



Predicting the likelihood of recurrence of pregnancy-associated breast cancer: Nomogram based on analysis of the French cancer network: Cancer Associé à La Grossesse

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1 Predicting the likelihood of recurrence of pregnancy-associated breast cancer:
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3 Grossesse

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Predicting the likelihood of recurrence of pregnancy-associated breast cancer: Nomogram based on analysis of the French cancer network: Cancer Associé à La Grossesse

Abstract :

Objective : Pregnancy associated breast cancer (PABC) are defined as breast cancer diagnosed during pregnancy and during the year following delivery. The prediction of poor prognosis events (PPE) such as recurrence is a major medical challenge of management for women with PABC. The aim of this study was to build a nomogram based on selected clinical and histological variables to predict recurrence.

Study Design: This retrospective study included 96 patients with PABC from January 2002 to January 2018. A multivariate Cox analysis of selected risk factors was performed and a nomogram to predict recurrence was built. The nomogram was internally validated.

Results: The overall recurrence rate was 22% (21/95) and the 3-years recurrence rate was 13% (12/95). Age at diagnosis, histological type, immuno-histological class, tumor stage (TNM), node stage (TNM) were associated with PPE in univariate analysis, and were included in the final Cox model to develop the nomogram. The predictive model had a concordance index of 0.83 (95% Confidence Interval (CI), 0.81-0.85) and 0.78 (95% CI, 0.76-0.80) before and after the 200 repetitions of bootstrap sample corrections, respectively, and showed a good calibration.

Conclusion: Our results support the use of the present nomogram based on 5 clinical and pathological characteristics to predict PPE in PABC with a high concordance. External validation is required to recommend this nomogram in routine practice.

Key words: Pregnancy-associated breast cancer, Recurrence, Prognosis, Recurrence free survival,

Introduction

Breast cancer is the most common malignancy associated with pregnancy [1,2]. The prevalence of pregnancy-associated breast cancer (PABC), commonly defined as breast cancer diagnosed during pregnancy or during the year following delivery. Approximately 0.2% to 2.6% of all breast cancers are discovered during pregnancy [3,4]. PABC constitutes a major treatment challenge due to its poor prognosis and its impact on both maternal and fetal health [3,5].

Women with PABC have been reported to have poor prognosis with a risk of recurrence and mortality of 40%[6]. Several epidemiological, histological, and immuno-histochemical risk factors have been reported, to identify patients for whom a personalized treatment and follow-up strategy should be adopted [7].

Amant et al. recently advocated a multidisciplinary decision-making approach for cancers diagnosed in a pregnant patient, always taking the patient's perspective into account [7]. In this setting, precision medicine is particularly relevant to overcome limitations due to the lack of evidence-based data especially for low incidence cancers. Clinicians lack reproducible and relevant data in PABC to, (i) predict the likelihood of recurrence, (ii) select women at high risk who would benefit from specific management and follow-up, and (iii) provide the patient with evidenced-based advice about her pathology [7].

Therefore, the aim of our study was to develop a nomogram to predict the likelihood of 3-year recurrence based on selected epidemiological, histological, and immuno-histochemical variables according to the database of the national network of Tenon – the CALG (Cancer Associé à La Grossesse) – created in France in 2008.

Materials and methods

Study population

We conducted a retrospective analysis using data extracted from the prospective database of women with histologically proven invasive breast carcinoma who were included in the PABC cancer network between January 2002 to January 2018, at the Tenon University tertiary referral center (France).

The study was approved by the Ethics Committee of the National College of French Obstetricians and Gynecologists (CNGOF) (reference number: CEROG 2012-GYN-10-03). All women had given written consent for the use of their data for clinical research.

Patients

For all the patients, epidemiological data (age at diagnosis, familial or personal history of cancer), histological and immuno-histochemical data (histological grade according to Ellis and Easton, hormonal-receptor status (estrogen receptors (ER) and progesterone receptors (PR)), HER2 overexpression, Ki67 expression) were recorded, as well as the molecular classification of the breast cancer. Patients were excluded if they did not have all these data available. The histological data corresponded to surgical specimens, except when neoadjuvant chemotherapy was performed in which case data from biopsy and initial imaging were used. For patients undergoing neoadjuvant chemotherapy, lymph node status was determined by sonography and axillary lymph node cytology before chemotherapy and on analysis of surgical specimen using the Sataloff criteria. ER and/or PR status was considered to be positive when $\geq 10\%$. For women with intermediate HER2 expression (score 2), a fluorescent in situ hybridization test (FISH) was performed. The decision whether to introduce adjuvant therapy was made by a multi-disciplinary oncology committee based on international and French guidelines[8-10]. Patients requiring chemotherapy received an anthracycline

agent (adriamycin or epirubicine), a taxane agent, or cyclophosphamide. No patient received tamoxifene or trastuzumab during pregnancy according to the European Society of Gynecology and Obstetrics (ESGO) recommendations [8,11]. Clinical follow-up consisted of physical examination and imaging techniques every 3 months for the first 2 years then every 6 months up to 5 years and then every year beyond 5 years.

Definition and classification of recurrence

Recurrent disease was assessed by physical examination, imaging techniques and biopsy when feasible.

We applied the following definition to describe the patterns of recurrence: local regional recurrence (LRR) was defined as recurrences in (i) the breast, (ii) the thoracic wall, or (iii) axillary lymph node. Distant recurrence (DR) was defined as (i) metastatic spread to organs whatever the location, (ii) peritoneal carcinomatosis, and (iii) extra axillary lymph node involvement.

Recurrence free survival (RFS) was defined as the time from the date of primary treatment to any recurrence and was censored at the date of the last follow-up or death without recurrence. Overall survival (OS) was defined as the time from primary treatment to death as a result of any cause.

Development of the model

The primary endpoint was the likelihood of recurrence at 3 years. A backward variable selection was performed to determine independent predictors. Significant risk factors in univariate analysis at the $P < 0.2$ level and known risk factors based on previous studies (lymph node status) were then included in a multivariate analysis. [12], [13]

Complexity of the model was controlled using Akaike information criteria[14]. The P-values in the multivariate analysis were based on Wald tests.

Accuracy of the model

The performance of the model was quantified with respect to discrimination and calibration

criteria [15,16]. Discrimination (i.e., whether the relative ranking of individual predictions is in the correct order) was quantified with the area under the curve (AUC) of the receiver operating characteristics (ROC). The AUC is a summary measure of the ROC that reflects the ability of a test to discriminate the outcomes across all possible levels of positivity. AUC ranges from 0 to 1 and a model is considered to have a poor, fair or good performance if the AUC lies between 0.5 and 0.6, 0.6 and 0.7 or is greater than 0.8, respectively [17]. Calibration (i.e., the agreement between observed outcome frequencies and predicted probabilities) was studied from graphic representations. The calibration curve can be approximated by a regression line with intercept α and slope β . These parameters can be estimated in a logistic regression model with the event as the outcome and the linear predictor as the only covariate. Well-calibrated models have an $\alpha=0$ and a $\beta=1$. Therefore, a sensitive calibration measure is a likelihood ratio statistic testing the null hypothesis that $\alpha=0$ and $\beta=1$. The statistic has a χ^2 distribution with two degrees of freedom [unreliability (U) statistic]. Average [E average (Eaver)] and maximal errors [E maximal (Emax)] between predictions and observations obtained from the calibration curve were estimated [18]).

Validation of the model

An internal validation was performed with 200 bootstrap resamples to obtain relatively unbiased estimates. The bootstrapping method provides an estimate of the average optimism of the AUC-ROC [15,19].

Other statistical analysis:

Baseline clinical characteristics are described in Table 1. All continuous variables are presented as mean \pm SD (standard deviation) and all categorical data are presented as frequency. The categorical and numerical variables were analyzed using the Chi 2-test and the Student t-test, respectively. P-values < 0.05 were considered as significant. The Kaplan Meier Method was used to estimate recurrence free survival (RFS). All analyses were performed using the R software available online (<https://www.r-project.org/>).

Results

Description of the study population

During the study period, 111 women with PABC were extracted from the CALG network database. Six women with a non-invasive breast carcinoma and 10 women with missing data were excluded. Finally, 95 women were included in the analysis (Fig 1). The demographics, clinical and pathological characteristics of the women in our cohort are reported in Table I.

The mean age at diagnosis was 35 years (Inter Quartile Range IQR: 8). Diagnosis was made during pregnancy for 49% (47/95), and during the first year after delivery for 51% (48/95). The median time of follow-up (from diagnosis to recurrence or last date of follow-up) was 40.9 months (IQR: 32). The median size of tumor was 35 mm (IQR = 8.58). Almost all the patients, 96% (92/95), underwent surgical treatment: 41% (39/95) underwent conservative breast surgery, and the remaining 56% of patients (53/95) had a mastectomy. Most of the patients, 87% (81/95), underwent radiotherapy. Forty-eight percent (46/95) of the patients had neoadjuvant chemotherapy, and 55% (52/95) adjuvant chemotherapy. Surgical and pathological characteristics are summarized in Table I.

Recurrence and survival rates

The median time to first recurrence was 25 months (IQR : 43). The overall recurrence and death rates were 22% (21/95) and 7.3% (7/95), respectively. At 3 years, the overall recurrence and survival rates were 13% (IC 95%, 0.07-0.21) and 95% (IC 95%, 0.90-1.00), respectively. At 5 years, the overall recurrence and survival rates were 21% (IC 95%, 0.11-0.31) and 88.5% (IC 95%, 0.80-0.98).

Among the 21 patients with recurrence, 66.7% (14/21) presented DR and 33.3% (7/21) LRR. LRRs were breast for six patients and lymph node for one. Breast recurrences were ipsilateral for five

patients and contralateral for one. The lymph node recurrence was ipsilateral. The DRs consisted of two patients with bone metastasis, two with brain metastasis, one with liver metastasis, eight with disseminated metastases and one with lymphangitis carcinomatosa. The median time to first recurrence was 29.4 months (IC 95%, 19.3-NA) and 22.9 months (IC 95%, 20.2-69.0) for women with LR and DR, respectively.

The OS rates for women with no recurrence, LRR and DR were 100% (IC 95%, 0.95-0.10), 71% (IC95%, 0.29-0.96) and 64% (IC 95%, 0.35-0.87), respectively. The respective 3-year OS according to recurrence location were: 100% (95% CI, 1.00 – 1.00), 80% (95% CI, 0.51 – 1.00), 80% (95% CI, 0.59 – 1.00) for women with no recurrence, LRR and DR.

Multivariate Cox model

After multivariate cox analysis, age at diagnosis, histological type, molecular classification, tumor stage, lymph node stage (nTNM) were associated based on clinical and statistical values with the likelihood of 3-year recurrence (Table II, Fig 2).

The predictive model had a concordance index of 0.83 (95% CI, 0.81-0.85) and 0.78 (95% CI, 0.76-0.80) before and after the 200 repetitions of bootstrap sample corrections, respectively. The predicted probability obtained from the bootstrap correction and the actual probabilities of recurrence are shown in the calibration plot (Fig 4). No significant difference was observed between the predicted percentages and the observed probabilities of recurrence ($p = 1$), meaning that the nomogram was well calibrated.

Discussion :

The current study suggests a predictive model to help determine the likelihood of 3-year recurrence in patients with PABC using a nomogram. Age at diagnosis, histological type, immunohistological class, tumor stage (TNM), node stage (TNM) were associated with 3-year recurrence and were included in the final Cox model to develop the nomogram. The clinical relevance of our nomogram was demonstrated by its internal applicability using the bootstrap approach.

Currently, both medical decision-making and patient counselling for women with PABC are mainly based on the physician's judgment. As underlined in a literature review [20], PABC is an under-documented but important and growing clinical problem worldwide with several aspects of the condition which are not fully understood, especially concerning the risk factors, prognosis, and its aggressiveness [20-23]. To overcome such limitations, a new paradigm has emerged based on counseling each patient in terms of prognosis, therapeutic options and monitoring strategies. The implementation of such predictive, personalized, preventive and participatory aspects of clinical medicine creates successful actionable models for use in patient care [22,24,25]. Due to its low incidence (PABC represents 0.4% of all breast cancers diagnosed in patients aged 16-49 years) rendering randomized controlled trials (RCT) inappropriate, impossible or insufficient, PABC can be considered a suitable candidate for such a model [23]. We report here that age at diagnosis, molecular classification, histological type, tumor stage, and lymph node status are determinant to identify women at high risk of recurrence after treatment. Interestingly, these variables are recognized as reliable factors of RFS and OS for breast cancer [26], and especially for women with PABC [27].

The prognosis of PABC has been addressed in several studies with inconsistent results[25,28-30]. Some studies have found that PABC is more commonly diagnosed at an advanced stage [28,29] suggesting that the poor prognosis is secondary to diagnostic delay rather than an inherent effect of pregnancy or lactation on breast cancer prognosis. In this setting, defining risk factors of recurrence is crucial to identify and select patients with poor prognosis. As previously reported [27], we found age at diagnosis and tumor stage to be statistically associated with recurrence in univariate analysis. In contrast, although their statistical weight was low in univariate and multivariate analysis, we included

the molecular classification and the lymph node status in the definitive cox regression model. We hypothesized their clinical value to improve the modeling of the likelihood of 3-year recurrence. The present results are in accordance with previous reports. Johansson et al. reported that age, and stage at diagnosis, were the principal driver of the increased mortality observed in women with PABC [28]. Similarly, Amant et al., based on a registry of 447 women with PABC mainly from Germany and Belgium, observed that molecular classification and lymph node status were relevant but did not emerge as criteria associated with RFS and OS in multivariate analysis. Our 5-year RFS and OS findings are comparable to other studies [31,32]. For example, Litton et al. reported a 5-years RFS of 72 % in a cohort of 75 women with PABC [31]. A study based on the Korean Breast Cancer Society Registry database including 344 women with PABC, reported a 10-year survival rate of 76.4%³⁰. The meta-analysis from Azim et al. reported poorer outcomes for women diagnosed in postpartum, at least for the relevant prognostic factors (pHR: 1.84; 95% CI 1.28–2.65), compared with those diagnosed during pregnancy (pHR: 1.29; 95% CI 0.74–2.24)²⁸. RFS analysis also showed a significantly higher risk of relapse associated with PABC (pHR: 1.60 [1.19–2.16]). Although, this point could be discussed, we opted not to include these factors in the multivariate cox model [33].

The strengths of this nomogram lie in its good exportability and its ability to provide evidenced-based information according to parameters which can be easily established preoperatively and confirmed after surgery. To the best of our knowledge, this is the first report applying the concept of precision medicine for patients with PABC. Its clinical value is to identify women with a poor prognosis for whom a personalized follow-up schedule must be planned.

A better knowledge of PABC patterns of recurrence is also needed to adapt follow-up modalities as post-treatment monitoring programs currently differ widely from country to country. We reported a high heterogeneity and pattern of recurrence: among the 21 recurrences, 66.7% (14/21) and 33.3% (7/21) are described as LRR (breast or lymph node recurrence) and DR, respectively. Interestingly, the median time to first recurrence was 29.4 months (IC 95%, 19.3-NA) and 22.9 months (IC 95%, 20.2-69.0) for women with LRR and DR, respectively. Although, the present tool takes into account these events, we could not distinguish a specific nomogram for predicting both the

likelihood of LRR and DR. However, it is important to note that the risk of recurrence differs widely according to molecular classification. This is crucial as patients with PABC are young and often wish to preserve their fertility. In this specific setting, our nomogram could be an interesting tool to help both patients and physicians to decide when a woman could attempt another pregnancy after her treatment with a relatively low risk of recurrence. However, to achieve a level of evidence in terms of generalizability the current model requires an external validation

Strengths and Limitations

The main limitation of our study is its retrospective nature and the long period of data collection from a single center. However, the population was homogeneous as all patients were treated and followed in the same institution. In addition, the sample size was relatively small, which may have reduced the power to detect relations between recurrence incidence and the risk factors evaluated. However, the small sample size also implies that the correlations detected between recurrence incidence and risk factors are strong. Another source of bias could be modifications to guidelines for the management of breast cancer over the years; especially with the emergence of targeted therapies [26]. Third, our population included women with breast cancer occurring during pregnancy and during the postpartum period. Lee et al. separated these two distinct groups in their study to improve clinical management and counseling [34]. Indeed it is now recognized that the tumor stage, histological characteristics as well as surgical and medical management differ between PABC occurring during pregnancy or during the postpartum period [35]. In this setting, we previously demonstrated the absence of differences between these two subpopulations of women with PABC which justifies why we did not include this criterion in the model [35].

Conclusion:

The nomogram described here may guide the decision-making process towards the most adapted treatment options or follow-up strategies for women with PABC. Further studies designed to evaluate such prediction tools are needed, especially to improve the quality of management and individual information for women with PABC.

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Table I. Characteristics of the whole population with breast cancer associated to pregnancy.

Characteristics (N=95)	
Age (years) (median, range)	35.0 (20-46)
Body mass index (kg/m ²) (median, range)	23.0 (18-39)
Family history of breast and ovarian cancer (% , n)	23% (22)
Personal history of breast cancer (% ,n)	3% (3)
Histological type :	
Invasive Ductal Carcinoma (% , n)	94% (89)
Invasive Lobular Carcinoma (% , n)	6% (6)
Tumor stage (TNM):	
T1 (% , n)	28% (27)
T2 (% , n)	35% (33)
T3 (% , n)	19% (18)
T4 (% , n)	16% (15)
NA (% ,n)	2% (2)
Lymph node metastasis : N1 (% , n)	65% (62)
Metastatic stage : M1 (% , n)	12% (11)
Tumor Size (mm) (median,range)	35.0 (2-110)
Focality:	
Unifocal (% , n)	73% (69)
Multifocal (% , n)	26% (25)
NA (% ,n)	1% (1)
Grade (SBR) :	
Grade 1 (% , n)	5% (5)
Grade 2 (% , n)	34% (32)
Grade 3 (% , n)	61% (58)
Estrogen Receptor status : positive (% , n)	61% (58)
Progesterone Receptor status : positive (% , n)	48% (46)
Hormonal Receptor status : positive (% , n)	62% (59)
HER2 positivity (% , n)	26% (24)
KI 67 rate	
Inferior 20% (% , n)	21% (20)
Superior 20% (% , n)	76% (72)
NA	3% (3)
Molecular Classification :	
Luminal A	31% (29)
Luminal B	31% (29)
HER 2	13% (12)
Triple negative	25% (25)

NA, not available

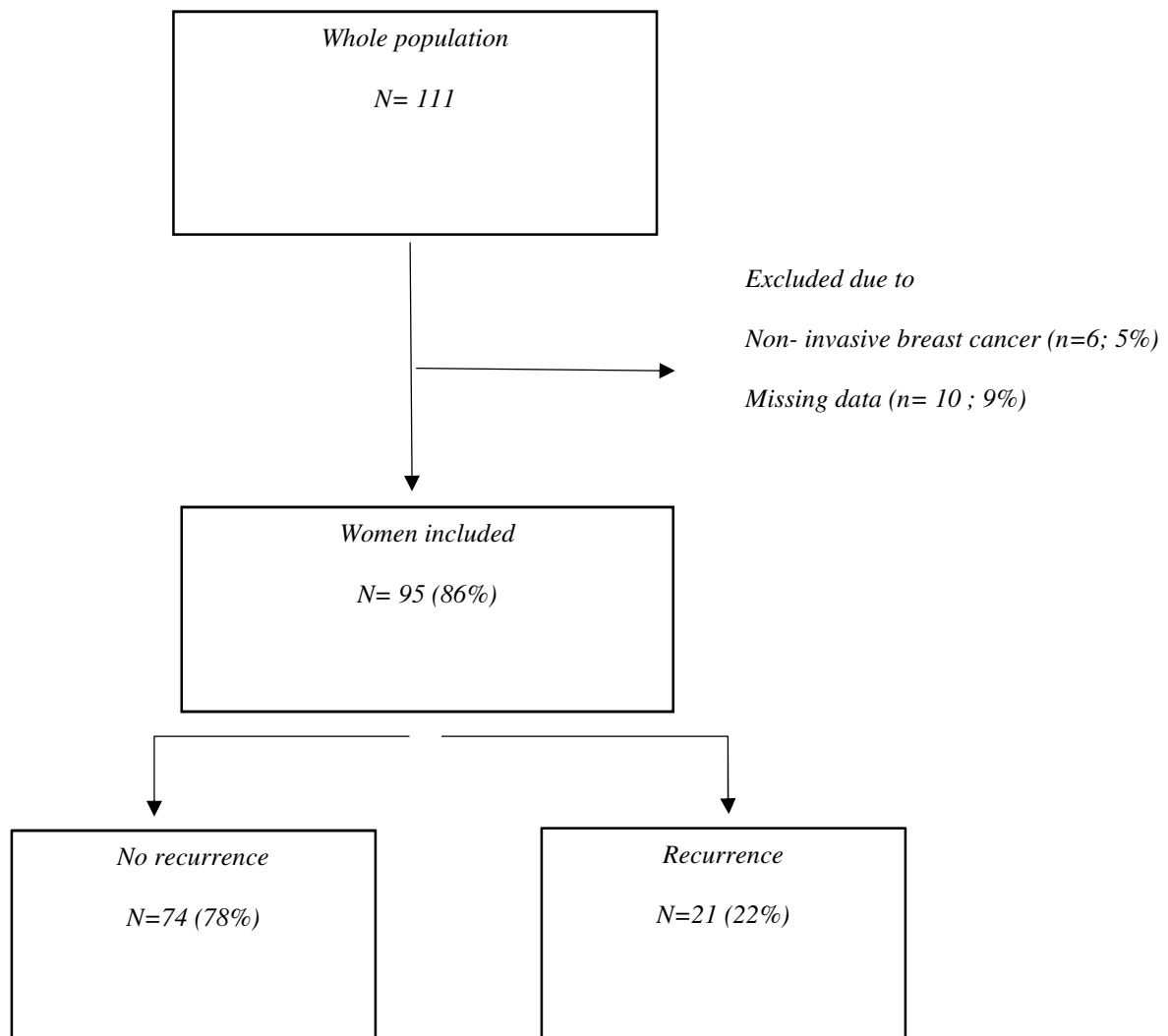
Table II: Predictive factors of 3-years recurrence in multivariate analysis

Variables	Univariate analysis		Multivariate analysis	
	HR (95% IC)	P value ^a	HR (95% IC)	P value ^a
Age	1.14 (1.01—1.29)	0.03	1.14 (0.99 – 1.31)	0.07
Histological type				
• IDC	Reference		Reference	
• ILC	3.07 (0.67-14)	0.15	2.12 (0.26-17.32)	0.48
Molecular classification				
• Luminal A	Reference		Reference	
• Luminal B	3.96 (0.44-35.41)		4.01 (0.42-37.91)	
• HER 2	6.04 (0.63-58.05)		3.14 (0.23-43.20)	
• Triple negative	4.16 (0.47-37.26)	0.2	5.40 (0.45-64.43)	0.18
Tumor stage				
• T1-T2			Reference	
• T3	4.38 (0.98-19.58)		4.00 (0.79-20.34)	
• T4	5.76 (1.29-25.74)	0.02	4.32 (0.82-22.82)	0.08
Lymph Nodal status				
• No lymph node metastases	Reference		Reference	
• Lymph node metastase	1.81 (0.49-6.69)	0.37	1.65 (0.30-9.13)	0.6

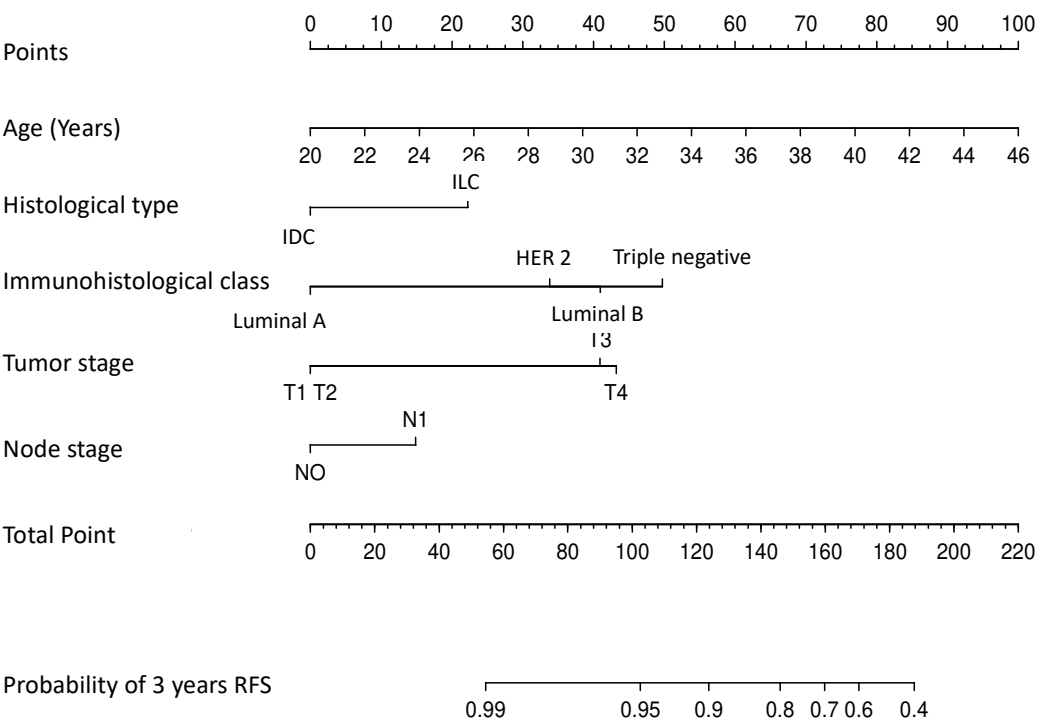
HR : Hazard ratio, IDC : Invasive Ductal Carcinoma, ILC : Invasive Lobular Carcinoma

^aLogistic regression model

Figure 1: Flow Chart of study participants.



413 Figure 2: Nomogram predicting probability of 3 years recurrence for women with PABC



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416 RFS : Recurrence free survival

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Figure 3: Calibration plot before and after bootstrapping

