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Assessment of the relationship between metabolic syndrome and breast cancer

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ABSTRACT

Introduction: Metabolic syndrome (MS) affects approximately 30% of women aged over 50 years. It is known to have a direct relationship with carcinogenesis and, therefore, with breast neoplasia. **Methods:** Retrospective longitudinal observational cohort study carried out at the Gynecology and Obstetrics Service of the São Paulo State Public Servant Hospital. The rates of local recurrence, distant metastases and overall survival of patients with malignant breast neoplasia in each group were evaluated. **Results:** Between 2017 and 2020, 375 patients underwent surgical treatment for breast cancer, of which 335 were eligible for the study, with an average age of 63.4 years old. MS is present in 32.5% of patients. Regarding the prognostic factor, patients with MS have a very similar distribution. The molecular profile in patients with MS is 39.4% of Luminal A patients, while in those without MS it is 42.5% of Luminal B. Regarding clinical staging, patients with MS have initial clinical stage I and IIA in 54 .1% of cases, while patients without MS present an initial clinical stage in 65% of cases. The average overall survival of the sample was 37.3 years, with a CI of 1.1 years; disease-free survival was 35.9 years, with CI 1.2 years; and invasive disease-free survival was 36.9 years, with CI 1.3 years. **Conclusions:** The presence of MS at diagnosis does not worsen survival.

KEYWORDS: malignant breast neoplasm; metabolic syndrome; prognosis; survival.

INTRODUCTION

Metabolic syndrome (MS) can be defined as a set of conditions — central obesity (waist circumference), high blood pressure, reduced HDL cholesterol, increased triglycerides and impaired glucose intolerance — which is known to be associated with a greater risk in development of cardiovascular disease and type 2 diabetes. It affects approximately 30% of the population of women over 50 years old[1,2].

Currently, breast cancer (BC) is the most common in Brazil, after skin cancer, and is the one that causes the most deaths in the female population[3]. According to the National Cancer Institute (INCA), in 2021, around 66,280 new cases were estimated, and in 2019, more than 18,000 deaths.

The risk of developing the disease becomes higher after the age of 50, and the risk factors are numerous: behavioral (sedentary lifestyle, obesity or overweight after menopause); hormonal (early menarche, late menopause, absence of children/breastfeeding, prolonged use of oral contraceptives and hormone replacement); and hereditary (family history of ovarian or breast cancer in males, or breast cancer in women before the age of 50, in addition to genetic alterations in the BRCA1 and BRCA2 genes)[3].

In view of the aforementioned risk factors, it is important to seek, in addition to the screening recommended by the Ministry of Health (a mammogram every two years in women aged 50 to 69 years), ways to reduce the risk of BC with regard to behavioral factors. Maintaining an adequate weight and performing physical activities can contribute to reducing this pathology.

Therefore, in the pathophysiology of breast neoplasia, its relationship with MS can also be seen, which is often its cause and even its consequence. Women treated for BC seem to have an additional risk of MS, resulting from excess adiposity and the effect of treatments[4].

MS is one of the most common public health problems worldwide, and its incidence has been continuously increasing, in a pandemic manner, over the last two decades, in both developed and developing countries. Epidemiological data confirm that MS is independently associated with an increased incidence of several tumors, including BC, and is a poor prognostic factor in patients with early and metastatic BC[5].

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The mechanism underlying the effects of MS remains unknown. Most researchers believe that MS is related to higher concentrations of sex hormones, insulin and insulin-like growth factor, which lead to a distortion of the normal balance between cellular differentiation and apoptosis and the progression and proliferation of BC cells[6-8].

It is also noteworthy that patients with MS, with or without breast cancer, have a higher cardiovascular risk. MS is well established as a prothrombotic state associated with increased levels of inflammatory markers[1,9], which constitutes an increased risk for cardiovascular disease.

Based on this context, the present study sought to correlate prognosis in patients with malignant breast cancer undergoing surgical treatment, whether or not they had previous MS; only deaths due to BC were evaluated, and not from other causes related to metabolic complications.

METHODS

This is a retrospective longitudinal observational cohort study. Epidemiological information was collected from the database of patients in the Mastology sector of Hospital do Servidor Público Estadual (HSPE), from January 2017 to December 2020, and the patients were divided into two groups: group 1 (those who had MS) and group 2 (those who did not have these characteristics).

To define MS, the NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III) criterion was based on: in order to establish the diagnosis of the syndrome, the patient must present at least three of the following five criteria: increased waist circumference (men: ≥102 cm; women: ≥88 cm); triglycerides ≥150 mg/dL; low HDL cholesterol (men <40 mg/dL; women: <50 mg/dL); high blood pressure (≥130 × 85 mmHg) and fasting blood glucose ≥100 mg/dL.

The epidemiological data obtained were many: age, date of BC diagnosis, previous comorbidities related to MS, date of recurrence or appearance of metastases, date of death due to BC, clinical staging and breakdown of the respective receptors present in each pathology.

The exclusion criteria were patients who were lost to follow-up for more than 12 months, due to an initial diagnosis of metastases, or who had missing data in the electronic medical record. All patients underwent surgical treatment at HSPE.

In both groups, the rates of local recurrence, distant metastases and overall survival of patients with malignant breast cancer were evaluated. Data were recorded in an Excel® spreadsheet and statistical analysis was conducted using the Mann-Whitney, Equality of Two Proportions and χ^2 tests.

The work was submitted to Plataforma Brasil and, as it was a retrospective study, the Free and Informed Consent Form (ICF) was waived (Figure 1).

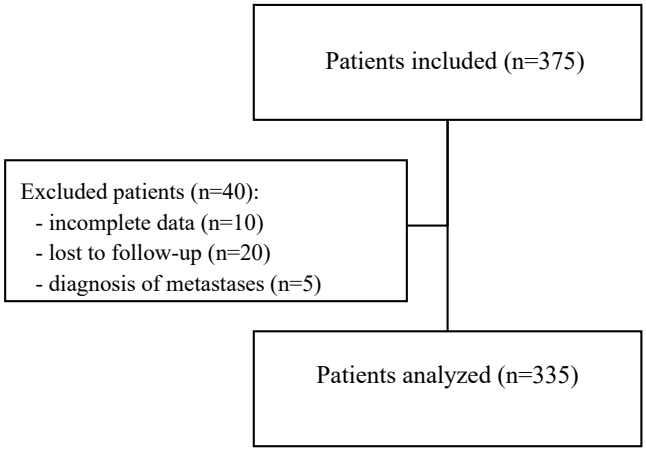

Figure 1. Patients included in the study.

RESULTS

From January 2017 to December 2020, 375 patients underwent surgical treatment for BC at HSPE, of which 25 were excluded due to loss to follow-up; 10, due to incomplete data; and five, due to diagnosis of metastases.

After exclusion, the medical records of 335 patients eligible for the study were analyzed, with mean age of 63.4±1.4 years and an average follow-up time of 48±1.4 years.

MS is present in 109 (32.5%) patients. The criteria used for MS are: waist circumference above 88 cm, HDL below 50 mg/dL, triglycerides above 150 mg/dL, diabetes mellitus or systemic arterial hypertension.

The mean age of patients with MS was 63.5±10.7 years, and of patients without MS, 65.1±10.0 years, with no significant difference. Of the patients evaluated with MS, 81.1% were menopausal, whereas of those without MS, 83.6% were menopausal. As expected, hypertension, diabetes, obesity, low HDL cholesterol, high triglycerides and waist circumference >88 cm are more recurrent among patients with MS, all with significant differences. These characteristics are shown in Table 1.

Regarding the characteristics of prognostic factors, i.e., Ki-67, molecular classification and staging, Table 2 shows that patients with MS have a very similar distribution, whereas those without MS present Ki-67 ≥14% in 62.4% of patients with a significant difference. In patients with MS, the molecular profile is 39.4% Luminal A patients, and in patients without SM, 42.5% Luminal B, with a significant difference in distribution. Regarding clinical staging, patients with MS present initial clinical stage I and IIA in 54.1% of the cases, advanced stage IIB in 20.2% and III in 25.7%, whereas patients without MS present initial clinical stage in 65% of cases, advanced stage IIB in 11.1% and III in 23.9%, results with a significant difference. When we evaluated the presence of obesity as a factor that worsens prognostic factors, we did not find significant differences. Table 2 shows these characteristics.

Table 1. Comparison of groups with and without metabolic syndrome.

	With MS (n=109)		Without MS (n=226)		p-value
Age (mean ± standard deviation) – years	63.5±10.7		65.1±10.0		0.85
BMI (mean ± standard deviation)	28.2±4.1		27.9±4.0		0.85
	n	%	n	%	
Menopausal *status*					
Pre-menopause	20	18.4	37	16.4	<0.001
Post-menopause	89	81.6	189	83.6	
Low HDL cholesterol (<50)	37	33.9	9	3.4	<0.001
Waist circumference >88 cm	49	44.9	42	18.6	<0.001
High triglycerides (>150)	82	75.2	13	5.7	<0.001
DM	81	74.3	21	9.3	<0.001
SAH	101	92.2	78	34.5	<0.001
Obesity	59	54.1	41	18.1	<0.001

MS: metabolic syndrome; BMI: body mass index; DM: diabetes mellitus; SAH: systemic arterial hypertension.
Source: database of the Mammary Pathology sector of Hospital do Servidor Público Estadual.

In the assessment of recurrences, diagnosis of metastases and deaths, there was a significant difference between the groups of patients with and without MS — relapses occurred in 4.6% of patients with MS and in 4.0% of patients without MS; metastases, in 8.3% of patients with MS and in 10.2% of patients without MS; and deaths, at 4.5% and 4.0%, respectively. When we re-evaluated obesity as a factor in worsening of recurrences, metastases and deaths, we found no differences, as can be seen in Table 3.

To evaluate the relationship between MS and adverse prognosis, a factor called "Prognosis" was created, which is the joint analysis of information on metastasis, recurrence and death. If the person presents at least one of these three factors, the prognosis is not considered a Good Prognosis, that is, only those who do not present these three factors will have a Good Prognosis. Therefore, a multivariate Logistic Regression analysis was carried out to determine the probability of a person having a Bad Prognosis based on the results of two independent factors: Ki-67 and Immune. This multivariate analysis was carried out for each MS group, that is, there are two statistical models, as shown in Table 4.

Since the two independent factors are qualitative, one of their classifications is the reference response. Thus, in KI-67, the reference is the classification of <14%, and in molecular profile, it was the best of them, that is, LUMINAL A.

Analyzing both models, it can be seen that only the TNBC classification proved to be statistically significant in the multivariate analysis — the coefficient was positive and, consequently, the odds ratio (OR) was greater than 1.00. In the non-MS model, the OR of triple negative tumors (TNBC) was 9.30, which shows that a patient with a TNBC molecular profile is 9.30 times more likely to have a poor prognosis than a LUMINAL A patient.

The temporal outcomes of overall survival, disease-free survival and invasive disease-free survival were assessed. The average overall survival of the sample was 37.3 years, with CI of 1.1 years; disease-free survival was 35.9 years, with CI of 1.2 years; and invasive disease-free survival was 36.9 years, with CI of 1.3 years. When these outcomes were compared with the presence of MS, a significant difference was observed in all outcomes.

DISCUSSION

Metabolic syndrome (MS), also known as insulin resistance syndrome or syndrome X, is a type of multifactorial metabolic disease[9]. Pathologically, patients with MS are characterized by chronic inflammation and oxidative stress, both involved in the process of carcinogenesis[10]. In the study in question, MS was present in 109 (32.5%) patients, while 226 (67.5%) were not carriers.

A literature review by Li et al., from March 2021[11], evaluates that MS and its components exert a great influence on the breast tumor and its microenvironment. In obese individuals — represented, in the present study, by 54% of patients with MS and 18% of patients without MS —, this tumor microenvironment presents a higher production of fibroblasts, immune and endothelial cells.

In the mammary gland, the interaction between obese adipocytes and BC cells leads to the transformation of mammary adipocytes into cancer-associated adipocytes, the so-called CAAs, which secrete more leptin and reduce adiponectin production[9]. These alterations show a close relationship between obesity and more aggressive BC phenotypes — increased size, high-grade tumors, triple negative tumors or tumors with multiple metastases[12].

Table 2. Distribution of prognostic factors (Ki-67, molecular profile and clinical staging) and the relationship with metabolic syndrome.

	With MS		Without MS		Total		p-value
	n	%	n	%	n	%	
General							
TNBC	23	21.1	26	11.5	49	14.6	0.010
HER-2 +	6	5.5	12	5.3	18	5.4	
Luminal HER	7	6.4	26	11.5	33	9.9	
Luminal B	30	27.5	96	42.5	126	37.6	
Luminal A	43	39.4	66	29,2	109	32.5	
Not obese							
TNBC	12	24.0	20	10.8	32	13.6	0.030
HER-2 +	3	6.0	8	4.3	11	4.7	
LUminal HER	4	8.0	22	11.9	26	11.1	
Luminal B	12	24.0	81	43.8	93	39.6	
Luminal A	19	38.0	54	29.2	73	31.1	
Obese							
TNBC	11	18.6	6	14.6	17	17.0	0.578
HER-2 +	3	5.1	4	9.8	7	7.0	
Luminal HER	3	5.1	4	9.8	7	7.0	
Luminal B	18	30.5	15	36.6	33	33.0	
Luminal A	24	40.7	12	29.3	36	36.0	
General (%)							
<14	54	49.5	85	37.6	139	41.5	0.038
≥14	55	50.5	141	62.4	196	58.5	
Not obese (%)							
<14	24	48.0	70	37.8	94	40.0	0.193
≥14	26	52.0	115	62.2	141	60.0	
Obese (%)							
<14	30	50.8	15	36.6	45	45.0	0.159
≥14	29	49.2	26	63.4	55	55.0	
General							
I	24	22.0	83	36.7	107	31.9	0.041
IIA	35	32.1	64	28.3	99	29.6	
IIB	22	20.2	25	11.1	47	14.0	
IIIA	13	11.9	30	13.3	43	12.8	
IIIB	9	8.3	19	8.4	28	8.4	
IIIB I	2	1.8	3	1.3	5	1.5	
IIIC	4	3.7	2	0.9	6	1.8	
Not obese							
I	14	28.0	69	37.3	83	35.3	0.212
IIA	15	30.0	50	27.0	65	27.7	
IIB	10	20.0	21	11.4	31	13.2	
IIIA	4	8.0	24	13.0	28	11.9	
IIIB	5	10.0	18	9.7	23	9.8	
IIIB I	0	0.0	2	1.1	2	0.9	
IIIC	2	4.0	1	0.5	3	1.3	
Obese							
I	10	16.9	14	34.1	24	24.0	0.453
IIA	20	33.9	14	34.1	34	34.0	
IIB	12	20.3	4	9.8	16	16.0	
IIIA	9	15.3	6	14.6	15	15.0	
IIIB	4	6.8	1	2.4	5	5.0	
IIIB I	2	3.4	1	2.4	3	3.0	
IIIC	2	3.4	1	2.4	3	3.0	

MS: metabolic syndrome; TNBC: triple negative tumors.
Source: database of the Mammary Pathology sector of Hospital do Servidor Público Federal.

Table 3. Comparison of metabolic syndrome with the presence or absence of metastasis.

	With SM		Without SM		Total		p-value
	n	%	n	%	n	%	
Metastases							
General							
No	100	91.7	203	89.8	303	90.4	0.575
Yes	9	8.3	23	10.2	32	9.6	
Not obese							
No	46	92.0	163	88.1	209	88.9	0.436
Yes	4	8.0	22	11.9	26	11.1	
Obese							
No	54	91.5	40	97.6	94	94.0	0.211
Yes	5	8.5	1	2.4	6	6.0	
Relapses							
General							
No	104	95.	217	96.0	321	95.8	0.795
Yes	5	4.6	9	4.0	14	4.2	
Not obese							
No	48	96.0	177	95.7	225	95.7	0.920
Yes	2	4.0	8	4.3	10	4.3	
Obese							
No	56	94.9	40	97.6	96	96.0	0.507
Yes	3	5.1	1	2.4	4	4.0	
Deaths							
General							
No	91	83.4	206	91.1	297	88.6	?
Yes	18	16.6	20	8.9	38	11.4	
Not obese							
No	40	80	167	90.0	207	88.1	?
Yes	10	20	18	10.0	28	11.9	
Obese							
No	51	86.5	39	95.1	90	90	?
Yes	8	13.5	2	4.9	10	10	

MS: metabolic syndrome.
Source: database of the Mammary Pathology Sector of Hospital do Servidor Público Federal.

Another factor that explains the association of MS with carcinogenesis is the increase in plasma estrogen concentrations resulting from the aromatization of peripheral androgens in adipose tissue. The synthesis of estrogens is catalyzed by the aromatase enzyme, which is expressed in increased amounts in the adipose tissue of the mammary gland, abdomen, hips and muscles[12]. Continuous exposure to this hormone, caused by obesity, therefore favors mitotic activity at the aforementioned sites.

In the present study, diabetes mellitus (DM) was the most frequent component of MS, second only to arterial hypertension. The hyperinsulinemia found in diabetic patients also has a clear relationship with increased body mass index (BMI). Chronic exposure to the hyperinsulinemic state stimulates DNA synthesis and, therefore, epithelial cell replication[12].

In general, the inflammatory profile of MS patients is a result of the fact that adipose tissue contains a large source of inflammatory cytokines (TNF-alpha, IL-1y and IL-6). These substances promote and generate greater insulin resistance and, therefore, the overproduction of insulin and IGF-1, with direct effects on tumor genesis[12].

This study evaluated 335 eligible patients, with mean age of 63.4±1.4 years and an average follow-up time of 48.0±1.4 years. Interestingly, in these patients, the majority of whom were postmenopausal, the presence of MS at diagnosis did not worsen

Table 4. Logistic Regression Model for worse prognosis.

	Coef. (B)	p-value	Odds ratio		
			OR	Lim. inferior	Lim. superior
With MS					
Constant	-2.277	<0.001			
KI-67 (≥14%)	-0.286	0.700	0.75	0.18	3.21
Luminal B	1.353	0.161	3.87	0.58	25.67
Luminal HER	1.604	0.170	4.97	0.50	49.24
HER-2 +	1.724	0.109	5.61	0.68	46.02
TNBC	1.871	0.036	6.49	1.13	37.20
Without MS					
Constant	-1.981	<0.001			
KI-67 (≥14%)	-0.818	0.153	0.44	0.14	1.36
Luminal B	1.027	0.135	2.79	0.73	10.72
Luminal HER	0.827	0.272	2.29	0.52	10.02
HER-2 +	1.621	0.079	5.06	0.83	30.91
TNBC	2.231	0,003	9.30	2.15	40.36

OR: odds ratio; MS: metabolic syndrome.
Source: database of the Mammary Pathology Sector of Hospital do Servidor Público Federal.

overall survival, disease-free survival or invasive disease-free survival. Despite going against what the literature shows, there are published studies that still question the real veracity of the relationship we seek to explain.

The first meta-analyses cited in the literature in 2013 and 2014 showed that MS may be a risk factor for BC, particularly in postmenopausal patients[10,13,14]. This conclusion was reached because the small number of studies included — only nine observational studies were available at the time — did not allow for in-depth analysis of factors such as menopausal status, ethnic groups, and histopathological characteristics of the tumor[10].

To try to evaluate this information, Guo et al., in November 2019[10], carried out a new updated meta-analysis seeking to better correlate MS and breast cancer. The analyses showed that MS was associated with an increased risk of BC in postmenopausal women, but this risk was reduced in premenopausal women. The 19 datasets, with 17 studies each, supported the idea that the menopausal status of patients may modify the association between MS and the incidence of BC, even under potentially unclear reasons.

When we look at TNBC, the impact of MS remains controversial. In May 2021, Yuan et al. designed a study to specifically examine mortality after diagnosis of TNBC by metabolic risk components in 544 postmenopausal women participating in the Women's Health Initiative (WHI)[15-17].

The conclusion was a 27% lower overall survival in patients with metabolic components associated with TNBC. However, in this study, patients who had MS coincidentally had lower income, were black and had lower attendance in follow-up exams, which may have indirectly contributed to the result.

In 2020, Buono et al., in a prospective observational study, observed that MS was significantly associated with an increased risk of overall death and death from BC in patients with early BC receiving neoadjuvant therapy at a median follow-up time of 7.1 years[17,18]. Although the results are inconsistent with the present study, it is noteworthy that, in the 2020 study, the lack of information on treatments for hypertension, dyslipidemia and diabetes may have underestimated the number of patients with BC.

Among the possible and main limitations of the present study are the small number of patients included, which led to divergence of results in relation to what is reported in the literature, and the effective treatment of MS, with compensation for associated factors (dyslipidemia, obesity, hyperinsulinemia and hypertension), which corroborates with lower tissue inflammatory and proliferative exposure of cancer cells.

It is important to remember that this study did not evaluate deaths from other causes, only from BC — the increased cardiovascular risk present in MS and its complications were not included in the statistics.

In view of these limitations, it is necessary to increase the number of medical records analyzed, as well as in-depth research, through recent laboratory tests, in order to assess the degree of real metabolic decompensation of patients with MS and breast cancer.

CONCLUSIONS

In this study, the presence of MS at the diagnosis of BC does not worsen overall survival, disease-free survival and invasive disease-free survival.

In multivariate analysis, triple-negative tumors — with or without MS — had a worse prognosis.

AUTHORS'CONTRIBUTION

ALG: Methodology, Writing – original draft. MA: Conceptualization, Data curation, Methodology, Writing – review & editing. OF: Validation, Visualization. JMR: Supervision. AM: Supervision. RGCL: Supervision.

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