Disease-Free Survival in Women with Breast Cancer: 36- and 60-Month Cohorts

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Sobrevida Livre de Doença em Mulheres com Câncer de Mama: Coorte de 36 e 60 Meses

Sobrevida Libre de Enfermedad en Mujeres con Cáncer de Mama: Cohortes de 36 y 60 Meses

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ABSTRACT

Introduction: The study of disease-free survival has contributed to understanding the behavior and prognostic factors following the diagnosis of breast cancer in women. **Objective:** To analyze disease-free survival in 36 e 60 months and prognostic factors in women with breast cancer treated at a private health service. **Method:** Historical cohort study of women diagnosed with non-metastatic breast cancer seen between 2010 and 2021. Demographic and clinical data were collected. The statistical, descriptive, bivariate, survival analysis used the Kaplan-Meier method and the log-rank test. **Results:** Disease-free survival at 36 months was 89.8% (95%CI: 84.8-93.3) and clinical stage III was the worst prognosis with an 11% reduction in the meantime compared to stage I. Compared to 60 months, disease-free survival was 80.6% (95%CI: 73.1-86.2), with stage II and III having the worst prognosis. The reduction in mean time for stage III was 21 per cent compared to stage I. **Conclusion:** Tumor and clinical characteristics are important for understanding disease-free survival and identifying risk profiles for recurrence, given the scarcity of research on the subject in the Brazilian population. It therefore emphasises the need for early diagnosis to reduce recurrence.

Key words: Breast Neoplasms/diagnosis; Survival; Prognosis; Cohort Studies.

RESUMO

Introdução: O estudo de sobrevida livre de doença tem contribuído para a compreensão do comportamento e dos fatores prognósticos após o diagnóstico do câncer de mama em mulheres. **Objetivo:** Analisar a sobrevida livre de doença em 36 e 60 meses e fatores prognósticos em mulheres com câncer de mama atendidas em um serviço privado de saúde. **Método:** Estudo de coorte histórica com população de mulheres com diagnóstico de câncer de mama não metastático atendidas no período de 2010 a 2021. Foram coletados dados demográficos e clínicos. A análise estatística foi descritiva, bivariada e de sobrevida pelo método de Kaplan-Meier com utilização do teste *log-rank*. **Resultados:** A sobrevida livre de doença em 36 meses foi de 89,8% (IC 95%: 84,8-93,3) e o estádio clínico III foi o de pior prognóstico com redução de 11% no tempo médio em comparação ao estádio I. Em relação a de 60 meses, a sobrevida livre de doença foi 80,6% (IC 95%: 73,1-86,2), com estádio II e III com pior prognóstico. A redução do tempo médio do estádio III foi de 21% em comparação com o estádio I. **Conclusão:** Características tumorais e clínicas são importantes para a compreensão da sobrevida livre de doença e identificação de perfis de risco para recidiva, dada a escassez de pesquisas relacionadas ao tema na população brasileira. Assim, reforça-se a necessidade de diagnóstico precoce para reduzir a recorrência.

Palavras-chave: Neoplasias da Mama/diagnóstico; Sobrevida; Prognóstico; Estudos de Coortes.

RESUMEN

Introducción: El estudio de la sobrevida libre de enfermedad ha contribuido a conocer el comportamiento y los factores pronósticos tras el diagnóstico de cáncer de mama en mujeres. **Objetivo:** Analizar la sobrevida libre de enfermedad a los 36 y 60 meses y los factores pronósticos en mujeres con cáncer de mama atendidas en un servicio sanitario privado. **Método:** Estudio de cohortes histórico con una población dinámica de mujeres diagnosticadas con cáncer de mama no metastásico atendidas entre 2010 y 2021. Se recogieron datos demográficos y clínicos. Los análisis estadísticos fueron descriptivos, bivariados y de sobrevida mediante el método de Kaplan-Meier y la prueba *log-rank.* **Resultados:** La sobrevida libre de enfermedad a los 36 meses fue del 89,8% (IC 95%: 84,8-93,3) y el estadio clínico III fue el de peor pronóstico, con una reducción del 11% del tiempo medio en comparación con el estadio I. En comparación con los 60 meses, la supervivencia libre de enfermedad fue del 80,6% (IC 95%: 73,1-86,2), siendo los estadios II y III los de peor pronóstico. La reducción del tiempo medio para el estadio III fue del 21% en comparación con el estadio I. **Conclusión**: Las características tumorales y clínicas son importantes para comprender la sobrevida libre de enfermedad e identificar perfiles de riesgo de recurrencia, dada la escasez de investigaciones sobre el tema en la población brasileña. Por tanto, se destaca la necesidad de un diagnóstico temprano para reducir la recurrencia.

Palabras clave: Neoplasias de la Mama/diagnóstico; Supervivencia; Pronóstico; Estudios de Cohortes.

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INTRODUCTION

Breast cancer is a public health issue in Brazil and around the world[1]. It is the most frequent and mortal type of malign neoplasm in women. Every year, about 2 million new breast cancer cases around the world and 94 thousand in Brazil are expected[2,3]. The total number of deaths associated with the disease in the world female population surpasses the 666 thousand figure and is concentrated mainly in less developed countries[2]. Among Brazilian women, it corresponds to the greatest *causa mortis* due to neoplasms and is responsible for over 22 thousand deaths[2,3].

Due to the persistence of mortality rates, with a tendency to increase in Brazil and Latin America[4,5], the study of breast cancer survival contributes to the description of the behavior of the disease and the prognostic factors related to it[6]. While overall survival (OS) is the analysis of overall mortality of patients with a certain health condition, disease-free survival (DFS) reflects the period after treatment for a specific disease, during which the patient survives with no sign of recurrence[7].

Generally, five-year OS estimates for breast cancer have been showing an upwards trend in developed countries. However, a great global disparity in this aspect is still observed[1]. In Brazil, the five-year survival estimate for breast cancer was 75.2% for the 2010-2014 period[8]. Still, it should be considered that the use of OS as primary outcome has been questioned by literature, giving space and evidence to the study of DFS, mainly because OS presents disadvantages, like the need for longer follow-up for assessment[9].

The breast cancer DFS analysis and the prognoses factors associated with it have allowed for a better understanding of patients' profile and characteristics related to recurrence, also providing theoretical support to guide therapeutic decisions. Nevertheless, studies investigating breast cancer recurrence within the Brazilian context are still scarce[10].

Factors considered for breast cancer survival analysis are those that interfere in the prognosis of the disease, that can be inherent to the biology of the tumor, as well as demographic and socioeconomic characteristics of the patient[6]. In this context, it becomes possible to identify the risk of specific groups, assessing their tumoral specificities, time to tumor diagnosis, therapeutic approach provided, among other aspects that directly affect the prognosis[11].

Description of those data is essential to assess the profile of women affected by breast cancer, but mainly, to determine a connection between strategies that have been applied and results on the disease prognosis. All factors related to survival of this neoplasm have been studied with the aim of improving prognostic evaluation of patients, in addition to fostering more knowledge on the behavior of the disease, enabling a more realistic and effective care that reflects on improving quality of life of people affected and guidance of future actions[12,13].

Given the relevancy of the breast cancer theme in the collective healthcare scope, as well as the reduced number of studies that analyze DFS in women that have received this diagnosis in Brazil, the following research question was elaborated: what are the prognostic factors that affect breast cancer DFS in women? With that in mind, the objective of this study is to analyze DFS in 36 months and 60 months, as well as the prognosis factors in women with breast cancer assisted by a private healthcare service.

METHOD

Non-concurrent (retrospective) cohort study[14] with dynamic population, using data from women diagnosed with breast cancer assisted by a private healthcare service located in the city of Florianópolis (SC). The study included cases of women diagnosed with breast cancer seen between 2010 and 2021. Exclusively *in situ* breast cancer diagnosis and clinical staging IV cases were excluded.

The analyzed variables were age group at diagnosis time (39 years or younger, 40 to 49 years, 50 to 69 years, 70 years or older), marital status (spouse [married], no spouse [single, divorced, widow]), histological type (invasive ductal carcinoma, invasive lobular carcinoma, associated invasive ductal and lobular carcinoma, and others), clinical staging (CS — CS I, CS II, CS III), status for estrogen receptor (positive and negative), progesterone receptor (positive and negative), HER-2 (positive and negative). Information regarding treatment was collected, such as surgical breast treatment (yes and no), chemotherapy treatment (yes and no), type of chemotherapy treatment (adjuvant, neoadjuvant), radiotherapy treatment (yes and no), hormone therapy (yes and no). From that information, a variable was created to contemplate the combination of types of treatment the patient underwent (surgery and hormone therapy; surgery, radiotherapy and hormone therapy; surgery and chemotherapy; surgery, chemotherapy and hormone therapy; surgery, chemotherapy and radiotherapy; surgery, chemotherapy, radiotherapy and hormone therapy).

The outcome of the study was recurrence of the initial breast cancer diagnosis (yes and no). The recurrence was

defined as local and/or metastatic at a distance (bone, lungs, liver, brain, lymph nodes and others). In addition, information on date of diagnosis, date of last consultation, date of recurrence was collected.

Time of disease-free survival was calculated between date of diagnosis and date of first recorded recurrence. The date of the last consultation was considered the final follow-up date for patients who had no recurrence with those cases being censored. Two cohorts were calculated, the first with all the included cases and 36-month follow-up and the second with 60-month follow-up, with cases diagnosed from 2010 to 2019.

A descriptive, bivariate analysis among exposure and outcome variables, DFS for both cohorts. The chi-square test was used to compare variables. The survival curves were estimated using the Kaplan-Meier method, in which the probability of survival up to the specified date is estimated considering that survival up to a time is independent from up to other times. To compare stratified survival curves, the log-rank test was used, that compares values observed and expected from each stratum under the null hypothesis that the risk is the same in every stratum. The rate of recurrence incidence was also calculated in 36 and 60 months for thousand people-month[15].

A hazard analysis was conducted using the semiparametric Cox model and the hazards proportionality test over time. Moreover, the interaction between variables and the moderating effect was tested. The independent variables age group, marital status, estrogen receptor, progesterone receptor, HER-2 and clinical staging were included in adjustment, since they are important. The variable combination of treatment was not included in the analysis, as it presented interaction and moderating effect with the clinical staging variable. Thus, the areas on the 36 and 60-month curves were estimated for the staging variable, adjusted for the other variables, using the restricted mean survival time (RMST) up to the specified points[16]. The data analysis was conducted on Stata 16.1 software[17].

This research follows Resolution number 466[18] of December 12, 2012, of the National Health Council and was approved by the Human Being Research Ethics Committee of the *Universidade Federal de Santa Catarina* (UFSC) on November 10, 2021, report number 5.097.894 (CAAE (submission for ethical review: 51838821.0.0000.0121).

RESULTS

The study collected information from 266 women diagnosed with breast cancer CS I, II or III, seen between 2010 and 2021. Those women were followed-up for 36 months (Table 1).

The histological types, clinical staging and immunohistochemical characteristics of tumors were assessed. The invasive ductal carcinoma (IDC) stood out among other histological types and was present in 74.4% of cases in isolation. Invasive lobular carcinoma (ILC), in isolation, affected 8.6% of women. Other tumor types were present in isolation in 12.8% of the total assessed. This category includes the micropapillary, mucinous, apocrine, cribriform, medullary, tubular and neuroendocrine types (data not presented). CS II was the most frequent type, identified in 40.6% of cases, followed by CS I (39.5%) and CS III (19.9%). Estrogen hormone receptors were positive in 81.5% of cases and progesterone in 72.3%. Positivity for the HER-2 oncogene was present in 20.5% of the population analyzed (Table 1).

Of the women included in the study, 87.2% were submitted to surgical breast treatment, with quadrantectomy – conservative surgery – being the most performed procedure among them, corresponding to 47.6% of cases. Followed by simple mastectomy (41.4%) and bilateral mastectomy (10.6%), sometimes preventive and sometimes therapeutic. For cases that affected lymph nodes, surgical treatment of armpits varied from sentinel lymph node excision (68.6%) to axillary dissection (31.4%). Regarding chemotherapy, 47.7% of women underwent adjuvant chemotherapy treatment and 26.7% underwent neoadjuvant chemotherapy. As to radiotherapy, 51.9% were submitted to this treatment. Regarding hormone therapy, 72.3% had information on the treatment (data not presented). Regarding the combination of treatments, most patients underwent surgery, chemotherapy, radiotherapy and hormone therapy (27.4%).

At the end of the 36-month follow-up, 21 (7.9%) women had recurrence and the average time of follow-up was 26.2 months (confidence interval – 95%CI: 24.6-27.7). The DFS was 89.8% (95%CI: 84.8-93.29) (Graph 1) and the average incidence rate by a thousand people-month was 3.10 (95%CI: 1.96-4.62). The most common metastasis site was bones (47.6%), followed by lymph nodes (38.1%), liver (23.8%), breast (19.1%), lung (18.8%), and brain (9.5%) (data not presented).

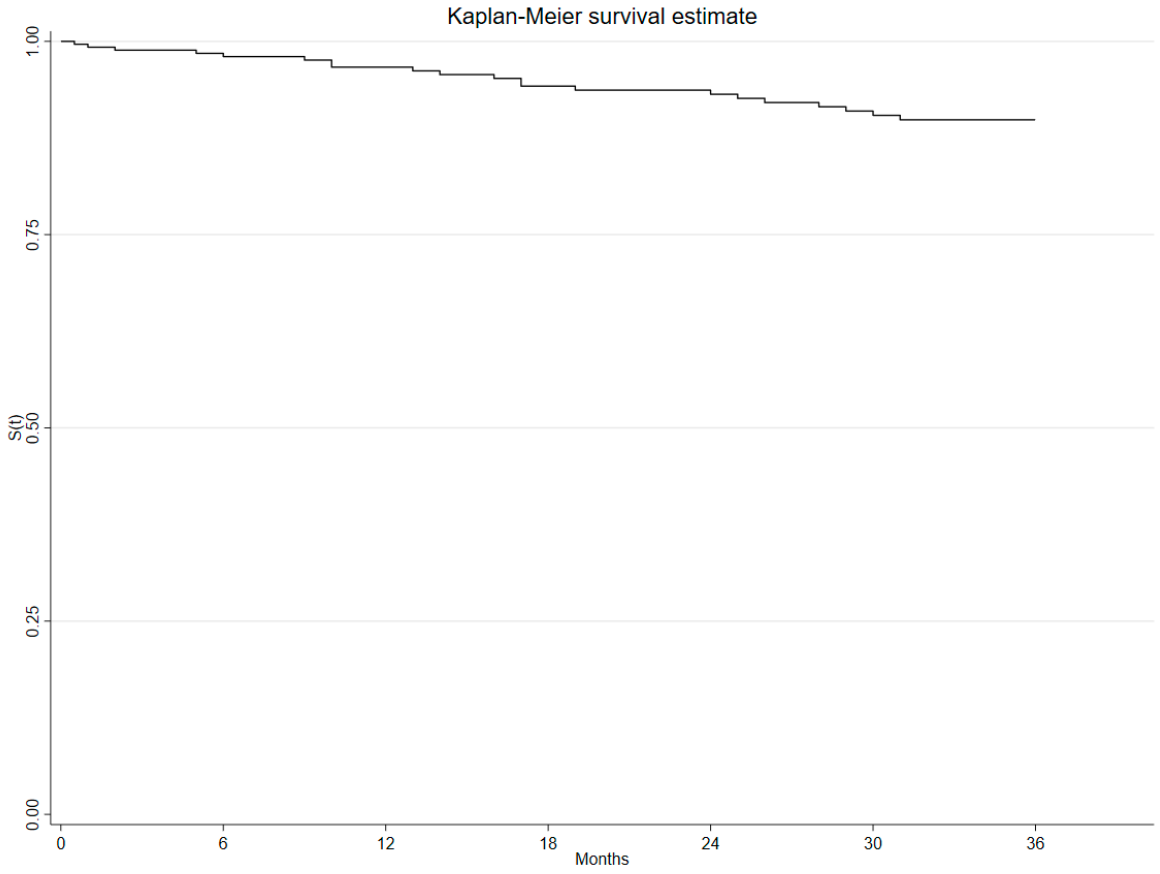
The variables associated with recurrence incidence at 36 months are presented in Table 1. In bivariate analysis, only staging was associated to recurrence, and CS III had a 20.9% recurrence incidence. Regarding survival analysis in 36 months, clinical staging, estrogen and progesterone receptors were associated. The worst

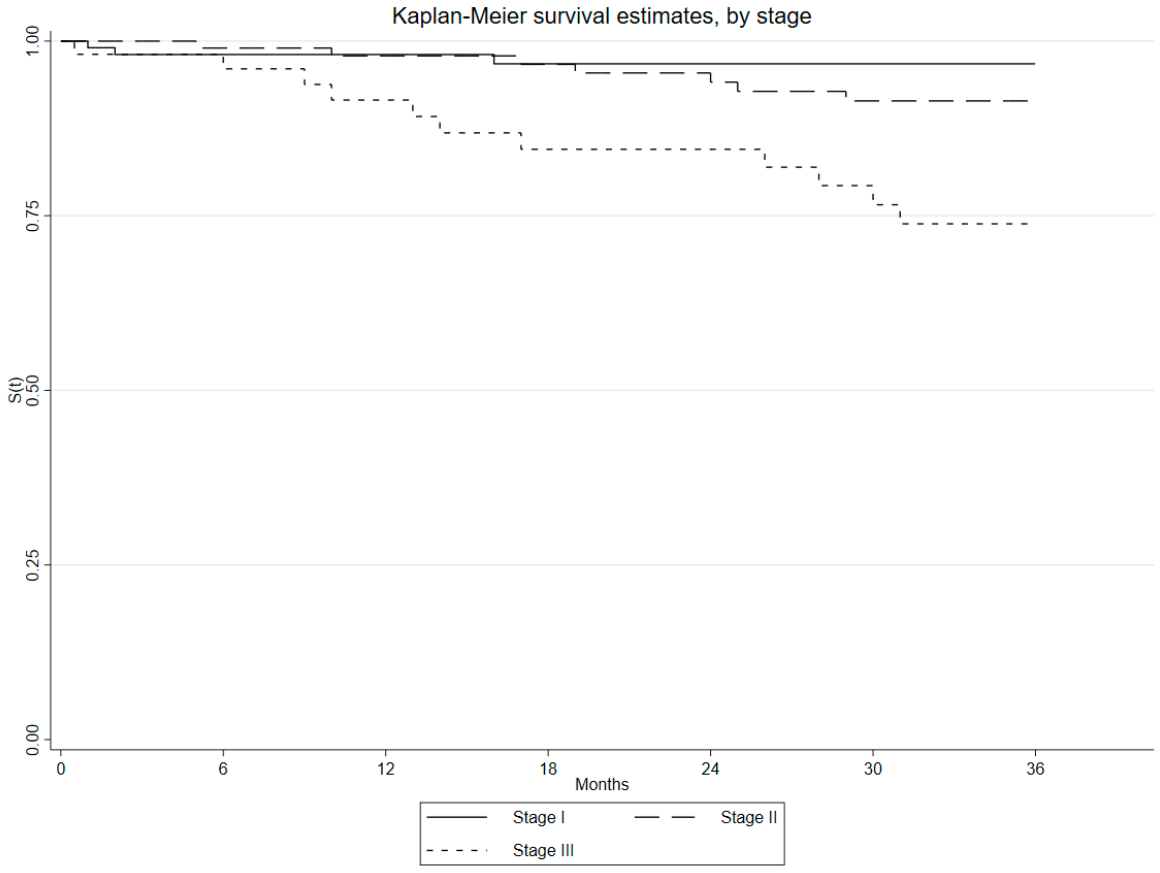
Table 1. Description of demographic and clinical characteristics of patients, 36 months, 2010-2024

Variable	n	%	Recurrence		Value of *p**	S(t)(95%CI)	Value of *p*†
			n	%			
Age group					0.215		0.1567
39 years-old or less	37	13.9	6	16.2		77.7 (56.2-89.6)	
40 to 49 years-old	47	17.7	3	6.4		91.1 (74.8-97.1)	
50 to 69 years-old	136	51.1	8	5.9		92.8 (86.0-96.3)	
70 years-old and over	46	17.3	4	8.7		88.9 (72.6-95.7)	
Marital status					0.576		0.5346
Spouse	150	61.7	10	6.7		91.5 (84.7-95.3)	
No spouse	93	38.3	8	8.6		88.6 (78.3-94.1)	
Histological type					0.581		0.5684
IDC	198	74.4	18	9.1		88.2 (81.8-92.4)	
IDC and ILC	11	4.1	1	9.1		90.9 (50.8-98.7)	
ILC	23	8.6	1	4.3		93.3 (61.3-99.0)	
Others	34	12.8	1	2.9		97.0 (80.4-99.6)	
Clinical staging					**<0.001**		**<0.001**
I	105	39.5	3	2.9		96.7 (90.1-99.0)	
II	108	40.6	7	6.5		91.4 (82.8-95.8)	
III	53	19.9	11	20.7		73.8 (57.5-84.7)	
Estrogen receptor					0.068		**0.0279**
Negative	49	18.5	7	14.3		79.0 (60.5-89.5)	
Positive	216	81.5	14	6.5		92.0 (86.7-95.2)	
Progesterone receptor					**0.033**		**0.0139**
Negative	73	27.7	10	13.7		80.3 (66.2-89.0)	
Positive	191	72.3	11	5.8		93.0 (87.6-96.1)	
HER-2					0.336		0.3647
Negative	210	79.5	15	7.1		91.0 (85.4-94.5)	
Positive	54	20.5	6	11.1		85.1 (69.5-93.1)	
Treatment protocol					0.230		0.0323
Other combinations	37	13.9	5	13.5		77.4 (52.0-90.4)	
Surgery, HTx	16	6	2	12.5		85.9 (54.0-96.3)	
Surgery, RTx, HTx	35	13.2	-	-		1	
Surgery, QTx	34	12.8	4	11.8		78.3 (50.8-91.6)	
Surgery, QTx, HTx	50	18.8	2	4		95.3 (82.3-98.8)	
Surgery, QTx, RTx	21	7.9	3	14.3		81.6 (53.0-93.7)	
Surgery, QTx, RTx, HTx	73	27.4	5	6.8		91.5 (80.8-96.4)	
Recurrence in 36 months							
No	245	92.1					
Yes	21	7.9					

Probability of survival	n	Person-month	Recurrence	Average incidence rate per thousand person-months	S(t)(95%CI)
12 months	205	2,791.5	8	2.9 (1.4-5.7)	96.7 (93.4-98.3)
24 months	176	2,238	7	3.1 (1.5-6.5)	93.2 (88.7-95.8)
36 months	150	1,939	6	3.1 (1.4-6.9)	89.5 (84.8-93.3)

Captions: S(t) (95%CI) = survival function (95% confidence interval); IDC = invasive ductal carcinoma, ICL = invasive lobular carcinoma, HTx = hormone therapy, RTx = radiotherapy; QTx = chemotherapy.
*chi-square test *p* value; †log-rank test *p* value.





Graph 1. Disease-free survival after breast cancer diagnosis, 36-month follow-up, 2010-2024

DFS was found in CS III, with a 73.8% probability of recurrence in 36 months (Graph 1). Regarding the estrogen receptor, those with a negative status had 79.0% and the ones with negative progesterone, 80.3% probability of survival (Table 1).

Adjusted analysis was performed to identify the variables with the highest hazard of recurrence over time. An interaction was detected between the treatment variable and staging, as well as a moderating effect of staging on the treatment variable.

When performing the analysis to estimate the risk of recurrence adjusted for age group, marital status, stage, histological type, estrogen hormone receptor, progesterone hormone receptor and HER-2, only stage was shown to be an independent factor of risk of recurrence. CS III increased in 10.48 (95%CI: 2.10-52.21) the risk of recurrence over time compared to stage I, regardless of the other diagnosis characteristics. CS II was not significantly different from CS I (HR: 3.26; 95%CI: 0.65-16.31) (data not presented). The model respected proportionality over time (p=0.339).

When analyzing the difference in average time to recurrence among stagings, CS I had an average of 30.5 months (95%CI: 18.5-41.5), CS II presented a non-significant time reduction of 1.02 months (95% CI: -2.5; 0.47), and CS III, significant reduction of 4.0 (95%: -6.95; -1.04) compared to CS I. The adjustment variables, age group, histological type, marital status, estrogen and progesterone receptors and HER-2 status, did not show significance in reducing time to recurrence. When analyzing the RMST ratio, differences remained, and CS III had an 11% reduction in time to recurrence (Coef: 0.89; 95%CI: 0.81; 0.97).

For the 60-month follow-up, 215 women were followed-up and characteristics are presented in Table 2. The average follow-up time was 39.5% (95%CI: 36.5-42.5). In the period, 29 (13.5%) had recurrence. The incidence rate was 3.42 (95%CI: 2.38-4.92) for thousand followed-up people-month. DFS at the end of 60 months was 80.6 (95%CI: 73.1-86.2) (Graph 2).

Regarding recurrence in 60 months, only the clinical staging variable was associated, in which the greatest incidence was in the CS III diagnoses (37.2%). This association was also present in the survival analysis, with that being the stage with the worst DFS, with a rate of 50.3% (Table 2 and Graph 2).

The estimated risk of recurrence in 60 months adjusted for age group, marital status, stage, histological type, estrogen hormone receptor, progesterone hormone receptor and HER-2, also showed only stage as an independent risk factor for recurrence. CS II increased in 4.55 (95%CI: 1.20-17.32) and CS III in 21.09 (95%CI: 5.58-79.76) the risk of recurrence over time compared to stage I, regardless of the other diagnosis characteristics (data not presented). The model respected proportionality over time (p=0.605).

Regarding the difference in average time to recurrence between stagings, CS I had an average of 54.7 months (95%CI: 30.3-70.0), CS II presented non-significant time reduction of 3.3 months (95%CI: -7.02-0.42), CS III presented non-significant reduction of 12.43 months (95%CI: -18.91; -5.94) compared to CS I. The adjustment variables, age group, histological type, marital status, estrogen and progesterone receptors and HER-2 status, did not show significance in reducing time to recurrence. CS III had a 21% reduction in time to recurrence (Coef: 0.79; 95%CI: 0.69; 0.90).

DISCUSSION

The present study analyzed the disease-free survival of 266 women diagnosed with non-metastatic breast cancer seen between 2010 and 2021. DFS was 89.9% (95%CI: 84.8-93.3) for 60 months and 80.6% (95%CI: 73.1-86.2) for 36 months.

Although the number of studies focused on DFS performed in Brazil are scarce, similar rates are found in recent national research. A retrospective cohort study conducted in a hospital in Juiz de Fora (MG) noted a DFS in five years of 79.5% (95%CI: 74.6-83.6) in a group of women diagnosed with non-metastatic breast cancer[19]. Another survival analysis with retrospective cohort with 253 patients diagnosed with breast cancer of the luminal subtype A, in the city of Itajaí (SC), identified a DFS in 3 years of 86.0%[7]. Those studies were conducted in their cities' reference public healthcare services and the data are close to those of private services. In the first[19], staging was also an independent factor for DFS, as in the findings of this study. This demonstrates the importance of early diagnosis for this outcome.

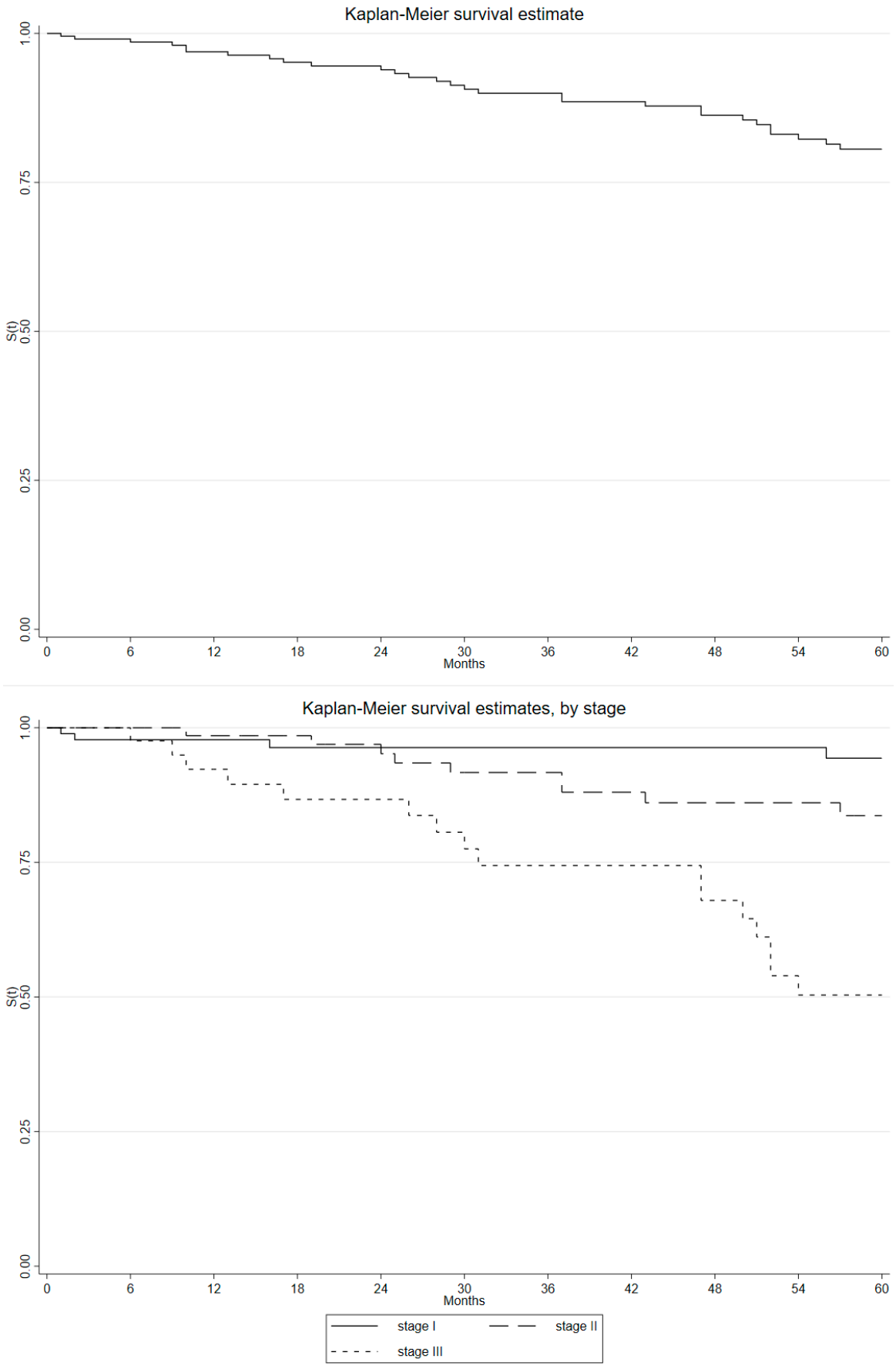
In international studies, the findings were also similar, or discreetly superior in some of them. A retrospective analysis conducted in the Netherlands noted an 88.1% DFS in five years in a group of women with breast cancer submitted to neoadjuvant chemotherapy[20]. Another research, set in an oncology center in Poland, presented an 80.5% DFS in five years[21] and a German study that analyzed DFS in women with non-metastatic breast cancer in three and five years obtained an 82.5% rate[22]. A hypothesis for the existing varieties among the results are the methodological differences, like the population selection criteria and time of analysis.

Table 2. Description of demographic and clinical characteristics of patients, 60 months, 2010-2024

Variable	n	%	Recurrence		p*	S(t)(95%CI)	p†
			n	%			
Age group					0.62		0.575
39 years-old or less	25	11.6	5	220		74.1 (48.2-88.4)	
40 to 49 years-old	35	16.3	4	11.4		81.4 (57.6-92.6)	
50 to 69 years-old	120	55.8	14	11.7		83.3 (73.1-89.9)	
70 years-old and over	35	16.3	6	17.1		74.6 (51.2-88.0)	
Marital status					0.658		0.627
Spouse	123	63.1	16	13		81.3 (71.0-88.2)	
No spouse	72	36.9	11	15.3		79.0 (65.0-87.8)	
Histological type					0.131		0.211
IDC	163	75.8	27	16.6		77.2 (68.4-83.9)	
IDC and ILC	9	4.2	-	-		100	
ILC	17	7.9	1	5.9		90.9 (50.8-98.7)	
Others	26	12.1	1	3.8		90.0 (47.3-98.5)	
Clinical staging					**<0.001**		**<0.001**
I	91	42.3	4	4.4		94.3 (85.2-97.9)	
II	81	37.7	9	11.1		83.7 (70.7-91.2)	
III	43	20	16	37.2		50.3 (31.8-66.3)	
Estrogen receptor					0.333		0.201
Negative	38	17.8	7	18.4		69.4 (45.8-84.2)	
Positive	176	82.3	22	12.5		82.7 (74.8-88.4)	
Progesterone receptor					0.380		0.243
Negative	59	27.7	10	16.9		74.0 (56.5-85.3)	
Positive	154	72.3	19	12.3		82.8 (74.2-88.8)	
HER-2					0.286		0.216
Negative	170	79.8	21	12.3		82.2 (73.9-88.2)	
Positive	43	20.2	8	18.6		73.4 (53.1-86.0)	
Treatment protocol					0.379		0.3
Other combinations	22	10.2	3	13.6		75.0 (38.2-91.7)	
Surgery, HTx	15	7	3	20		72.7 (34.9-90.8)	
Surgery, RTx, HTx	33	15.3	1	3		96.1 (75.7-99.5)	
Surgery, QTx	30	13.9	3	10		78.4 (46.4-92.6)	
Surgery, QTx, HTx	40	18.6	5	12.5		82.7 (62.6-92-6)	
Surgery, QTx, RTx	16	7.5	4	25		70.5 (38.9-87.8)	
Surgery, QTx, RTx, HTx	59	27.5	10	17		77.5 (62.1-87.3)	
Recurrence in 60 months							
No	186	86.5					
Yes	29	13.5					

Probability of survival	n	Person-month	Recurrence	Average incidence rate per thousand person-months	S(t)(95%CI)
12 months	171	2,320.5	6	2.6 (1.2-5.8)	96.7 (93.4-98.3)
24 months	148	1,887	5	2.6 (1.1-6.4)	93.9 (82.2-96.6)
36 months	128	1,642	6	3.6 (16-8.2)	90.0 (84.3-93.7)
48 months	114	1,438	5	2.5 (1.5-8.4)	86.3 (79.8-90.8)
60 months	83	1,196	7	5.8 (2.8-12.3)	80.6 (73.1-86.2)

Captions: S(t) (95%CI) = survival function (95% confidence interval); IDC = invasive ductal carcinoma, ICL = invasive lobular carcinoma, HTx = hormone therapy, RTx = radiotherapy; QTx = chemotherapy.
*chi-square test *p* value; †log-rank test *p* value.



Graph 2. Disease-free survival after breast cancer diagnosis, 60-month follow-up, 2010-2024

Among the variables analyzed, clinical staging gained prominence and is relevant for the analysis of DFS as it deals, above all, with severity according to the TNM classification, proposed by the Union for International Cancer Control (UICC)[23], which considers tumor size, lymph node involvement and the presence of metastasis. In the case of CS III, the tumors are always larger than 2 cm, there may or may not be lymph node involvement and there is no presence of metastasis[24].

In the present study, DFS for CS III diagnoses was significantly lower and was in line with the findings of other analyses, which showed decreasing rates as the clinical stage of the disease increased. The study by Dong et al.[25] obtained a 63.3% rate in five years within CS III, reaching 33.8% in 10 years. The study by Nowikiewicz et al.[21] noted an even lower rate for CS III, with 52% DFS in five years. Another retrospective cohort study conducted in Taiwan, which followed 559 women who underwent treatment from 2004 to 2022, with an average 45-month follow-up, found CS III as independent factor, with increase of 4.84 (95%CI: 2.88-8.22) for recurrence[26].

In a study in India with 3,256 women with breast cancer in the period of 2004 to 2020, followed-up until June 2023, DFS in five years was 94.3% (95%CI: 93.3-95.4). The worst DFS rates were observed in women with tumoral size classified as pT3/4 (greater than 5 cm diameter or any size that invaded the chest or skin) and ≥4 positive lymph nodes. The ones classified as CS III had a DFS of 74.0 (95%CI: 70.0-77.0), and this staging had a hazard ratio to recurrence of 2.61 (95%CI: 2.08, 3.27) greater than CS I, but with no adjustments for other characteristics[27].

In Istanbul, a cohort with 1,247 patients with breast cancer diagnosed and treated between January 2011 and June 2019, with a 31-month average follow-up, showed a DFS rate of 73.8% in five years. And the independent predictors of DFS were lymphovascular invasion [hazard ratio – HR: 4,35 (95%CI: 1.18–15.94)], residual *in situ* carcinoma [HR: 7.37 (95%CI: 1.52–35.71)], tumoral size ypT III [HR: 5.42 (95%CI: 1.69–17.35)], and molecular non-luminal subtypes [HR: 4.41 (95%CI: 1.33–14.58)][28].

It is therefore suggested that higher stagings have a worse prognosis, since the best survival rates are related to early-stage disease, just as recurrence is related to advanced-stage disease. In this sense, early detection is important because it allows the diagnosis of less aggressive forms and the establishment of appropriate treatments in a timely manner, impacting the quality of life and survival of patients.[19,25].

In Morocco, for example, a cohort with 1,901 women diagnosed from January 2008 to August 2017, in CS I to CS III, analyzed DFS comparing appropriate treatment or not following national and international recommendations according to type of surgery, tumor size and immunohistochemical characteristics. Results show that adequate management of cases increased DFS significantly (88% *vs.* 62%) in three and five years (80% *vs.* 50%). However, the study did not consider as adequate management cases of intermediate luminal cancer, in which chemotherapy followed by hormone therapy based on genomic signatures or Ki67 may or may not be used[29]. Furthermore, they report that there may have been classification with inadequate management of some patients undergoing hormone therapy due to lack of registration.

Although not significant in the bivariate analysis, another important finding was related to estrogen receptivity, determining worse prognoses among patients with negative status. An important factor is that this hormonal status prevails among younger women, who tend to develop more aggressive cancers. Such correlation and similarities referring to the negative status as a predictor factor for recurrence were found in many of the reviewed studies[25,30-32]. The analysis by Pruessmann et al.[22] concluded that patients with negativity for hormonal receptors have an increased risk of death, disease progression and lower survival rates. The cohort of 1,858 women included in their study found a five-year DFS of 81.3% for those with estrogen receptor negative status, compared with 86.8% for those with estrogen receptor positive status. Another study also showed association only in bivariate analysis[26].

Receptivity for HER-2 oncogene, despite not significant in the present study, is also worth mentioning, since it presented conformity with other findings in research. Its expression is also concentrated in women diagnosed with cancer at younger ages, and unlike hormone receptors, HER-2 gene positivity is what usually determines worse prognoses. This was stated in the present analysis due to the lower DFS rate in women with positive HER-2 and in other evaluated studies[20,25,31,33].

Regarding sociodemographic characteristics, the less favorable DFS rates were identified in single women and women in the 39 years or younger age group. Both variables had no significant difference regarding DFS. However, being young at the time of diagnosis is a predictor factor for unfavorable tumoral characteristics and, consequently, a bad prognosis, with worse OS and DFS rates when compared to older women[30,34-36].

The DFS study conducted by Pruessmann et al.[22] demonstrated this relationship and concluded that there is influence of biological, pathological and clinical tumor factors, such as greater negativity for estrogen and progesterone receptor, HER-2 positivity and greater lymph node affliction among younger women. A study that compared immunohistochemical characteristics of young women (≤45 years; n=104) and older (≥65 years; n=96) found that the former had a 70.1% DFS in five years, while the latter had 84.6% (p=0.001). Furthermore, the study shows, in bivariate analysis, that younger women have greater tumors, more frequency of negative estrogen receptor, positive HER-2 and greater axillary involvement[37].

A cohort with 2,518 women with breast cancer diagnosis from 2007 to 2010 in Germany compared women with ages younger than 70 years old. Older women had a higher frequency of diagnosis at an advanced stage (26% CS III *vs.* 14% in the younger women) and more lymph node involvement (58% *vs.* 48%). The average DFS, in months, was 12.2 (95%CI: 10.8-13.3) in the younger, and 7.6 (95%CI: 6.6-8.9) in the older women. The authors suggest those differences may be due to older women not having been included in the screening recommendations. However, DFS in three years showed similar rates[38].

Another study, with the aim of analyzing the relationship between age and prognosis of 5,438 women with breast cancer diagnosis, from September 1997 to January 2018, with ≤5 cm tumoral size and 1 to 3 positive lymph nodes with data, used data from 11 Chinese hospitals. Other criteria included mastectomy and axillary dissection with negative margins treatment, absence of distant metastasis evidence and no neoadjuvant chemotherapy. The average follow-up was 67 months. DFS was 83.9%. Age presented a U curve in the association of DFS outcome when used as continuum, with 50 years as reference. That age presented a lower recurrence risk. The analysis was adjusted for treatment period (1997-2007 *vs.* 2008-2018), tumoral site, pathological tumoral size (pT2 *vs.* pT1), tumoral grade (G3 *vs.* G1-2), presence of lymphovascular invasion, hormone receptors, positive lymph nodes, radiotherapy chemotherapy and HER-2[39].

Data from 192 women with breast cancer who performed neoadjuvant treatment at the Kaohsiung Medical University Hospital in Taiwan were analyzed regarding the impact of age in DFS. There was no difference among the age groups regarding complete answer response. However, women under 50 years old showed better DFS compared to older women, among the ones who had no complete response[40]. The group with complete pathological response had only 17 patients and the group with women aged 50 or older had better response. The authors suggest the complete pathological response may be a substitute outcome for DFS in women over 50.

The marital status variable, though not statistically significant, also had results that coincided with other OS and DFS studies, which showed worse rates among single women[13,41], in addition to being common for unmarried women to have a more advanced disease at the time of diagnosis[42].

Some limitations should be considered in this research, especially the fact it was a retrospective study, susceptible to absence and omission of information. The absence of race/skin color and education information in the presented data should be noted. Both variables could not be included in the study due to lack of data. However, the importance of such data for diagnosis and survival after breast cancer treatment is not ignored. Another limitation is that this is a dynamic cohort study, and not all individuals included had the same time of follow-up, which may generate bias in hazard estimates, but all tests respected the proportionality of hazards over time. It should also be considered that the studies consulted in the literature review for validation of the results found, even when in line, followed different methodologies, which can interfere directly and indirectly in the quality of the presented data.

CONCLUSION

DFS was 80.6% in 36 months and 89.9% in 60 months in this open cohort of a private healthcare service and was independently associated with staging at the time of diagnosis. Even though it was carried out in a service with characteristics that can be considered differentiated due to easy access and part of the population being below the screening age range, the study is important for understanding the disease and the factors related to its recurrence in all areas of health. The data found showed similarities to other studies carried out in Brazilian public healthcare services. Staging at diagnosis is a factor that independently determines clinical results in this population, demonstrating the importance of raising awareness for early diagnosis of breast cancer.

The results can significantly contribute to the identification of risk profiles, as well as validating therapeutic interventions adopted over the last years, a relevant advancement in breast cancer healthcare.

Moreover, the study is relevant to the national scenario, given the scarcity of research related to DFS in the Brazilian population.

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CONTRIBUTIONS

Both authors have substantially contributed to the study design, acquisition, analysis and interpretation of the data, wording, and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

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