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Clinicopathologic and sociodemographic factors associated with late relapse triple negative breast cancer in a multivariable logistic model: A multi-institution cohort study

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ABSTRACT

Background: Most metastatic recurrences of triple negative breast cancer (TNBC) occur within five years of diagnosis, yet late relapses of TNBC (lrTNBC) do occur. Our objective was to develop a risk prediction model of lrTNBC using readily available clinicopathologic and sociodemographic features.

Methods: We included patients diagnosed with stage I–III TNBC between 1998 and 2012 at ten academic cancer centers. lrTNBC was defined as relapse or mortality greater than 5 years from diagnosis. Features associated with lrTNBC were included in a multivariable logistic model using backward elimination with a $p < 0.10$ criterion, with a final multivariable model applied to training (70%) and independent validation (30%) cohorts.

Results: A total 2210 TNBC patients with at least five years follow-up and no relapse before 5 years were included. In final multivariable model, lrTNBC was significantly associated with higher stage at diagnosis (adjusted Odds Ratio [aOR] for stage III vs I, 10.9; 95% Confidence Interval [CI], 7.5–15.9; $p < 0.0001$) and BMI (aOR for obese vs normal weight, 1.4; 95% CI, 1.0–1.8; $p = 0.03$). Final model performance was consistent between training (70%) and validation (30%) cohorts.

Conclusions: A risk prediction model incorporating stage, BMI, and age at diagnosis offers potential utility for identification of patients at risk of development of lrTNBC and warrants further investigation.

1. Introduction

Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer characterized by an absence of estrogen receptors, progesterone receptors, and HER2. While TNBC accounts for a disproportionate amount of poor outcomes among breast cancers, making up 10–15% of cases yet accounting for around 35% of breast cancer-related deaths [1], most metastatic recurrences of TNBC occur within five years of diagnosis [1,2]. We previously evaluated multi-level features associated with rapid relapse of TNBC (rrTNBC; relapse or mortality within 2 years of diagnosis). In this work we identified distinct genomic features associated with rrTNBC [3–5] but also found that rrTNBC was strongly

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associated with social determinants of health (SDH, e.g. Medicaid/indigent insurance, lower income, race) in two separate large cohorts [6–8]. We hypothesized that SDH associated with rrTNBC could reflect lack of access to optimal (neo)adjuvant treatment and subsequent lead to higher rate of rapid relapse.

Despite the vast majority of TNBC relapses occurring within the first five years, there are nonetheless late relapse TNBC (lrTNBC), which we define as distant metastatic relapse or death ≥5 years from diagnosis [1]. While any TNBC relapse >2 years from diagnosis could be considered late, we focused on an outlier population with relapse or death ≥5 years from diagnosis. The goal of the present study was to evaluate features associated with lrTNBC in an established, multi-institutional cohort with detailed clinicopathologic and sociodemographic data. Specifically, our objective was to develop a risk prediction model of lrTNBC using readily available clinicopathologic and sociodemographic features.

2. Methods

2.1. Patients

This large multi-institutional study analyzed a cohort of invasive breast cancer patients diagnosed with TNBC who received treatment at one of ten academic centers that previously participated in a National Comprehensive Cancer Network (NCCN) outcomes database between 1998 and 2012 (Fig. 1) [9]. The participating institutions included City of Hope, Dana-Farber Cancer Institute, Fox Chase Cancer Hospital, Johns Hopkins University, Massachusetts General Hospital, MD Anderson Cancer Center, Ohio State University, Roswell Park Cancer Center, Seattle CancerCare Alliance/Fred Hutchinson Cancer Center, and University of Utah. This dataset was utilized because of its pertinent granularity and so that adequate follow-up could be reviewed in as large of a cohort as possible. Diagnosis, treatment, and outcomes data were collected by abstractors using procedures originally developed by the NCCN. TNBC was defined as ER<1%, PgR<1%, and HER2 IHC<3+ and FISH negative (if performed). We included only patients with ≥60 months (5 years) follow-up, who could thus be defined as lrTNBC versus not late relapse. lrTNBC was defined as distant metastatic relapse or death (without prior documented relapse) ≥5 years from diagnosis. We excluded patients with *de novo* metastatic disease. We also excluded patients who did not receive chemotherapy within 9 months of diagnosis and included those patients who received either neoadjuvant or adjuvant chemotherapy. These investigations were performed after approval by the Ohio State University institutional review board and the institutional review board of all participating sites.

2.2. Statistical analyses

The dataset was randomly divided into 70% training and 30% validation cohorts, balanced by the proportion of lrTNBC events. 70/30 training and validation splits was established *a priori* to ensure adequate events in the validation cohort for model application. Covariates of interest included study site, age at diagnosis by decade, body mass index (BMI), race/ethnicity, education, median annual household income based on 2000 census tract, insurance type, Charlson comorbidity index, tumor stage at diagnosis, tumor grade at diagnosis, and adjuvant radiation treatment. Insurance type was categorized as Managed Care, Medicare, Medicaid/Indigent (including dual eligible patients), and Other. Missing variables were not imputed and outliers were not excluded. Bivariable logistic regression was performed among the

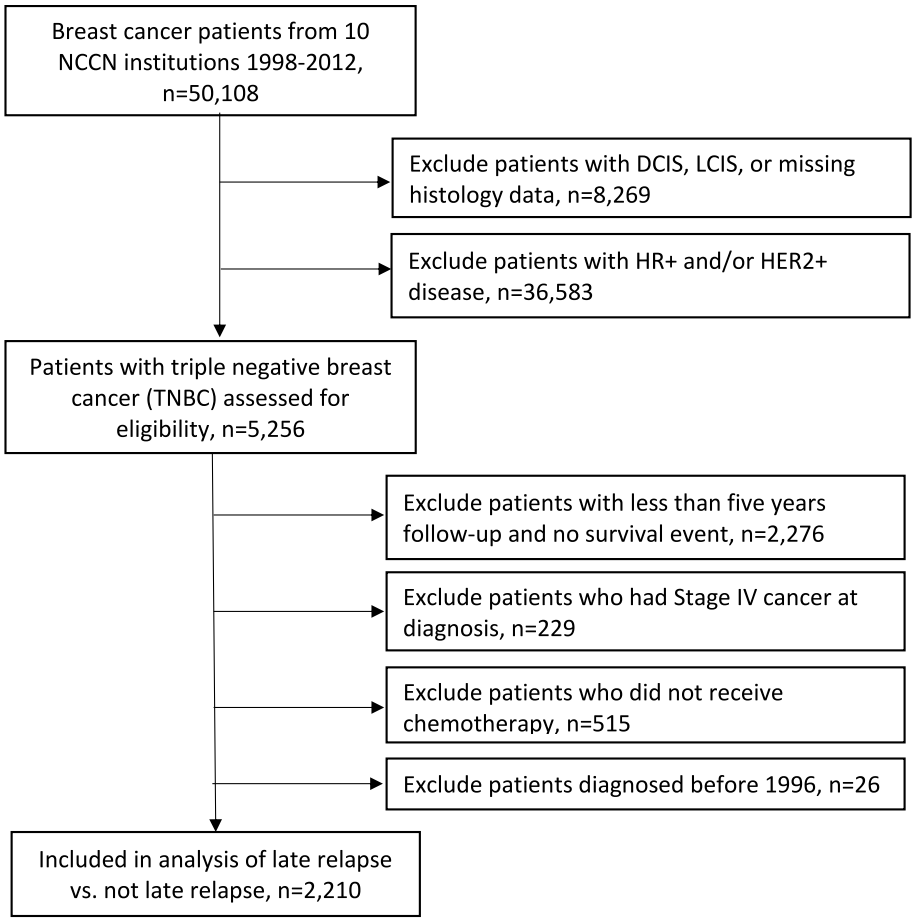

Fig. 1. Consort diagram.

training dataset for associations between each covariate and late relapse status. Features with a p-value <0.10 were included in a multivariable logistic regression model. Backward selection was performed on the multivariable model with a $p < 0.10$ criterion to identify the final multivariable model, upon which sensitivity analysis was performed. Bootstrapping was also performed on the final model to establish coefficients, and the bootstrapped coefficients were applied to the training and independent validation cohorts.

3. Results

Among 41,839 patients with invasive breast cancer treated in these ten centers during the study period, 5256 (12.6%) had TNBC. Of those, 2210 had adequate follow-up to be included in the analysis. Demographic features (Table 1), including race/ethnicity, were balanced between training and validation cohorts (Supplementary Table 1). Overall, 14.3% (750/5256) of TNBC patients had late relapse, comprising 33.9% (750/2210) of patients with at least 5 years of follow-up who were evaluable for these analyses (at least 5 years follow-up, no relapse or survival event prior to 5 years, received chemotherapy, diagnosed after 1996). Most patients excluded from analyses either developed relapse within 5 years, were lost to follow up, or did not receive chemotherapy (CONSORT diagram Fig. 1).

Bivariable analyses of the training cohort (n = 1547) identified a significant ($p < 0.10$) association between lrTNBC and higher body mass index (BMI), African American race, lower income, high school education, Medicare or Medicaid/indigent insurance, older age at diagnosis, and later stage at diagnosis (Supp Table 2). Multivariable analyses (Table 2) and backward selection resulted in the final model (Table 3). In this final multivariable model, lrTNBC was significantly associated with higher stage at diagnosis (adjusted Odds Ratio [aOR] for stage III vs I, 10.9; 95% Confidence Interval [CI], 7.5–15.9; $p < 0.0001$) and BMI (aOR for obese vs normal weight, 1.4; 95% CI, 1.0–1.8; $p = 0.03$). Sensitivity analyses of the final model were repeated with the BMI categories combined into two larger categories, demonstrating that a BMI greater than or equal to 25 (which represents overweight and obese patients) was significantly associated with lrTNBC (Supp Table 3). In further sensitivity analyses stratified by stage (I and II vs. III), obese and overweight BMI was associated with lrTNBC in stage III patients, whereas only obese BMI was associated with lrTNBC in stage I and II patients (Supp Table 4). Receiver Operating Characteristic (ROC) curves used to assess the final model performance resulted in an AUC of 0.725 for the training cohort and 0.785 for the validation cohort, indicating consistency between the two (Supp Fig 1).

Table 1
Characteristics of women diagnosed with triple negative breast cancer (TNBC) from the National Comprehensive Cancer Network (NCCN) Outcomes Database among training and validation cohorts.

	Overall (N = 2210)		Training cohort (N = 1547)		Validation cohort (N = 663)		Chi-square
	No.	%	No.	%	No.	%	p-value
Age at diagnosis							0.37
<50	1071	48.5	732	47.3	339	51.1	
50-59	653	29.6	462	29.9	191	28.8	
60-69	358	16.2	260	16.8	98	14.8	
≥70	128	5.8	93	6.0	35	5.3	
Race/ethnicity							0.77
White, non-Hispanic	1613	73.2	1127	73.1	486	73.5	
African American, non-Hispanic	323	14.7	231	15.0	92	13.9	
Hispanic/Other	267	12.1	184	11.9	83	12.6	
Education							0.95
<High school	147	8.0	104	8.1	43	7.8	
High school	489	26.7	345	27.0	144	26.0	
Some college, vocational/ technical school	526	28.7	363	28.4	163	29.5	
College grad or higher	669	36.5	466	36.5	203	36.7	
Median annual household income[a]							0.39
Quartile 1	532	25.0	382	25.7	150	23.4	
Quartile 2	529	24.9	358	24.1	171	26.6	
Quartile 3	534	25.1	366	24.7	168	26.2	
Quartile 4	531	25.0	378	25.5	153	23.8	
Insurance type							0.72
Managed Care	1545	70.6	1081	70.5	464	70.7	
Medicare	279	12.7	200	13.0	79	12.0	
Medicaid/Indigent	201	9.2	135	8.8	66	10.1	
Other	165	7.5	118	7.7	47	7.2	
Body Mass Index							0.16
<18.5	144	6.5	109	7.1	35	5.3	
25 > BMI≥18.5	686	31.0	468	30.3	218	32.9	
30 > BMI≥25	631	28.6	432	27.9	199	30.0	
≥30	749	33.9	538	34.8	211	31.8	
Comorbidity score							0.19
0	1758	79.6	1220	78.9	538	81.2	
1	307	13.9	216	14.0	91	13.7	
≥2	145	6.6	111	7.2	34	5.1	
Stage at diagnosis							0.24
I	516	23.4	346	22.4	170	25.6	
II	1145	51.8	814	52.6	331	49.9	
III	549	24.8	387	25.0	162	24.4	
Histologic grade							0.16
I	11	0.7	9	0.86	2	0.42	
II	152	10.0	113	10.9	39	8.1	
III	1357	89.3	919	88.3	438	91.4	

[a] Calculated with 2000 Census.

4. Discussion

Triple-negative breast cancer (TNBC) is associated with a disproportionate contribution to breast cancer mortality relative to other breast cancer subtypes [1]. In this study, we found that lrTNBC was

Table 2
Multivariable analysis of late relapse versus no late relapse (Training Cohort).

Correlate	aOR	*P*-value
BMI Category		
<18.5	0.7	0.24
25 > BMI≥18.5	ref	–
30 > BMI≥25	1.1	0.56
≥30	1.3	0.097
Race/ethnicity		
White, non-Hispanic	ref	–
African American, non-Hispanic	0.9	0.79
Hispanic/Other	0.9	0.66
Education		
<High school	1.1	0.67
High school	1.3	0.11
Some college, vocational/technical school	1.0	0.87
College grad or higher	ref	–
Median annual household income*		
Quartile 1	1.3	0.20
Quartile 2	1.2	0.40
Quartile 3	1.1	0.71
Quartile 4	ref	–
Insurance type		
Managed Care	ref	–
Medicare	1.2	0.49
Medicaid/Indigent	1.0	0.88
Other	1.0	0.89
Age at diagnosis		
<50	1.3	0.31
50–59	0.8	0.32
60–69	ref	–
≥70	1.0	0.98
Stage at diagnosis		
I	ref	–
II	2.2	0.0002
III	11.7	<0.0001

Table 3
Final model analysis of late relapse versus no late relapse.

	Training Cohort (n = 1547)		
Correlate	aOR	95% CI	*P*-value
Body Mass Index			
<18.5	1.1	(0.65,1.8)	0.79
25 > BMI≥18.5	ref	–	–
30 > BMI≥25	1.1	(0.84,1.6)	0.40
≥30	1.4	(1.0,1.8)	0.03
Age at diagnosis			
<50	1.1	(0.83,1.6)	0.40
50–59	0.9	(0.61,1.2)	0.42
60–69	ref	–	–
≥70	1.5	(0.89,2.5)	0.13
Stage at diagnosis			
I	ref	–	–
II	2.5	(1.8,3.5)	<0.0001
III	10.9	(7.5,15.9)	<0.0001

associated with higher stage at diagnosis and higher BMI and developed a risk prediction model for lrTNBC based on these data.

While the vast majority of TNBC-related recurrences occur within five years [2], [[,10-12] there are late recurrences that occur more than five years after diagnosis. The rate of late relapse in this cohort is similar to a large prior single institution study, which found 84% distant-recurrence free survival at 15 years; of note, some patients form that work may also have been included in this study [13]. Intriguingly, a more recent SEER analysis assessing 20-year risk of breast cancer-specific mortality suggested that the magnitude of late relapse in ER- and/or PR-negative disease is likely greater than anticipated [14]. Late relapse of breast cancer is of great interest in the breast cancer field, yet most investigations have focused on ER+/HER2-breast cancer where late recurrence is far more common [15–17]. Timing of relapse is not well studied in TNBC, potentially due to smaller overall numbers; yet with modern therapies that now include multi-agent neoadjuvant chemoimmunotherapy for many high risk patients, we hypothesize that the number of late relapses may increase. The risk prediction model in this study offers a starting point and warrants validation in additional, modern cohorts with long-term follow-up with additional methodological rigor including more detailed model calibration. In addition, this study emphasizes the need for consistent definition or nomenclature of 'late relapse' for TNBC, which we advocate should be considered ≥5 years from diagnosis. Better definitions of 'late relapse' within each subset of breast cancer would facilitate more standard research across the field.

An intriguing finding was the association of body mass index with lrTNBC. There are multiple possible hypotheses around this association, including obesity associations with impaired immune surveillance, inflammatory milieu, or aberrant induction of signaling pathways [18–20]. There are accumulating data that obesity may have distinct effects on TNBC relative to other breast cancer subtyes [21,22]. While potential mechanisms are diverse, several ongoing studies are underway to evaluate the impact of weight loss interventions and breast cancer outcomes, including the large Breast Cancer Weight Loss trial (Alliance A011401), which has completed accrual with results not yet reported [23].

Our prior study of rrTNBC in the NCCN outcomes database also reflected stage and age, but was associated Medicaid or no insurance [8]. Age at diagnosis showed significant association with lrTNBC in bivariable analyses, specifically age 70 or over was associated with higher risk of lrTNBC; age remained part of the final model but did not contribute as significantly as other variables. Further, we found that patients with rrTNBC may be less likely to receive guideline-concordant care (including breast surgery) [6–8], leading us to hypothesize that SDH associated with rrTNBC could reflect lack of access to optimal treatment and subsequent lead to higher rate of rapid relapse. This may suggest that while SDH may impact rapid relapse, biological factors such as BMI likely influence late relapse.

This cohort study's strengths include diverse participating institutions and detailed, uniform clinical data abstraction. Limitations of this study include the time period of the cohort, which ceased enrollment in 2012, as standards-of-care have shifted. We excluded patients who did not receive chemotherapy to avoid receipt of treatment as a significant confounder, yet relatively few patients in this cohort received neoadjuvant therapy. One possible important outcome of more effective modern chemotherapy regimens, such as the FDA approved combination with chemo-immunotherapy neoadjuvant regimen [24] based on KEYNOTE-522 (NCT03036488), is that timing of relapse may be delayed, which may lead to a higher rate of lrTNBC. The data were already abstracted and fully deidentified thus limiting the variables available, resulting in potential unmeasured confounders due to inability to perform further chart review of patients. For example, it will be important to assess the impact of other factors on lrTNBC not evaluable in this cohort including germline BRCA status and type of chemotherapy (e.g. carboplatin use). Evaluable patients in our study may not reflect the general breast cancer population, as it is possible that patients lost to follow up at would be enriched for patients without recurrence, which would prompt return to their oncologist; this may have influenced the relatively high proportion of patients with lrTNBC. There are other factors that could impact potential sampling bias, as all patients were initially treated and followed for 5+ years at a comprehensive cancer center, possibly selecting for younger patients, healthier patients, and those with higher risk cancers. Despite these limitations, our prior study of rrTNBC in this cohort validated multiple findings in alternate cohorts [3–5] and we similarly plan to investigate the hypothesis-generating observations from this cohort in additional, modern datasets.

In conclusion, late relapse in TNBC is associated with stage at diagnosis and BMI. We provide an initial risk prediction model with consistent performance in training and validation subsets of a retrospective cohort. Future work to further validate this model in additional datasets is ongoing.

Credit author statement

Study concept and design: Asad, Lin, Hassett, Stover. Data generation and coordination: Barcenas, Bleicher, Cohen, Javid, Levine, Lin, Moy, Niland, Wolff, Hassett, Stover. Writing – original draft: Asad, Stover. Writing – review and editing

Ethics approval and consent to participate

Patients provided consent for under approval by local human research protections programs and institutional review board at D Ohio State University, and studies were conducted in accordance with the Declaration of Helsinki.

Consent for publication

N/A.

Data availability

All data used in analyses consist of deidentified versions of the prior NCCN outcomes database and is controlled access.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2023.01.004.

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