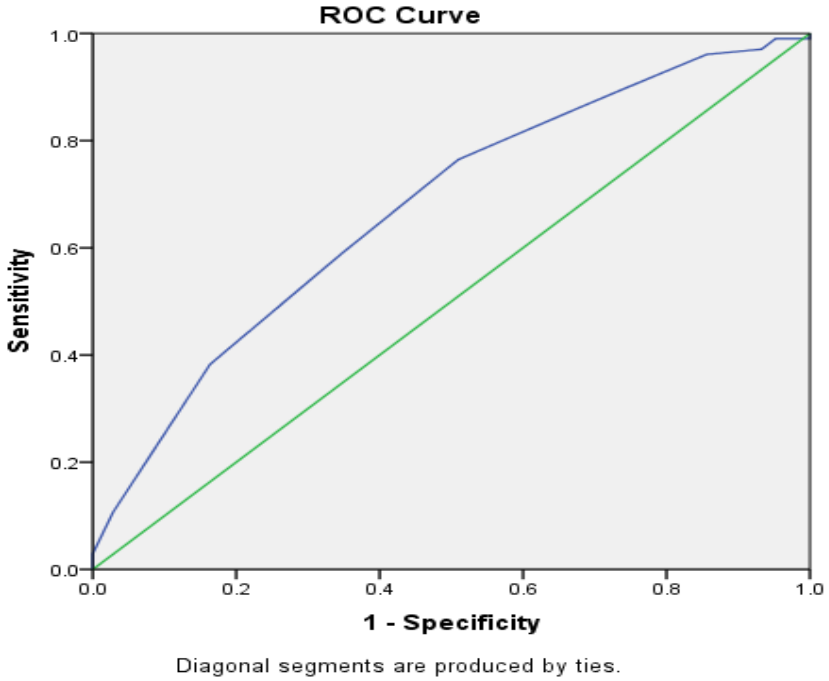

Fig. 1. AUC (Area under curve) curve showing diagnostic accuracy of the risk score model to detect recurrence

DFS according to different risk categories

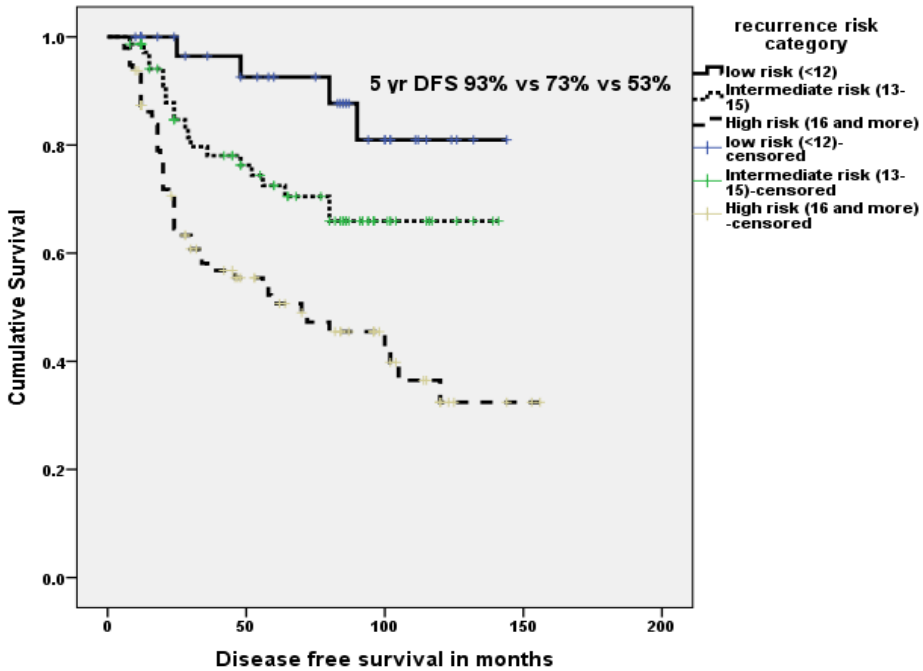

Fig. 2. Disease free survival (DFS) according to different risk categories

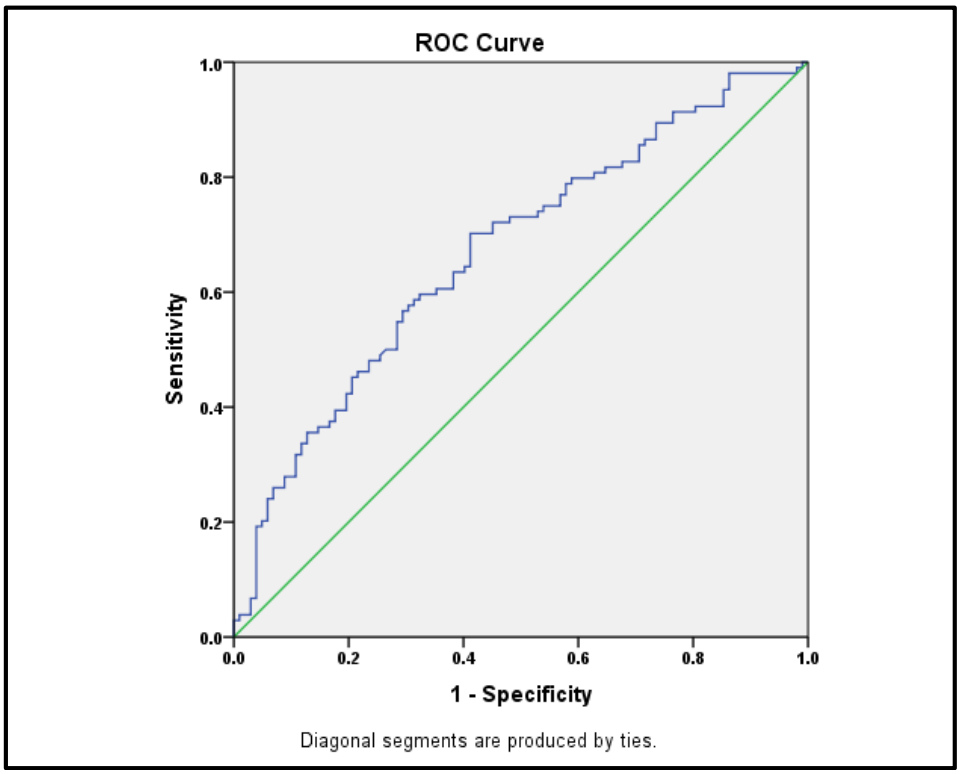

Fig. 3. AUC showing diagnostic accuracy of the predicted probability of time to event analysis to discriminate recurrence

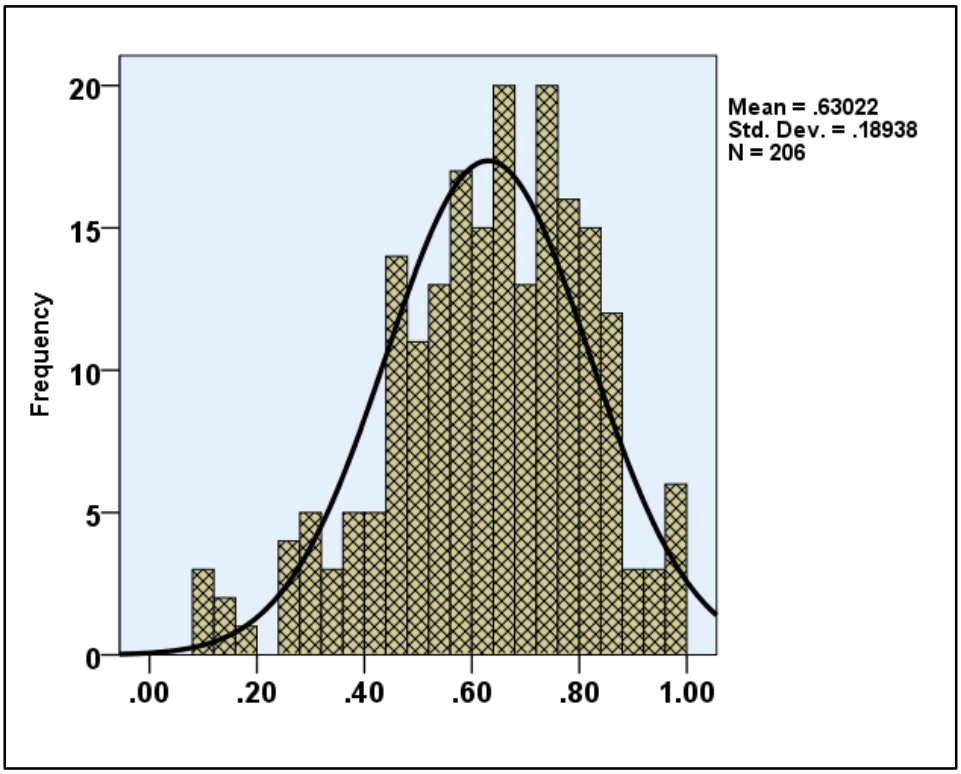

Fig. 4. Histogram showing the normal distribution of predicted probability values

4. DISCUSSION

Our findings reveal that the 1, 5, 10 years DFS was 95%, 54% and 41%. No event was reported after 10 years. The incidence of recurrences in our study patients was 49.5% which was also insignificantly higher in young women (57.4% vs 46.2%, p=0.143), increasing nodal stage from N0 to N3 (35.3% vs 41.9% vs 57.1% vs 63.2%, p=0.080) , and significantly higher in patients with absence of pCR (34.8% vs 53.8%, p=0.023). The poor prognosis of young women with breast cancer, high nodal burden, and non-achievement of pCR is well known [4-6]. The variables selected by us for risk scoring were those which were retained as significant factors in multivariate modelling and have been reported as important prognostic factors for breast cancer in many studies [4-6]. Even though grade was not significant on univariate analysis, we incorporated it because it is a proven prognostic factor for predicting recurrence risk in BC [7]. The poor prognosis of young women with breast cancer is well known and also emerged as a significant prognostic factor in our population [5] While data from the west report only 9% women with BC under 35 years age, our population comprised of 30% women under 40 years, thereby leading to higher recurrence risk [7]. As expected, the higher T and N status were associated with higher recurrence risk, consistent with other predictive models and a large number of studies [8]. We also found that the intrinsic subtype had a strong association with relapse which is also consistent with other studies [9]. The importance of pCR as a predictive and prognostic factor in LABC is well known and was also seen in our patients also. Though it's well known that the selected variables have an impact on recurrence and survival, the modelling proposed by us establishes the extent of impact of these factors. T3, T4, N2, N3 status, Her-2 neu enriched, triple negative disease and absence of pathological complete response had the highest RR scores as compared to grade and type of surgery.

We constructed and internally validated a scoring system to predict recurrence in LABC using one of the most accurate statistical methods. We realise the limitations of internal validation and we shall try to do an external validation in future. Our model has acceptable discriminatory capability (71.8%) and is well calibrated, as the curve is fairly smooth. Regarding selection bias, all patients with BC over a specific period were included in this study, i.e., none were excluded due to comorbidities, stage of disease or treatment received. Information bias was minimized through rigorous data collection. Many models are available in literature for early breast cancer, but only one for large operable and none for LABC [10]. The risk model available in literature for large operable disease is based on the combined analysis of NSABP-18 and 27 found age, T, N stage, and presence of pCR as significant factors predicting recurrence risk [6]. They created separate nomograms to be used for patients with BCS and mastectomy and this may not be handy to use in the clinic. The predictor variables of our system are easily obtainable in the clinic, allowing its routine use. Based on our model, patients can be categorised into 3 risk categories with significant differences in disease free survival time and proportion of recurrence free patients. Broadly speaking, presence of 4 risk factors at presentation indicates low risk, 5-6 risk factor as intermediate risk and equal or more than 7 as high risk. Patients in low risk group have least chance of recurrence as compared to those in intermediate (30% chance of recurrence) or high risk group (more than 50% chance of recurrence). The implications of worse score are to employ efforts to intensify treatment in these patients to decrease the incidence of recurrence. Since the main reason for relapse in our population was distant metastases, intensification of treatment could be either in form of intensifying neoadjuvant therapy or by offering maintenance therapy after entire course of treatment in partial responders. Likewise patients with 4 or less risk factors can be spared treatment intensification. Patients with pCR may be spared postoperative radiotherapy, the outcomes of which will be revealed by results of an ongoing RTOG study [11]. Our results are based on patients who received either anthracyclines or a combination of anthracyclines and taxanes as NACT. The evidence today shows that anti-Her 2 neu based NACT along with anthracyclines and taxanes induces higher pCR rates and impacts survival. Use of trastuzumab alone or in combination with pertuzumab along with standard chemotherapy is now the standard of care for NACT in Her-2 neu positive cases [12] Another strategy is to give carboplatin along with taxanes in triple negative tumours to increase pCR rates [13-14] Maintenance capecitabine or TDM1 (trastuzumab emtansine) has also shown promising results in triple negative and Her2 neu enriched tumours as revealed by CreatX and Katherine trials [15,16] Preoperative radiotherapy in partial responders to NACT also has shown to

increase pCR rates to 45% in some studies [17,18]. Immunotherapy also has recently shown improved outcomes in metastatic triple negative breast cancer and has immense scope for being explored in high risk women.

Another risk model for LABC (in abstract form) found absence of pCR, lymph node positivity, ER negativity, inflammatory histology and lack of radiotherapy as high risk features [19]. The impact of pCR was greatest in this database (hazard ratio: 4) which is similar to our results. This model is based on a heterogenously treated population, while ours is a homogenously treated population. We did not include inflammatory histology in our database since its behaviour is different from other LABC.

The strength of this study is that the model is based on patients with locally advanced breast cancer treated homogenously. All patients received PORT and all with hormone receptor positive status received hormone therapy for at least 5 years. Our results apply to both operable and inoperable patients. The model can be applied to all patients with LABC regardless of their clinical, histopathological or treatment characteristics. It is easy to use in clinic and does not need a nomogram or mobile app. Our results should be validated prospectively in other cohorts of LABC.

5. CONCLUSIONS

Our recurrence risk prediction model accounts for readily available clinico-pathologic factors (age, stage, grade, intrinsic subtype, pathologic response and type of surgery) and can reliably identify LABC patients likely to have a high-risk of recurrence who would benefit with treatment intensification. Our risk score models capable to detect the risk of recurrences evident from recurrence free survival plot. Our findings warrant validation in independent datasets of LABC.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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