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Original article

Predictive model of early chemotherapy-induced cardiotoxicity in patients with breast cancer

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Predictive model of cardiotoxicity precocious induced by chemotherapy -based em risk factors in patients breast cancer

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SUMMARY

Introduction : Chemotherapy is a fundamental strategy in the treatment of breast cancer, as it significantly improves survival. However, it is associated with significant cardiovascular adverse effects, primarily cardiotoxicity, which can manifest early or late. It is one of the main causes of

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morbidity and mortality in surviving patients. Identifying early predictors of cardiotoxicity is vital to optimize clinical management and prevent serious complications.

Objective: To identify risk factors for early chemotherapy-induced cardiotoxicity in patients with breast cancer.

Method : An analytical cohort study was carried out with 511 patients undergoing oncological treatment, seen in the Cardiooncology consultation at the Carlos Manuel de Céspedes Hospital between September 2021 and April 2023. Bivariate analysis and logistic regression were applied to determine significant associations with an α level of 0.05.

Results : The prevalence of cardiotoxicity was 14.4% (mean age 59.9 ± 12.6 years). Factors with independent association were atrial fibrillation (Exp . β = 22.3; p < 0.001), anemia (Exp . β = 14.9; p < 0.001), dyslipidemia (Exp . β = 5.7; p < 0.001), QTc interval prolongation (Exp . β = 5.5; p < 0. 001), smoking (Exp . β = 4.8; p < 0.001), decreased glomerular filtration rate (Exp . β = 4.4; p = 0.002) and hypertensive heart disease (Exp . β = 4.1; p = 0.001).

Conclusions: These factors allow for the construction and validation of robust predictive models for early intervention and preventive management of cardiotoxicity in patients with breast cancer undergoing chemotherapy.

Keywords : Breast cancer; Cardiotoxicity ; Chemotherapy; Risk factors; Predictive model; Cardiooncology .

ABSTRACT

Introduction: chemotherapy is a fundamental strategy in the treatment of breast cancer, as it significantly improves survival. It is associated with significant cardiovascular adverse effects, mainly cardiotoxicity , which can manifest early or late. It is one of the main causes of morbidity and mortality in cancer survivors. Identifying early predictive factors of cardiotoxicity is vital to optimize clinical management and prevent severe complications.

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Objective: to develop a predictive model of early chemotherapy-induced cardiotoxicity based on risk factors in breast cancer patients.

Method: an analytical cohort study was conducted with 511 oncology patients, treated at the Cardio-oncology consultation of Carlos Manuel de Céspedes Hospital between September 2021 and April 2023. Bivariate analyzes and logistic regression were applied to determine significant associations with an α level of 0.05.

Results: the prevalence of cardiotoxicity was 14.4% (mean age 59.9 ± 12.6 years). Factors with independent association were atrial fibrillation (Exp. β = 22.3; p < 0.001), anemia (Exp. β = 14.9; p < 0.001), dyslipidemia (Exp. β = 5.7; p < 0.001), prolonged QTc interval (Exp. β = 5.5; p < 0.001), smoking (Exp. β = 4.8; p < 0.001). 0.001), reduced glomerular filtration rate (Exp. β = 4.4; p = 0.002), and hypertensive heart disease (Exp. β = 4.1; p = 0.001).

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Conclusões : esses factors allows us to build and validate robust predictive models for intervention early and preventive management of cardiotoxicity in patients with breast cancer undergoing chemotherapy.

Keywords : Breast cancer ; Cardiotoxicity ; Chemotherapy; Cliff factors ; predictive model ; Cardio-oncology .

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Introduction

Cancer and cardiovascular diseases (CVD) are the leading causes of death globally, accounting for over 46.0% of annual deaths. [1,2] Breast cancer is one of the most common malignancies and has the highest survival rate thanks to advances in diagnosis and treatment. [3,4] Chemotherapy (CMT) improves survival but is known for its cardiotoxic potential, which increases the risk of

cardiovascular events threefold . Such cardiotoxicity (CTX) is a clinical challenge that affects quality of life, with variable incidence rates due to differences in definitions and detection methods. [5]

CTX is defined as clinical or subclinical myocardial damage induced by oncological agents, which may manifest as heart failure (CHF), arrhythmias, ischemia, or structural alterations. It is classified as acute, early chronic, and late. Early chronic occurs within the first year after treatment, and early detection is crucial to prevent irreversible progression. [6]

Classic risk factors include advanced age, comorbidity (hypertension, diabetes, dyslipidemia), history of cardiovascular disease, cumulative chemotherapy dose, and altered electrocardiographic parameters. Recent studies have proposed predictive models based on multivariate analysis to identify high-risk patients, facilitating the use of cardioprotective therapies and avoiding unnecessary discontinuation of cancer treatment. [7]

This study aims to identify risk factors associated with early CTX in Cuban patients with breast cancer, providing clinical evidence for the construction of a predictive model useful in daily practice.

Methods

A prospective, single-cohort, analytical observational study was conducted involving 511 patients with breast cancer undergoing chemotherapy (CMT). Patients were followed up in the Cardiooncology Department of the Specialty Polyclinic of the Carlos Manuel de Céspedes Provincial General Hospital in Bayamo, Granma, from September 15, 2021, to April 16, 2023.

Definition of cardiotoxicity

Cardiotoxicity was defined according to clinical and echocardiographic criteria. Clinically, it was defined as chemotherapy-induced acute cardiomyopathy with cardiovascular manifestations (systolic or diastolic left ventricular dysfunction, heart failure, new-onset hypertension,

coronary vasospasm, thromboembolic disease, pericarditis, or arrhythmias), in accordance with the 2017 European Society of Cardio-Oncohematology consensus.

From an echocardiographic perspective, cardiotoxicity was defined as a decrease of at least 5% in left ventricular ejection fraction (LVEF) with values less than 55% in symptomatic patients, or a reduction of at least 10% in LVEF with values less than 55% in asymptomatic patients compared with baseline values, according to the modified Simpson method.

Composition of the sample

The sample size for the study was determined using EPIDAT 4.2 software. The following parameters were used to estimate the sample size: 95% confidence interval (CI), 80% power, 28% risk in exposed patients, 16% risk in unexposed patients, and 2.0 unexposed/exposed ratio. The prevalence of the disease was estimated based on information provided in the literature and was 26.0%. These parameters led to a minimum required sample size of 447 patients. However, in order to conduct a broader risk factor study, a sample of 511 patients was selected. Patients were selected by simple random method.

Inclusion and exclusion criteria

Women over 18 years of age with a histological diagnosis of breast cancer who received treatment with anthracyclines (doxorubicin) combined with taxanes (paclitaxel or docetaxel) and who signed informed consent approved by the hospital Ethics Committee were included.

Patients with a history of congenital heart disease, valvular heart disease, ischemic heart disease, or grade III or IV hypertensive heart disease, systemic diseases such as thyroid or autoimmune diseases, history of prior chemotherapy, incomplete medical records, and patients in terminal stages were excluded.

Monitoring and data collection

Patients were evaluated at baseline and followed up for 12 months in a multidisciplinary consultation. Clinical information was collected through interviews, physical examinations,

electrocardiograms (ECGs), and biochemical tests (blood glucose, creatinine, cholesterol, triglycerides, uric acid).

Transthoracic echocardiography was performed at baseline and at 3, 6 and 12 months post-treatment to assess systolic and diastolic function using the modified Simpson method according to the European guidelines. Association of Cardiovascular Imaging and American Society of Echocardiography .

Operationalization of variables

Dependent variable (cardiotoxicity)

Two categories were considered: developing cardiotoxicity, no/yes; considering exposed (1), any patient who met the clinical and echocardiographic criteria explained above in the definition of CTX.

Independent variables

These were understood as those factors whose influence on the appearance of early CTX were being evaluated and are described below. All variables were dichotomized, one category being called exposed (1) (which, according to prior knowledge, implied a greater probability of evolving to CTX) and the other, which will be considered as unexposed (2).

Age (<65 years /≥65 years (exposed), high blood pressure (HTA) (no/yes exposed), diabetes mellitus DM (no/yes exposed), obesity (BMI >29.9 kg/m2 and abdominal circumference (women) ≥88 cm, (no/yes exposed), dyslipidemia (no/yes exposed), smoking (smokers/non-smokers exposed), atrial fibrillation (no/yes exposed), maximum QTc interval≥470 msec (no/yes exposed), hypertensive heart disease (no/yes exposed), LV mass index ≥120 gr/m2 (no/yes exposed), left atrial diameter ≥36 mm (no/yes exposed) and analytical variables:

hemoglobin ≤ 100 g/L, glomerular filtration rate < 70 ml/min/1.73 m^2 , blood glucose ≥ 5.4 mmol/L, creatinine ≥ 90 µmol/L, uric acid > 370 µmol/L.

Statistical analysis

The statistical analysis began with a comprehensive characterization of the sample, including a description of all variables. For the qualitative variables, the absolute and relative frequencies (percentages) of the different categories were determined. For the quantitative variables, the means, medians, and standard deviations were obtained, as well as the maximum and minimum values for each distribution.

A bivariate strategy was used to determine risk factors for developing CTX. This approach was based on estimating the percentage of patients with CTX, the incidence rate of CTX in both the exposed and unexposed groups, and then the incidence ratio or relative risk (RR) of acquiring CTX. Point estimates and 95% confidence interval estimates of the RRs were obtained.

The multivariate strategy was based primarily on the adjustment of a binary logistic regression model, initially using the "introduction" method (evaluating possible interaction between variables) with all the variables that constituted predictive factors of CTX in the bivariate analysis and subsequently using the "forward stepwise " method .

In this way, the independent influence of each variable on the probability of developing CTX was evaluated, while controlling for all other variables. The logistic regression function was fitted using the maximum likelihood method.

Regression coefficients (β) and the standard error of each coefficient (SE) were estimated. The significance of each coefficient (null hypothesis β=0) was tested using the Wald statistic and the corresponding chi-square test. RRs were also estimated as an exponent (β) with a 95.0% confidence interval (CI).

Hosmer - Lemeshow chi-square goodness-of-fit statistic was applied . If the probability associated with the test statistic was greater than 0.05, the models were considered to fit the data. Statistical processing was performed using SPSS version 25.0.

Ethical considerations

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The study was approved by the institution's Ethics Committee. The study applied the principles stipulated in the Nuremberg Code. [8] of 1947 and the ethical principles for biomedical studies postulated in the Helsinki Declaration of 1989. [9]

Regarding the bioethical vision, the principles of autonomy, justice, equity, beneficence and non-maleficence are considered and respected in this work.

Confidentiality and the right to voluntary withdrawal were guaranteed without affecting medical care.

Results

Clinical characteristics and baseline values

The sample consisted of 511 breast cancer patients receiving chemotherapy, who presented an overall incidence of cardiotoxicity of 14.4% (74 cases). The mean age was 59.9 years (SD ± 12.6), and the median was 60 years, with no statistically significant differences between groups. The predominant tumor site was the left breast (54.0%).

In qualitative variables, 25.4% were smokers, 27.2% had dyslipidemia , 36.0% were obese, and 18.4% had diabetes mellitus. Arterial hypertension was observed in 55.2%. Atrial fibrillation occurred in 6.3 %, and left ventricular hypertrophy, along with hypertensive heart disease, occurred in 33.1%, respectively. (Table 1)

Table 1. Overall characterization of the sample. n = 511.

Variables	Categories	Results	
		No.	%
Age (years)	Average + SD	59.9 ±12.6	
Median (years)	Median	60.0	
Age	< 65 years	221	48.9

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	≥ 65 years	230	51.1
Location of the affected breast	Left breast	276	54.0 z 2.50; p = 0.012
	Right breast	176	34.4
	Bilateral tumor	59	11.5
High blood pressure	Yeah	282	55.2
Diabetes Mellitus	Yeah	94	18.4
Smoking	Yeah	130	25.4
Dyslipidemia	Yeah	139	27.2
Obesity	Yeah	184	36.0
Left ventricular hypertrophy	Yeah	229	44.8
Hypertensive heart disease	Yeah	164	33.1
Atrial fibrillation	Yeah	32	6.3
Cardiotoxicity	CTx	74 / 511	14.4

Standard deviation, CTX cardiotoxicity .

Risk factors associated with early cardiotoxicity

Bivariate analysis performed in a subsample of 327 patients (67 with cardiotoxicity) found a significant association with traditional cardiovascular factors: dyslipidemia (RR = 3.9; $p < 0.001$), arterial hypertension (RR = 3.7; $p < 0.001$), diabetes mellitus (RR = 2.7; $p < 0.001$), smoking (RR = 2.7; $p < 0.001$) and age ≥ 65 years (RR = 2.52; p = 0.011). (Table 2)

Table 2. Results of the bivariate analysis of classic cardiovascular risk factors.

n = 327.

Variables	Yeah CT $_X$	n = 67 20.4%	No CTx	n = 260 79.6%	RR	95.0% CI	p
	No.	%	No.	%			
Dyslipidemia	43	42.2	59	57.8	3.95	2.54 - 6.14	0.000
High blood pressure	56	29.8	132	70.2	3.76	2.04 - 6.91	0.000
Diabetes mellitus	28	41.8	39	58.2	2.78	1.85 - 4.17	0.000

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Smoking	36	36.7	62	63.3	2.71	1.78 - 4.12	0.000
Age ≥ 65 years	35	30.4	80	48.3	2.52	1.32 - 3.07	0.011
Obesity	37	28.2	94	71.8	1.84	1.20 - 2.83	0.004

Legend: CTX cardiotoxicity , RR relative risk, 95.0% CI confidence interval 95.0%. Significance p < 0.005.

Regarding non-classical factors, atrial fibrillation (RR = 4.3; p < 0.001), prolonged QTc interval ≥ 470 ms (RR = 3.3; p < 0.001), diastolic dysfunction (RR = 3.1; p < 0.001) and hypertensive heart disease (RR = 2.9; p < 0.001) showed a strong correlation with cardiotoxicity. (Table 3)

Table 3. Results of the bivariate analysis of non-classical cardiovascular factors. n = 327.

Variables	Yeah CT_X	n = 67 20.4%	No CTx	n = 260 79.6%	RR	95.0% CI	p
	No.	%	No.	%			
Atrial fibrillation	16	72.7	6	27.3	4.34	3.04 - 6.22	0.000
Maximum QTc interval ≥ 470 msec	45	36.0	80	64.0	3.30	2.09 - 5.22	0.000
Hypertensive heart disease	43	35.0	80	65.0	2.97	1.90 - 4.64	0.000
Body mass index VI ≥ 120 gr/m^2	48	30.2	111	69.8	2.66	1.64 - 4.33	0.000
Left atrial diameter ≥ 36 mm	46	29.7	109	70.3	2.43	1.52 - 3.88	0.000

Legend: CTX cardiotoxicity , RR relative risk, 95.0% CI confidence interval 95.0%. Significance p < 0.005.

The influential laboratory variables were low hemoglobin (RR = 4.5; p < 0.001), reduced glomerular filtration rate (RR = 2.2; p = 0.001), and high blood glucose (RR = 2.0; p = 0.001). (Table 4)

Table 4. Results of the bivariate analysis of the analytical variables. n = 327.

Variables	Yeah CTX n = 67 20.4%		No CTx n = 260 79.6%		RR	95.0% CI	p
	No.	%	No.	%			
Hemoglobin ≤ 100 g/L	19	73.1	7	26.9	4.58	3.23 - 6.49	0.000
Glomerular filtration < 70 mL/min/1.73 m ^{2}	50	26.7	137	73.3	2.20	1.32 - 3.64	0.001
Blood glucose ≥ 5.4 mmol/L	37	30.1	86	69.9	2.04	1.33 - 3.13	0.001
Creatinine ≥ 90 (µmol/l)	27	28.1	69	71.9	1.62	1.06 - 2.48	0.021
Uric acid > 370 µmol/l	27	18.0	123	82.0	0.79	0.51 - 1.23	0.187

Legend: CTX cardiotoxicity , RR relative risk, 95.0% CI confidence interval 95.0%. Significance p < 0.005.

Multivariate predictive model

Logistic regression analysis identified 10 independent influencing variables including: atrial fibrillation Exp . (β) = 22.2; p < 0.001), low hemoglobin (Exp . (β) = 14.9; p < 0.001), dyslipidemia (Exp . (β) = 5.74; p < 0.001), prolonged QTc interval (Exp . (β) = 5.55; p < 0.001), smoking (Exp . (β) = 4.83; p < 0.001), reduced glomerular filtration rate (Exp . (β) = 4.49; p = 0.001) and hypertensive heart disease (Exp . (β) = 4.11; p = 0.001). (Table 5)

Table 5. Multivariate logistic regression model. Results of the model fit with all variables that constituted risk factors in the bivariate analysis.

Variables	β	Mistake standard	Next.	Exp (β)	95.0% CI for Exp .(β)	
					Lower	Superior

Atrial fibrillation	3.10	0.80	0.000	22,23	4.60	107.38
Hemoglobin ≤ 100 g/L	2.70	0.73	0.000	14.95	3.57	62.50
Dyslipidemia	1.74	0.42	0.000	5.74	2.49	13.23
Maximum QTc interval ≥ 470 msec	1.71	0.41	0.000	5.55	2.44	12.62
Smoking	1.57	0.42	0.000	4.83	2.12	11.02
Glomerular filtration < 70 mL /min/1.73 m ^{2}	1.50	0.47	0.002	4.49	1.77	11.39
Hypertensive heart disease	1.41	0.41	0.001	4.11	1.81	9.31
Ventricular mass index Left ≥ 120 gr/m ^{2}	0.91	0.42	0.033	2.49	1.07	5.77
Blood glucose ≥ 5.4 mmol /L	0.87	0.41	0.034	2.40	1.07	5.38
Left atrial diameter ≥ 36 mm	0.84	0.42	0.048	2.31	1.09	5.32
Constant	-25.54	3.57	0.000	0.000		

Hosmer and Lemeshow test : $X^2 = 6.06$ degree of freedom: 8 p = 0.640.

Legend: 95.0% CI confidence interval 95.0%.

The model showed good statistical fit (Hosmer-Lemeshow test , p = 0.640), confirming its validity for predicting early cardiotoxicity in this cohort.

Discussion

Chemotherapy-induced cardiotoxicity in patients with breast cancer is a growing concern because the substantial improvement in cancer survival exposes patients to short- and long-term cardiovascular adverse events. The prevalence observed in this study is consistent with international estimates, which report incidences between 10.0 and 20.0% in similar populations receiving anthracyclines. [(10)]

The independent factors identified as predictors of early cardiotoxicity confirm the complex multifactorial nature of this complication.

Age is one of the most important non-modifiable risk factors for the development of chronic diseases, including the risk of CTX due to CT. In conditions such as heart failure, ischemic heart disease, and high blood pressure , the prevalence doubles every decade starting at age 40–45. Before age 50, the incidence of CTX in women is lower, attributed to the protective role of estrogen; however, after menopause, the incidence equals and even exceeds in women over 50. Age over 65 years, along with traditional cardiovascular factors and exposure to specific cancer treatments, has been associated with an increased rate of cardiac complications, reaching 8.9% at 5 years. Advanced neurohormonal dysfunction and atherosclerosis influence a poorer response to cancer therapy. This risk also affects older adults, with greater vulnerability in pediatric patients exposed to anthracyclines. [11]

Atrial fibrillation (AF) is the most common sustained arrhythmia in cancer patients, with a higher prevalence than the general population. It is correlated with systemic inflammation and myocardial dysfunction. In the context of CT/CT, AF is emerging as an independent predictor of early CT/CT and associated complications, validated by multiple international cohorts and registries.

AF, with a strong association, reflects the close relationship between arrhythmias and myocardial damage induced by chemotherapy agents. This finding is consistent with studies showing that arrhythmia may be a sensitive marker of early ventricular dysfunction and a risk factor for major clinical adverse events. ([4]

Anemia and dyslipidemia are metabolic factors that can exacerbate cardiotoxicity through mechanisms of oxidative stress, chronic inflammation, and endothelial dysfunction, pathogenic processes well documented in the cardio-oncology literature.

Anemia is associated with a higher risk of CTX and is an independent prognostic factor for overall survival, with an estimated risk of death of 65.0%. Evidence indicates that optimal hemoglobin levels between 110 and 120 g / L are associated with better outcomes, while decreases greater than 20 g/L increase the risk of mortality. The pathophysiology involves

increased cardiac output and refractory heart failure in anemic patients, highlighting the need to optimize this variable in cancer patients.

Dyslipidemia , although identified as an independent factor in the present study, shows contradictory results in the literature. Epidemiological and experimental studies attribute dyslipidemia to a chronic inflammatory state that favors cardiovascular progression, especially in cancer patients undergoing chemotherapy.

Prolongation of the QTc interval and smoking add a direct electrical and toxic component to the myocardium, which increases the likelihood of ventricular arrhythmias and systolic dysfunction. (3,5.7, 12)

Smoking negatively impacts survival and increases mortality in breast cancer, associated with accelerated vascular damage, a prothrombotic state , and metabolic dysregulation. It was identified as an independent risk factor in the model presented in this study, a finding in meta-analyses and epidemiological studies. Prolonged QTc interval is another early marker associated with the risk of potentially lethal ventricular arrhythmias due to direct damage to ion channels and oxidative stress. The reported incidence of prolonged QTc varies between 3.0% and 22.0%, with clinical relevance for follow-up. (10-13)

Left ventricular hypertrophy represents the initial stages of ventricular damage induced by cancer therapy, and although the results in the literature vary, its presence correlates with an increased risk of CTX.

Elevated blood glucose , a reflection of metabolic syndrome and insulin resistance, is also associated with negative progression and unfavorable response to cancer treatment and currently represents an emerging area for research in Cardio-oncology.

Decreased renal function, reflected in reduced glomerular filtration rate, adds a dimension of comorbidity that compromises the pharmacokinetics of antineoplastic agents and promotes hemodynamic stress, increasing the potential for cardiac damage. Hypertensive heart disease,

for its part, acts as a classic cardiovascular risk factor that increases myocardial vulnerability to toxic therapies. [13]

Finally, variables such as left atrial enlargement and inflammatory factors, although not included in all models, contribute to a broader cardiovascular risk profile in cancer patients under QMTP.

These results underscore the importance of early, multidimensional cardiovascular risk assessment in women candidates for chemotherapy for breast cancer. The implementation of standardized monitoring protocols, including baseline and serial measurements of left ventricular ejection fraction and electrocardiographic parameters, is crucial for early detection and risk stratification.

Serial echocardiographic evaluation, recommended by international guidelines from the European Society of Cardiology and the American Society of Echocardiography , should be performed before the start of treatment, during its course (with special emphasis on reaching critical cumulative doses) and in post-treatment follow-up at 3, 6, 9 and 12 months, as reflected in the reviewed literature and the protocol used in this cohort. [14-16]

The use of advanced techniques such as global longitudinal strain (GLSS) may improve the sensitivity to detect subclinical dysfunction before frank decline in LVEF. [17,18]

Early cardiotoxicity, although often reversible with timely intervention, represents a challenge in preventing the unnecessary interruption of effective cancer therapies. Identifying patients at higher risk through a combination of clinical and laboratory factors allows not only for fine-tuning cardioprotective therapy but also for personalizing follow-up and improving overall outcomes in terms of survival and quality of life. [6, 11, 14]

One limitation of the study is its single-centeredness , which may restrict the generalization of results to other populations with different characteristics. Furthermore, body surface area, cumulative chemotherapy dose, GLS, and specific serum biomarkers, although relevant, were not included in the model and may be the subject of future research.

However, the arguments explained above support the robustness of the predictive model based on several clinical and biochemical factors linked to chemotherapy-induced cardiotoxicity, and underscore the need for a multidisciplinary approach with rigorous monitoring to prevent serious cardiac complications in this vulnerable population.

Overall, this study provides valuable evidence for the identification and validation of predictive factors for early cardiotoxicity , reinforcing the need to integrate clinical, analytical and echocardiographic strategies into a multidisciplinary approach to cardio-oncology .

Conclusions

Chemotherapy-induced cardiotoxicity in breast cancer is a complex complication influenced by multiple clinical factors. In this study, the following independent factors were identified as significantly influencing the development of cardiotoxicity: atrial fibrillation, low hemoglobin levels (<100 g/L), dyslipidemia, QTc interval prolongation , smoking, reduced glomerular filtration rate, hypertensive heart disease, left ventricular mass index, elevated blood glucose, and left atrial dilation.

These results corroborate and expand the scientific evidence on the multifactorial role of traditional and specific factors in cardiovascular risk during and after chemotherapy, as well as the need for multidimensional and individualized assessments to prevent complications.

Recommendations

It is recommended to use the factors identified in the logistic regression model that develops and validates predictive indices of cardiotoxicity in patients with breast cancer undergoing chemotherapy, to facilitate individualized and accurate risk stratification.

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Conflicts of interest

The authors declare that there are no financial, personal or professional conflicts of interest that could have influenced the performance or interpretation of the results of this study.

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