Original Research Article

Age Under 30 Years As a Predictor of Poor Survival in a Cohort of Mexican Women With Breast Cancer

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Abstract

Introduction: Young women under 30 years with breast cancer (BC) are an emerging challenge. The purpose is to identify prognostic factors for survival in young women under 30 years of age with BC.

Material and methods: A retrospective cohort study was conducted among women younger than or equal to 40 years with BC and who were treated at the State Cancer Center during the period 2012–2017. Overall survival was assessed using the Kaplan–Meier method and the log-rank test. Univariate and multivariate analysis assessed survival predictors using Cox proportional hazards regression model.

Results: 282 young women were included. The >30-year-old subgroup showed a significant association with excess weight ($P = .002$) compared to the <30-year-old group. The <30-year-old subgroup showed a poor overall survival (56.7%), as well as highly significant values in advanced clinical stages, metastatic nodules, metastasis, and neoadjuvant therapy ($P < .001$). In Model 3 of the multivariate analysis, age <30 years (HR = 3.0; 95% CI 1.1 to 8.6), triple negative subtype (HR = 2.6; 95% CI 1.1 to 6.0), tumor size >5 cm HR = 2.3; 95% CI 1.03 to 5.1), and advanced clinical stages (HR = 6.6 95% CI 1.3 to 35.5) persisted as predictors.

Conclusions: Being very young (<30 years) is a predictor for limited survival compared to the age of 30–40 years, as well as the tumor covariates for a worse prognosis: triple negative subtype, advanced stages, positive lymph nodes, and distant metastases in liver.

Keywords

prognostic, factors, survival, age, breast cancer, metastasis, molecular subtypes

Introduction

Breast cancer is the most common cancer in women around the world. Although it rarely occurs before the age of 40, it is the most common within this age group.[1] In Mexico, the incidence of these cases is reported in a range of 10 to 15%.[2] Due to a later diagnosis associated with multiple factors, such as lack of knowledge of the disease, financial status,[3] level of education, and lack of medical training to detect cancer early, young women generally present advanced clinical stages with molecular subtypes and more aggressive biological characteristics.[4,5] Increased body mass index (BMI) in premenopausal women shows a higher proportion of hormone receptor negative, with a predominance of triple negative breast cancer (TNBC) molecular subtype.[6,7]

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Table 1. Clinical and Pathological Characteristics and Treatment.

Variables	n = 282	%
Age subgroup		
<30 years	27	9.6
≥30 years	255	90.4
Place of residence		
Rural	131	46.5
Urban	151	53.5
Scholarship		
Without studies	14	5.0
Basic studies	184	65.2
Higher school	84	29.8
Occupation		
Housewife	240	85.1
Worker	42	14.9
Socioeconomic level		
2–3	267	94.7
4–6	15	5.3
Menarche		
Early (≤12 years)	138	48.9
Late (>12 years)	144	51.1
Body mass index (kg/m^2)[a]		
Normal weight	92	32.7
Overweight	94	33.3
Obesity	96	34.0
Diabetes mellitus type 2		
No	272	96.5
Yes	10	3.5
Arterial hypertension		
No	271	96.1
Yes	11	3.9
Family history		
No	162	57.4
Yes	120	42.6
Histologic grade (n = 256)		
1	39	13.8
2–3	217	77.0
Unknown	26	9.2
Metastatic lymph nodes		
Negative	151	53.5
Positive	131	46.5
Clinical stage (n = 280)[b]		
Early	91	32.5
Advanced	189	67.5
Metastasis		
Negative	234	83.0
Positive	48	17.0
Treatment (n = 269)		
Neoadjuvant	188	69.9
Adjuvant	81	30.1

[a]Body mass index (BMI): normal weight: ≥18.5 to <25 kg/m^2; overweight: ≥25 to 29.9 kg/m^2 and obesity: ≥30 kg/m^2.
[b]2 phylloides tumor and a sarcoma.

Young women have been reported to have a poorer survival rate compared to their older counterparts,[8,9] which is associated with an advanced clinical stage and the presence of metastases.[10] Survival tends to be less favorable in the human epidermal growth factor receptor 2 (HER-2) and TNBC phenotypes, and these molecular subtypes are overrepresented in young women at diagnosis.[11] TNCBs usually stand out for their biological peculiarities, reduced survival rate, and lack of effective treatment, as well as an evident tendency to present distant metastases,[12] mainly in bone and liver.[13] Previous studies reported that women <40 years have stronger treatment and additional reproductive challenges. However, the prognostic impact of age remains unclear in this clinical context. This study aimed to identify the main predictors of survival in young women under 30 years of age with BC.

Material and Methods

Participants and Study Design

We conducted a retrospective cohort study from a database that included all women diagnosed with invasive BC and who were ≤40 years old during the period January 2012–December 2017 who were treated at the State Cancer Center (CECan), in Veracruz, Mexico. The sample size was delimited by 100% of the women with invasive BC, aged ≤40 years and who met the rest of the selection criteria from a database with N = 1462 patients. Statistical power will be calculated if no significant association is found between the group <30 years with poor survival.

The maximum monitoring time was 60 months, with a prior evaluation at 24 months. Patients were classified as exposed or unexposed according to age <30 years and ≥30 years. Monitoring included the time interval between the date of diagnosis and the date of the last visit or the date of death from any cause. For the rest of the cohort, the monitoring time ended on December 31st, 2017. The selection criteria were women aged ≤40 years, residing at the state of Veracruz with a confirmed diagnosis of BC during the period January 2012–December 2017 who were treated at the CECan and had a complete clinical record. Information was collected from secondary sources, such as medical records and information provided by the Department of Social Work.

Variables

Survival was the main response variable, which was defined as the time elapsed between the confirmation of the diagnosis of BC and the death of the patient. Death was verified through the death certificate provided by the social work area, or the records made by the Epidemiological System and Death Statistics.

Patients were classified into two groups: <30 years and 30 to 40 years. Predictor variables were: age at diagnosis, clinical stage (according to the criteria established by the American Joint Committee on Cancer, AJCC),[14] positive lymph nodes, metastasis (present or absent at the time of diagnosis), and type of treatment (neoadjuvant or adjuvant). Other recorded covariates were overweight and obesity, which were defined

Table 2. Demographic and Clinical Factors Related to Young and Very Young Subgroups.

	Age				
	Age <30		Age 30–40		
Variable	n = 27	%	n = 255	%	P[a]
Urban provenance	17	63.0	134	52.5	.302
Basic studies[b]	14	51.9	184	72.2	.028
Housewife occupation	22	81.5	218	85.5	.578
Excess weight (BMI ≥25 kg/m^2)	11	40.7	179	70.2	.002
Histologic grade 2–3	16	64.0	201	85.0	.664
Metastasis nodes	7	25.9	124	48.6	.025
Clinical stage advanced	20	80.0	169	66.3	.162
Metastasis	6	22.2	42	16.5	.450
Bone metastasis	3	11.1	22	8.6	.666
Liver metastasis	2	7.4	11	4.3	.466
Lung metastasis	3	11.1	7	2.7	.025
Central nervous system metastasis	3	11.1	7	2.7	.025
Luminal B	1	4.8	29	12.9	.274
HER-2	2	9.5	31	13.8	.580
Triple negative	7	33.3	84	37.1	.706
Chemotherapy (n = 269)	16	61.5	204	80.0	.030
Neoadjuvant treatment	16	76.2	172	69.4	.512

[a]Proportions were compared through the chi-square test. Significant value $P < .05$.
[b]Basic level of education: primary and secondary. BMI = Body mass index.

according to the BMI classification proposed by the World Health Organization.[15] The sociodemographic variables included education (no studies, basic education, and secondary-junior high education), occupation (housework or worker), and socioeconomic status, which was classified according to the following variables: family income (55%), work (10%), family expenses (10%), housing (20%), and family health (5%).

The histologic grade score was assessed using standard institutional protocols (considering the following differentiation status: well, moderately, poorly differentiated, and unknown). According to the molecular subtypes for BC, the status of ER, PR, and HER-2 was determined by immunohistochemical analysis (IHC), which was performed by standard procedures on 2–5 mm thick sections for staining, fixed a minimum of 6 and a maximum of 48 hours, and with the use of antibody clones validated for ER, PR, and HER-2. ER and PR are considered positive with a percentage of 1% of positive neoplastic cells. HER-2 overexpression was determined by IHC or FISH technique, scoring a scale from 0 to 3+ and was evaluated as follows: Positive (3+, intense and uniform staining, >10% neoplastic cells), indeterminate (2+, complete and weak staining in >10% of neoplastic cells), and negative (0–1+, no staining is identified, it is weak or incomplete in at least 10% of neoplastic cells). The molecular subtype classification used for this study was as follows: Luminal A: ER +, PR >20%, Ki67 <20%, histologic grade (HG) 1 or 2, and HER-2−; Luminal B: ER +, PR <20%, ki67 >20%, HG 3, HER-2±; HER-2: HER-2 +, ER−, and PR−; Triple negative: ER−, PR−, and HER-2−. These criteria are in accordance with the 2019 Colima Consensus Statement.[16]

Statistical Analysis

The continuous variables were expressed as means and standard deviations or as medians and ranges. The categorical variables were expressed as percentages and compared using the chi-square or Fisher's exact test. Survival analysis was calculated using the Kaplan–Meier method. Patients who were still alive at the end of the monitoring or whose status was unknown were considered as censored data. The survival probabilities for each possible prognostic factor were compared using the Log–Rank test. A multivariate Cox regression analysis was conducted to identify those predictors of survival adjusted for the rest of the covariates. Model 1 included Age, overweight, schooling, and tumor size, while Model 2 included, in addition to the previous ones, histological grade, clinical stage, and metastasis (liver). Finally, Model 3 included metastatic nodes, molecular subtypes, and treatment. In the multivariate analysis, the hazard ratio (HR) and its 95% confidence intervals were estimated. Analyses were carried out using the statistical software SPSS, version 25.0 (IBM Inc., NY, USA).

Results

From a database of 1462 with BC patients, 282 met the age of selection (≤40 years), of which 27 were very young (<30 years) (9.6%). The mean age at the time of diagnosis was 35.18 years. Most patients dedicated to do household work, they had basic education and almost all of them had a low socioeconomic level. The mean BMI was 28.03 kg/m^2. We found a large percentage of family history of cancer and the

presence of metastatic nodes. Tumors 2 to 5 cm in size predominated, followed by tumors >5 cm. Almost 70% of the cohort showed an advanced clinical stage at the time of diagnosis. Early clinical stages represented 32.5% of the total, while stages IIIA and IIIB prevailed in advanced stages (21.6% and 15.2%, respectively). Clinical stages IV represented 13.8% of the total cohort. The organ most affected by distant metastasis was bone, followed by liver. A total of 86.87% of the cohort showed immunohistochemistry results. The distribution by molecular subtypes was Luminal A = 91 (37.14%), Luminal B = 30 (12.24%), HER-2 = 33 (13.47%), and TNBC = 91 (37.14%) (Table 1).

In a comparison of the patients <30 years and ≥30 years with the variables of schooling, BMI, metastatic nodules, pulmonary metastasis, and to the central nervous system, all of them showed significant differences, among which overweight stands out ($P = .002$) in both groups (Table 2). In our study, women under the age of 30 are less likely to have completed higher education ($P = .028$) and more likely to have positive metastatic nodes at presentation ($P = .025$), which is known to have a detriment on survival outcomes.

The 5-year overall survival was 56.7% (95% CI, 53.5 to 59.9) and this was significantly lesser in women under the age of 30 (55%) vs women in the age group of 30–40 (72%, $P = .053$). The factors that significantly impacted survival included tumor size, histological grade, metastasis, clinical stage, and molecular subtype (Table 3). Survival curves yielded possible prognostic factors after 5 years of monitoring were Advanced clinical status ($P < .001$), HER-2 molecular subtype ($P = .028$), the presence of metastases, and neoadjuvant treatment ($P < .001$) (Figure 1).

Table 4 shows the multivariate analysis of the predictors for poorer survival rate in patients with BC, considering age as the main predictor to be assessed. In Model 1, age <30 years (HR = 2.7; 95% CI 1.1 to 6.8) and tumor size >5 cm (HR = 2.6; 95% CI 1.2 to 5.1) showed a statistically significant association after adjusting for overweight and schooling. In Model 2, age did not show a significant association when adjusted for the rest of the covariates. Finally, in Model 3 (final model), when adjusting for overweight, schooling and the rest of the variables related to the clinical characteristics of the disease or the type of treatment, age <30 years showed a significant association with a poor survival rate (HR = 3.0; 95% CI 1.1 to 8.6). Other covariates identified as predictors in Model 3 were tumor size (HR = 2.3; 95% CI 1.0 to 5.1), advanced clinical stage (HR = 6.6; 95% CI 1.3 to 35.5), liver metastasis (HR = 7.8; 95% CI 1.9 to 32.8), metastatic nodules (HR = 2.4; 95% CI 1.1 to 5.5), and the triple negative subtype (HR = 2.6; 95% CI 1.1 to 6.0).

Discussion

Very young women with BC have been distinguished by presenting histopathological and biological characteristics of

Table 3. Survival According to Age, Clinical Variables and Treatment at 5-Year of Follow-Up.

Variable	n = 282	Survival[a]/5 Years n (%)	*P*-value[b]
Age			
<30 years	27	20 (55)	.053
≥30 years	255	230 (72)	
Excess weight[c] (BMI ≥25 kg/m^2)	190	169 (74)	.263
Tumor size (n = 249)			
<2 cm	18	14 (94)	.022
2 cm–5 cm	130	117 (79)	
>5 cm	101	91 (62)	
Histologic grade (n = 256)			
1	39	34 (79)	.055
2	126	112 (77)	
3	91	85 (61)	
Metastatic nodes	131	118 (59)	.002
Advanced clinical stage	189	169 (61)	<.001
Metastasis	48	40 (46)	<.001
Molecular subtype (n = 245)			
Luminal A	91	81 (80)	.081
Luminal B	30	30 (82)	
HER-2	33	29 (55)	
Triple negative	91	87 (68)	
Neoadjuvant treatment	188	170 (63)	<.001

[a]Kaplan–Meier method.
[b]Log–Rank test.
[C]Body mass index (BMI): overweight ≥25 kg/m^2 + obesity ≥30 kg/m^2.[15]

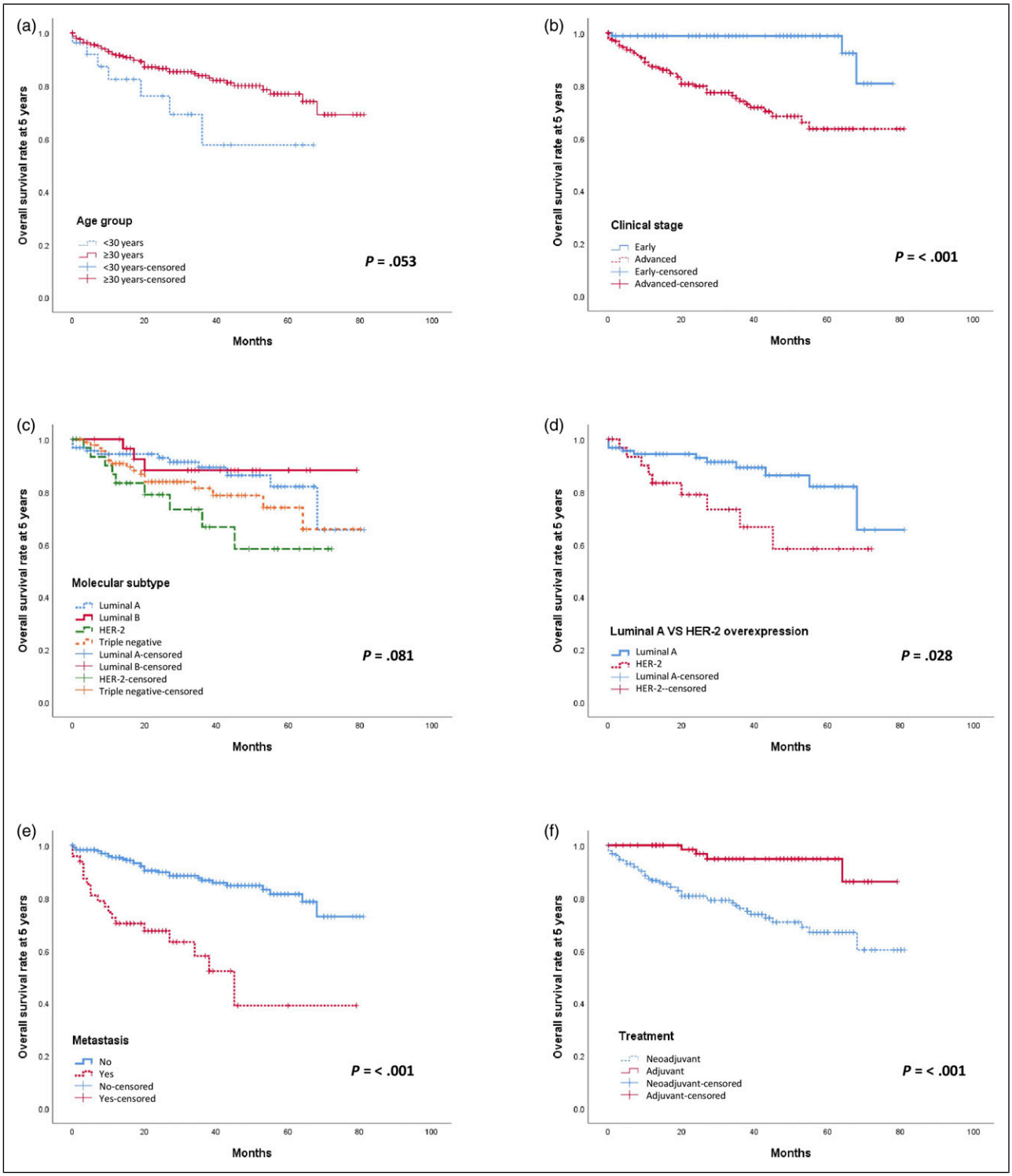

Figure 1. Overall survival according to age, clinical variables, and tumor subtypes. Estimation of survival function using Kaplan–Meier curves. (A) Age groups, (B) clinical stage, (C) molecular subtypes, (D) luminal A vs HER-2 overexpression, (E) metastasis, and (F) type of treatment.

reserved impact and lower survival. Our study revealed that age <30 years in women with BC turned out to be a predictor for poor survival rate (HR = 3.0; 95% CI 1.1 to 8.6, $P = .04$), compared to its counterpart (30–40 years). The lower survival rate was significantly related to a wide variety of aggressive characteristics, such as tumor size (HR = 2.3 95% CI 1.03 to 5.1; $P = .04$), advanced clinical stage ($P = .03$), positive nodes (HR = 2.4; CI 95% 1.1 to 5.5; $P = .03$), and triple negative

Table 4. Predictive Factors of Poor Survival in a Multivariate Analysis.

Variable	Model 1		Model 2		Model 3	
	HR[a] (95% CI)[b]	*P*-value	HR[a] (95% CI)[b]	*P*-value	HR[a] (95% CI)[b]	*P*-value
Age <30 years	2.7 (1.1 to 6.8)	.03	2.0 (.7 to 5.4)	.17	3.0 (1.1 to 8.6)	.04
Excess weight[c]	.9 (.5 to 1.6)	.65	.9 (.5 to 1.9)	.88	.7 (.3 to 1.5)	.34
Basic studies[d]	1.1 (.6 to 2.2)	.77	1.2 (.5 to 2.7)	.66	1.3 (.5 to 3.1)	.55
Tumor size >5 cm	2.6 (1.2 to 5.1)	.003	1.8 (.9 to 3.8)	.09	2.3 (1.03 to 5.1)	.04
Low/moderate histological grade			1.8 (.9 to 3.7)	.09	1.3 (.6 to 2.9)	.51
Advanced clinical stage			3.9 (1.1 to 13.5)	.03	6.6 (1.3 to 35.5)	.03
Metastasis			1.3 (.5 to 3.5)	.63	1.3 (.5 to 3.8)	.58
Liver metastasis			4.1 (1.1 to 15.6)	.04	7.8 (1.9 to 32.8)	.005
Metastatic lymph nodes					2.4 (1.1 to 5.5)	.03
HER-2					.6 (.14 to 2.4)	.45
Triple negative					2.6 (1.1 to 6.0)	.03
Neoadjuvant therapy					.7 (.2 to 2.8)	.62

Dependent variable: survival.
[a]HR: hazard ratio obtained by Cox regression.
[b]95% CI: confidence interval at 95%.
[c]Excess weight included to subjects with overweight and obesity. It was defined as body mass index (BMI) ≥ 25 kg/m^2.[15]
[d]Basic level of education = primary and secondary. HER-2 human epidermal growth factor receptor 2 positive.

molecular subtype. The characteristics describing this very young subgroup are consistent with other studies.[17-19] Likewise, Han et al reported that, in patients <35 years, the risk of death increases by 5% for each 1-year decrease in age.[20]

In consistence with the age subgroup, a predominance of the triple negative molecular subtype (37.14%) was observed and, in addition to being an important subtype of poor prognosis, it was associated with the probability of survival in the multivariate analysis (HR = 2.6; 95% CI 1.1 to 6.0, $P = .03$), in addition to that reported in previous studies.[21] The presence of HER-2 tumors was also evident in 13.47% of the total; a similar figure was reported by Sabiani et al,[11] who also showed a poor survival rate, although not as significant as in our cohort.

Of clinical importance was the high percentage of diagnoses in advanced stages among the very young population (80.0%), a figure comparable to that reported by Goksu et al,[22] but higher than those reported in the Latin American population.[23] The association between the clinical stage and low survival can be explained by the higher risk of late diagnosis in young women, due to the low perception and suspicion of cancer risk from the first symptoms to the first contact with a doctor, as well as the time interval between diagnostic biopsy results and initiation of treatment.[24]

The results of this research add evidence supporting the fact that very young women show quite violent local growth and rapid progression and presented a high rate of metastasis with a direct impact on significantly lower survival ($P < .001$) and the main organs remotely affected were bones and liver, as observed in a study in Moroccan women.[25] However, in the multivariate result, only liver metastasis was associated with a higher risk of death (HR = 7.8; $P = .005$). In contrast, Mustillo et al emphasize that survival was higher in women <40 years with initial brain metastasis.[26] However, it must be remembered that metastasis is an important predictor of severe and poor survival, but prognosis will be determined by metastatic pattern and molecular subtype.

Notably, almost all women of the cohort were from a low socioeconomic status (94.7%). Regarding formal education, 65.2% had completed at least junior high school, which is consistent with economic and education levels reported by Mexican authors and other Latin American cohorts.[21,27] Other authors suggest that low socioeconomic status and lower education are associated with poor survival from BC, additionally, social and cultural environment may have influenced her late visit to the doctor and access to some aspects of treatment.[28]

Epidemiological studies of the combination of BC and obesity pose unique challenges, experience more treatment-related complications, and worse prognosis,[21,29] and are associated with an increased risk of progression, recurrence, and survival decrease of young women with BC.[30] Although in our study these data were not significant in the multivariate analysis, we found a predominance of overweight in women ≥30 years, as reported in previous studies[31] and that is related to that reported by the National Health and Nutrition Survey 2018 (ENSANUT, since it is an acronym in Spanish).[32]

An aggressive treatment has been justified in young women with BC due to its worse prognosis.[33] More than half of the patients in our cohort received neoadjuvant treatment, which was significantly associated with the probability of survival ($P < .001$). The nature of the disease at a young age may foster the implementation of new diagnostic, preventive, and therapeutic approaches to reduce the mortality figures that most afflict this population.

The previously described variations on very young women with BC may be strongly related to the low identification of

various risk factors and the performance of self-care practices among younger women, as well as differentiated conditions for access to health services, early detection tests, and timely treatment that, as a consequence, make young women look for medical assistance at advanced stages at the time of diagnosis, presence of metastases, and a significant predominance of excess weight, among other elements associated with a poor outcome.

The main limitations of this study include its retrospective nature and the inherent restrictions on the quality of information in clinical records. Our cohort represented 5 years of follow-up at the largest State Oncology Center; taking into account the significance of these results, they need to be validated with a larger sample size in more hospitals.

Conclusions

Our results show poor survival for the very young subgroup (age <30 years) and are related to aggressive characteristics of the tumor, the influence of the triple negative subtype, as well as the presence of very large tumors, positive nodes, advanced disease, and presence of distant metastases at the time of diagnosis. These findings may have important implications regarding the etiology and prognosis of BC in very young women. However, more research is required to support or reject this hypothesis.

Author Contributions

Conceptualization, M.T.A.B., K.A.S.J and R.E.G.G.; methodology, M.T.A.B., K.A.S.J, E.C.G.R. and J.M.R.; validation, M.T.A.B., K.A.S.J. and E.C.G.R.; formal analysis, J.M.R and C.A.A.R.; investigation, K.A.S.J, E.C.G.R. and M.T.A.-B.; writing-original draft preparation, M.T.A.B., K.A.S.J., C.L.L.S and J.M.R; writing-review and editing, M.T.A.B, J.M.R. and R.E.G.G.; CLLS supervision, M.T.A.B., J.M.R

Declaration of Conflicting Interests

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Ethical Approval

This study was approved by the Research Ethics Committee of the CECan, of State Cancer Center, Ministry of Health of the State of Veracruz, with registration number C.E.I./2018/053.

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