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Postmenopausal breast cancer survivors: Influence of follow-up time on metabolic health

Luciana de Araujo Brito Buttros[1], Daniel de Araujo Brito Buttros[1], Paulo Gustavo Tenório do Amaral[1], Carla Priscila Kamiya Carvalho Pessoa[1], Eduardo Carvalho-Pessoa[1], Heloisa Maria de Luca Vespoli[1], Eliana Aguiar Petri Nahas[1]*

ABSTRACT

ntroduction: Advances in the early detection and treatments have contributed to increased longevity in breast cancer (BC) patients. The aim of this study was to evaluate the metabolic health at different times after BC diagnosis in postmenopausal women. **Methods:** A cross-sectional study was conducted with 439 women, aged 45–75 years, with a diagnosis of BC, and without metastatic disease or cardiovascular disease. Women were distributed into three time periods: T0, time of diagnosis (n=241); T4, 4-year follow-up (n=94); and T9, 9-year follow-up (n=104). The groups were paired by age and time since menopause. The following criteria were considered to assess metabolic health: body mass index; blood pressure; serum values of triglycerides (TGs), high-density lipoprotein-cholesterol (HDL-C), and glucose; and occurrence of the metabolic syndrome (MetS). **Results:** The mean age per group was 58.4±11.3 years in T0, 59.7±9.2 years in T4, and 60.7±8.6 years in T9 (p=0.134). On average, women were overweight at T0 and T4, and obese at T9, with differences between time periods (p=0.029). Women at T9 had higher mean values of TGs and blood pressure when compared to women at T0 and T4 (p<0.05). There was no difference in the occurrence of MetS between time periods (p=0.409). On risk analysis, women with at least 9 years of follow-up (T9) were at a higher risk of developing hypertriglyceridemia (odds ratio [OR]=1.67, 95% confidence interval [CI] 1.04–2.66, p=0.032) and arterial hypertension (OR=2.04, 95%CI 1.27–3.26, p=0.003). **Conclusion:** Postmenopausal BC survivors with a longer follow-up period had worse metabolic health due to a higher risk of hypertriglyceridemia, arterial hypertension, and obesity when compared to women with a shorter oncological follow-up period.

KEYWORDS: breast neoplasms; health; obesity; menopause.

INTRODUCTION

Advances in the early detection and treatment of breast cancer (BC) have contributed to increased longevity in BC patients. Therefore, strategies are required to improve quality of life, control post-treatment complications, and consequently prevent all-cause and cancer-specific mortality[1,2]. It has been well established that weight gain occurs in BC patients[3,4]. This could be explained, in part, by the lifestyle adopted after cancer diagnosis. Factors responsible for weight gain include a reduction in physical activity and inadequate diet, associated with the physical and psychological stress of treatment[5,6]. The resulting obesity is associated with a chronic inflammatory state that has a negative impact on metabolic health, caused by homeostatic imbalance due to excessive fat tissue[7-9].

Inflammatory cytokines produced in fat tissue are known to participate in the pathophysiology of BC and cardiovascular disease (CVD)[7,10-12]. A recent observational study evaluated half a million postmenopausal women with and without BC. Women with BC were at a substantially higher risk of CVD after 5 years of cancer diagnosis[13]. Therefore, women treated for BC require long-term follow-up to assess the metabolic health and risk of CVD[13-15]. The relationship between metabolic disease and worsening of BC prognosis was well described in a publication, where women with metabolic syndrome (MetS) were at a higher risk for BC and other diseases[16]. These data demonstrated that metabolic disease is intimately related to BC[9,17-19]. The National Comprehensive Cancer Network (NCCN) recently manifested itself, emphasizing the need for multidisciplinary effort to identify risk factors that can compromise metabolic health in BC patients and achieve a better prognosis for this population[20]. Therefore, the present study aimed to evaluate the metabolic health at different time periods after BC diagnosis in postmenopausal women.

[1]Universidade Estadual Paulista "Júlio de Mesquita Filho", Faculdade de Medicina de Botucatu – Botucatu (SP), Brazil.
***Corresponding author:** eliana.nahas@unesp.br
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METHODS

Study design and sample selection

This study is a single-center, cross-sectional study. The population group consisted of 439 patients attending the Mastology Center of the Botucatu Medical School – UNESP. Calculation of sample size was based on a study by Buttros et al.[17], who found MetS in 50% of postmenopausal women with BC. Considering this rate, with a significance level of 5%, and type II error of 10% (power of the test: 90%), a minimum number of 93 BC patients per group had to be evaluated and a total of at least 279 patients were required. Women with the following characteristics were included: age 45–75 years, amenorrhea ≥12 months prior to presentation, and histological diagnosis of BC without metastatic disease. Exclusion criteria were current or past manifestation of CVD, insulin-dependent diabetes mellitus, morbid obesity, alcohol dependence, and drug abuse. The women were distributed into three time periods, considering the time elapsed since BC diagnosis: T0, at the time of cancer diagnosis; T4, at least 4 years after diagnosis; and T9, at least 9 years after diagnosis. Groups were matched based on age and time since menopause. The following criteria were considered to assess metabolic health: body mass index (BMI), blood pressure, serum values of triglycerides (TGs), high-density lipoprotein-cholesterol (HDL-C), glucose, and occurrence of MetS.

Data collection

In the current study, the following variables were evaluated: age (years), age and time since menopause (years), smoking history (yes/no), personal history of systemic arterial hypertension (SAH) (yes/no), diabetes (yes/no), dyslipidemia (yes/no), CVD (yes/no), and arterial blood pressure (mmHg). Women were considered to have MetS if they met three or more of the following diagnostic criteria, as proposed by the US National Cholesterol Education Program/Adult Treatment Panel III (NCEP-ATP III)[21]: waist circumference (WC) ≥88 cm; TGs≥150 mg/dL; HDL-C<50 mg/dL; blood pressure≥130/85 mmHg; and glucose≥100 mg/dL or under treatment[21]. The following data were obtained for anthropometric evaluation: weight, height, BMI (weight/height^2), and WC. Women were classified according to BMI, as recommended by the World Health Organization: <24.9 kg/m^2––normal; 25–29.9 kg/m^2––overweight; 30–34.9 kg/m^2––obesity grade I; 35–39.9 kg/m^2––obesity grade II; and ≥40 kg/m^2––obesity grade III. WC was measured midway between the lowest ribs and the iliac crest. A WC above 88 cm was considered indicative of increased cardiometabolic risk[21].

Biochemical analysis was performed after patients fasted for 12 h. Lipid and glucose profile were evaluated by total cholesterol, HDL-C, low-density lipoprotein-cholesterol (LDL-C), TGs, and glucose values. Measurements of TGs, total cholesterol, HDL-C, and glucose were processed by the RAXT automatic biochemical analyzer (Technicon, USA), quantified by the colorimetric method, using specific commercial reagents (Sera-Pak, Bayer, USA). The method was linear until 800 mg/dL for TG and 900 mg/dL for TC. LDL-C was calculated by the Friedewald formula that has limitations when TG value is >400 mg/dL. LDL-C was obtained by subtracting TC value from the sum of HDL-C and TGs, divided by 5. Values considered optimal were: TC<200 mg/dL, HDL-C>50 mg/dL, LDL-C<100 mg/dL, TG<150 mg/dL, and glucose<100 mg/dL[21].

Anatomopathological and immunohistochemical analyses

The following data were obtained from medical record review: histopathological diagnosis of BC, histological grade, hormone receptor status (estrogen receptor [ER]; progesterone receptor [PR]), human epidermal growth factor receptor-2 (HER2) status, epithelial proliferative activity (Ki67), tumor stage, and treatments performed (surgery, radiation therapy, chemotherapy, and hormone therapy). Tumor diameter was obtained from histopathological reports and histologically graded as grade 1 (well differentiated), grade 2 (moderately differentiated), and grade 3 (undifferentiated) according to the method proposed by Elston and Ellis[22], which uses architectural aspects, nuclear differentiation levels, and mitotic index as criteria. Axillary lymph node status was classified as positive lymph node involvement if there was at least one positive lymph node according to clinical and/or histopathological examination.

Statistical analysis

From all data, tables of clinical variables and parameters were created for each group according to the time elapsed since BC diagnosis: T0, at the time of cancer diagnosis; T4, at least 4 years after diagnosis; and T9, at least 9 years after diagnosis. Variables were analyzed using the Shapiro-Wilk test for normal distribution and the Levene test for homogeneity. For data analysis, mean and standard deviation were calculated for quantitative variables and frequency and percentage for qualitative variables. Groups were compared by the chi-square test of association. When statistical difference assumed more than two categories, partitioning with p-value adjustment (p≤0.010) was performed. On analyses between the outcome variable and quantitative predictor variables, normal distributions were first tested. For data that were not normally distributed, the Mann-Whitney and Kruskal-Wallis nonparametric tests were applied. Multiple comparison analysis was conducted by Dunn's test. Analysis by binary logistic regression was performed considering the presence of MetS and obesity as response (dependent) variables and the time elapsed since BC diagnosis as the explanatory (independent) variable. The odds ratio (OR) and 95% confidence interval (CI) were obtained, adjusting for age and time since menopause (confounders). A level of significance of 5% or the corresponding p-value was adopted in all tests. Data were analyzed using the SPSS program, version 23.0 for Windows.

RESULTS

A total of 439 postmenopausal women with BC were included: 241 at the time of diagnosis (T0), 94 with 4-year follow-up (T4), and 104 with a 9-year follow-up (T9). The mean age per group was 58.4±11.3 years in T0, 59.7±9.2 years in T4, and 60.7±8.6 years in T9 (p=0.134). The clinical characteristics and biochemical parameters of each group are represented in Table 1. On average, patients were overweight in T0 and T4, and obese in T9, with a significant difference between time periods (p=0.029). The T9 group had the highest mean level of TGs and blood pressure, both with statistical significance, when compared to women at T0 and T4 (p<0.05) (Table 1).

There was no difference in the occurrence of MetS between time periods (p=0.409). Regarding the number of altered criteria for MetS, among all participants, 12.1% had no criteria, 21.2% had only one criterion, 21.2% had two criteria, and 45.6% had three or more altered criteria. Women in T9 had a higher rate of hypertriglyceridemia (47.1%, p=0.014) and arterial hypertension (61.5%, p=0.002) and were overweight (76.9%, p=0.029) (Table 2). On risk analysis, women with at least 9 years of follow-up (T9) had a

Table 1. Comparison of clinical and laboratory characteristics of postmenopausal women with breast cancer, according to groups and follow-up time.

Variables	T0	T4	T9	p-value*	*post hoc(Dunn)*
Age, years	58.4±11.3	59.7±9.2	60.7±8.6	0.134	T0=T4=T9
Menopause, years	47.4±4.9	47.6±3.6	47.5±4.4	0.978	T0=T4=T9
BMI, Kg/m²	28.8±5.7	27.6±5.6	30.0±6.2	0.029	T0=T4≠T9
SBP, mmHg	130.4±15.8	133.8±12.0	139.2±22.0	0.001	T0=T4, T0≠T9
DBP, mmHg	81.8±10.4	87.7±10.3	81.4±11.9	<0.001	T0≠T4, T4≠T9
HDL, mg/dL	56.3±14.5	52.9±11.9	54.4±13.1	0.176	T0=T4=T9
LDL, mg/dL	120.6±34.4	114.6±30.7	119.4±30.8	0.398	T0=T4=T9
TG, mg/dL	135.8±65.5	135.6±75.6	156.5±77.1	0.025	T0=T4 ≠ T9
Glucose, mg/dL	101.0±27.7	108.0±36.0	102.4±30.0	0.355	T0=T4=T9

T0: at diagnosis; T4: after 4 months; T9: after 9 months; values are expressed as mean±standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; *significant difference if p<0.05 (Mann-Whitney or Kruskall-Wallis).

Table 2. Comparison of the occurrence of metabolic syndrome, its components and body mass index of postmenopausal women with breast cancer, according to group and follow-up time.

Features	Total	T0m	T4m	T9m	p-value
Metabolic Syndrome Yes	200 (45.6)	103 (42.7)	47 (50.0)	50 (48.1)	0.409
No BP≥130X85mmHg Yes	239 (54.4) 227 (51.7)	138 (57.3) 106 (44.0)	47 (50.0) 57 (60.6)	54 (51.9) 64 (61.5)	0.002
No TG≥150mg/dL Yes	212 (48.3) 159 (36.2)	135 (56.0) 84 (34.9)	37 (39.4) 26 (27.7)	40 (38.5) 49 (47.1)	0.014
no	280 (63.8)	157 (65.1)	68 (72.3)	55 (52.9)	
Glucose≥100 mg/dL Yes	151 (34.4)	78 (32.4)	35 (37.2)	38 (36.5)	0.610
No HDL<50mg/dL Yes	288 (65.6) 179 (40.8)	163 (67.6) 91 (37.8)	59 (62.8) 42 (44.7)	66 (63.5) 46 (44.2)	0.365
No IMC, Kg/m² ≤24.9	260 (59.2) 121 (27.6)	150 (62.2) 61 (25.3)	52 (55.3) 36 (38.3)	58 (55.8) 24 (23.1)	0.029
≥25.0	318 (72.4)	180 (74.7)	58 (61.7)	80 (76.9)	

T0: at diagnosis; T4: after 4 months; T9: after 9 months; values expressed as absolute numbers (%); BP: blood pressure; TG: triglycerides; HDL: high-density lipoprotein cholesterol; BMI: body mass index; *significant difference if p<0.05 (χ^2 test for trend).

higher risk of developing hypertriglyceridemia (OR=1.67, 95%CI 1.04–2.66, p=0.032) and arterial hypertension (OR=2.04, 95%CI 1.27–3.26, p=0.003) in comparison to T0 and T4 groups (Table 3). Regarding cancer characteristics (Table 4), the majority of participating women (80.5%) had early-stage disease at the time of BC diagnosis. Node-negative axilla was found in 61.2%, hormone receptor-positive tumors in 77.5%, and HER2 oncoprotein expression was absent in 80.9% of patients (Table 4). Concerning groups that received follow-up care, after treatment (T4 and T9), 65.2% underwent breast-conserving surgery, 89.9% underwent radiation therapy, 55.6% underwent chemotherapy, and 68.7% underwent endocrine therapy.

Table 3. Descriptive oncological characteristics of postmenopausal women with breast cancer.

Parameters	Frequency (n)	%
Status (n=395)		
I	138	34.9
II	180	45.6
III	77	19.5
Axillary lymph node (n=402)		
Negative	246	61.2
Positive	156	38.8
Estrogen Receptor (n=417)		
Negative	94	22.5
Positive	323	77.5
Progesterone Receptor (n=417)		
Negative	124	29.7
Positive	293	70.3
HER2 (n=409)		
Negative	331	80.9
Positive	78	19.1
Ki67 (n=325)		
≤14%	109	33.5
>14%	216	66.5

HER 2: human epidermal growth factor receptor-2; Ki67: epithelial proliferative activity.

DISCUSSION

In the current study, postmenopausal BC survivors had a worse metabolic health throughout oncological follow-up period. Impaired metabolic health was mainly due to weight gain, in addition to a significant risk of increased levels of TGs and blood pressure. These are predictive factors for increased cardiovascular risk and worse BC prognosis that determine a higher mortality[2,19,23]. Metabolic diseases are factors of poor oncological prognosis in women treated for BC[2,3,6,16,18]. On the other hand, these diseases are associated with an increased risk for BC in postmenopausal women[18] and an increased risk of death from CVD in both premenopausal and postmenopausal women treated for BC[2,3].

Women with a 9-year cancer follow-up had a higher BMI than women with a 4-year follow-up and those recently diagnosed with BC. Since groups were matched for age and time since menopause, weight gain was an important finding that provided a better understanding of the negative impact of BC on patient lifestyle. In agreement with our results, a recent study, analyzing 140 women with BC, observed a significant increase (≥5%) in BMI from diagnosis to most recent follow-up, particularly among those who were overweight at diagnosis and among those up to 5 years since diagnosis[4]. Chan et al.[3] evaluated the risk of death in 213,075 women at the time of BC diagnosis, taking BMI into consideration. Those authors demonstrated that women with a BMI>30 kg/m^2 (obese) were at a higher risk of death than women with a BMI of 20–25 kg/m^2 (non-obese) (OR=1.41, 95%CI 1.29–1.53). Considering menopausal status, obesity at the time of BC diagnosis was associated with a higher risk of death in premenopausal women in comparison to postmenopausal women in the long term (OR=1.75, 95%CI 1.26–2.41 vs. OR=1.34, 95%CI 1.18–1.53). The authors observed that the risk of all-cause mortality in obese women is cumulative over time[3].

An increase in risk factors that have a negative impact on metabolic health is intrinsically connected to a large amount of visceral fat due to its endocrine activities. Visceral fat tissue produces more than 600 adipocytokines that regulate not only metabolic processes including insulin secretion, hunger, satiety, and energy balance, but also inflammatory processes[7,8]. Abdominal obesity resulting from inadequate eating and sedentary behavior promotes dysfunctional fat tissue with excess secretion of adipocytokines. In addition,

Table 4. Univariate binary logistic regression analysis between metabolic syndrome criteria at the three time points.

Variables	T0	OR	T4 95%CI	p-value	OR	T9 95%CI	p-value
BMI≥25.0 kg/m^2	Ref	0.55	0.33–0.91	0.019	1.13	0.66–1.94	0.659
HDL<50 mg/dL	Ref	1.33	0.82–2.16	0.245	1.31	0.80–2.10	0.260
TG≥150 mg/dL	Ref	0.75	0.42–1.21	0.209	1.67	1.04–2.66	0.032
Glucose≥100 mg/dL	Ref	1.24	0.75–2.04	0.397	1.2	0.74–1.95	0.452
BP≥130X85 mmHg	Ref	1.96	1.21–3.19	0.007	2.04	1.27–3.26	0.003
MS positive	Ref	1.34	0.83–2.16	0.230	1.24	0.78–1.97	0.360

BP: blood pressure; TG: triglycerides; HDL: high-density lipoprotein cholesterol; BMI: body mass index; MS: metabolic syndrome.

altered secretion profile is characterized by increased levels of leptin, interleukin (IL)-6, and tumor necrosis factor (TNF)-α. This metabolic cascade leads to increased oxidative stress and reduction of adiponectin, leading to low-grade chronic inflammation[9]. A recent meta-analysis examined the effects of central obesity on BC. This dose–response analysis showed that central obesity, as measured by WC and WHR, was associated with both premenopausal and postmenopausal BC risk and ER+/ER– BC risk. This study suggests that women should prioritize body type management to prevent BC[24]. Maintaining high percentages of lean body and appendicular skeletal muscle mass and preventing an increase in fat mass may be beneficial in preventing CVD in BC survivors[25].

In our study, 45.6% of the women included had been diagnosed with MetS. No difference in the occurrence of MetS was identified between groups, according to follow-up duration. However, when criteria were individually evaluated, arterial hypertension and hypertriglyceridemia were more prevalent in the group with the longest cancer follow-up. MetS is considered a risk factor for poor prognosis in women treated for BC, with a worse overall and specific survival[16,19]. Buono et al.[16], following women with BC for 10 years, divided into two groups, with (n=173) or without MetS (n=544), observed that the presence of MetS reduced overall survival (OR=3.01, 95%CI 1.72–5.28) and specific for BC (OR=3.16, 95%CI 1.64–6.07). The study also found that the isolated components of MetS were correlated with worse survival. With the exception of HDL-C<50 mg/dL, all other MetS components significantly correlated with worse overall and BC-specific survival[16].

Dyslipidemia is a characteristic of MetS found in obese and diabetic patients. An elevated total cholesterol, hypertriglyceridemia, and decreased HDL-C were associated with an increased risk for cancer in 18%, 15%, and 20% of patients, respectively[26]. In women treated for BC, dyslipidemia is associated with a worse prognosis. In studies on mortality due to BC, the use of statins for the treatment of dyslipidemia is beneficial for survival, suggesting that cholesterol may promote tumor progression[27]. The Women's Health Initiative study indicated that the administration of lipophilic statins has contributed independently to the reduction in advanced-stage BC, especially for patients with ER+ tumors[27].

Increased serum levels of TGs and a higher prevalence of hypertriglyceridemia were identified in the group with the longest BC follow-up. This finding may be associated with weight gain (statistically relevant). However, a prolonged time of exposure to endocrine therapy may also explain the lipid alteration. The majority of patients in the study (77.7%) had receptor-positive tumors and received endocrine therapy. Tamoxifen, a selective estrogen receptor modulator (SERM), exerts a favorable effect on lipid profile, decreasing total serum cholesterol and LDL-C, despite a lack of significant changes in HDL-C[28,29]. On the other hand, some studies have reported increased levels of TGs and risk of hypertriglyceridemia in patients treated with tamoxifen[30,31]. Aromatase inhibitors (AIs) induce an excessive hypoestrogenic state and are directly correlated to increased levels of total cholesterol. The ATAC (Arimidex, Tamoxifen, Alone or in Combination)[32] and the Breast International Group (BIG) 1-98[33] studies reported a higher incidence of hypercholesterolemia in patients treated with anastrozole and letrozole, respectively, when compared to women treated with tamoxifen[32,33].

The higher prevalence of arterial hypertension in the 9-year BC follow-up group reflects inadequate lifestyle and consequent weight gain, resulting in an increased risk of death from CVD. An observational study evaluated cardiovascular outcomes in about half a million postmenopausal American women, with and without BC (proportion of one BC patient to five controls without cancer). An increased risk of arrythmia, cardiac failure, pericarditis, and deep venous thrombosis persisted up to 5 years after cancer diagnosis. The authors concluded that women with a history of BC are at an increased risk of CVD when compared to women without cancer. Monitoring cardiovascular risk during long-term follow-up of women treated for BC must be prioritized[13]. A study observed a significantly increased risk of MetS, abdominal obesity, atherosclerotic disease, diabetes, and hypertriglyceridemia (important risk factors for CVD) in Brazilian postmenopausal women treated for BC, when compared to women without cancer (groups matched for age, time since menopause, and BMI)[10].

The concept of longevity in patients treated for BC has been well established. Strategies are required to improve quality of life, control complications, and prevent all-cause and cancer-specific mortality[14]. The longevity of women with luminal tumors was well described in a recent meta-analysis that evaluated approximately 63,000 women aged <75 years with tumors measuring up to 5 cm, treated for BC with adjuvant endocrine therapy. After 20 years of follow-up, the authors demonstrated that 85% of women with node-negative axilla were alive. Concerning distant recurrences, 86% of the women with tumor size up to 2 cm had no evidence of metastases. Tumor grade was directly related to disease-free survival, since 90% of the women with low-grade tumors showed no metastases in the study period. The authors concluded that women with early-stage tumors, positive hormone receptors, and low histological grade had a good cancer prognosis after 5 years of endocrine therapy[1]. The population of women evaluated in our study were considered to have a good cancer prognosis, since 80.5% had early-stage disease (Stages I and II) and 77.5% responded to endocrine therapy. Considering the favorable cancer prognosis in our study participants, it is important to focus on lifestyle changes to improve metabolic health, decreasing the risk of death from CVD and cancer-related complications.

The current study has some limitations. First, it was a cross-sectional study, in which a causal–effect relationship could not be established. Therefore, other non-controlled variables might have influenced the results. Second, the study was conducted in a single tertiary center that manages a reduced number of patients. Third, the study was based on clinical and laboratory data from a database retrieved from electronic medical records, without a

control group. We understand that it might be more appropriate to conduct a prospective cohort study of these same women at different time periods after cancer diagnosis. Nevertheless, our findings clearly show that weight gain occurred at different time periods in the study participants with long-term cancer follow-up after BC diagnosis. Weight gain was positively associated with diseases linked to chronic inflammation, worse metabolic health, and increased mortality risk in these women.

CONCLUSION

Postmenopausal BC survivors with a longer follow-up period had worse metabolic health due to a higher risk of hypertriglyceridemia, arterial hypertension, and obesity when compared to women with a shorter oncological follow-up period.

AUTHORS' CONTRIBUTION

LABB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Writing––original draft, Writing––review and editing. DABB: Conceptualization, Project administration, Supervision, Visualization, and Writing––review and editing. PGTA: Visualization, Writing––original draft, Writing––review and editing. CPKCP: Data curation, Formal analysis, Validation, Visualization, Writing––review and editing. ECP: Data curation, Formal analysis, Validation, Visualization, Writing––review and editing. HMLV: Data curation, Formal analysis, Validation, Visualization, Writing––review and editing. EAPN: Conceptualization, Data curation, Methodology, Project administration, Validation, Visualization, Writing––review and editing.

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