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Original Article

Baroreflex Sensitivity, Vascular Status, and Cardiorespiratory Fitness In Breast Cancer Survivors – A Cross–sectional Analytical Study

Aashish S Raman[1], Rajalakshmi Rajasegaran[2], Govindarajan Vishnukanth[3], Rajeswari Aghoram[4], Biswajit Dubashi[5], Usha Dhanaradja[6], Allen Timothy[7]

[1]III Year MBBS Student, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605006, India.
[2]Associate Professor, Department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605006, India.
[3]Additional Professor, Department of Pulmonary Medicine, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605006, India.
[4]Additional Professor, Department of Neurology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605006, India.
[5]Professor, Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605006, India.
[6]M.Sc., Medical Physiology, Department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605006, India.
[7]III Year MBBS Student, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605006, India.

Abstract

Background: Breast cancer is the most prevalent malignancy, affecting millions annually. Although advancements in therapeutic measures have resulted in diminished mortality rates, the cardiovascular and pulmonary side effects of these therapies raise clinical concerns.

Methods: This cross–sectional study evaluated baroreflex sensitivity (BRS), vascular status, pulmonary function and cardiorespiratory fitness (CRF) in 33 breast cancer survivors (BCS) aged 30–60 years, two to three years post–treatment, compared to 33 age and BMI–matched healthy females.

Results: BRS was significantly lower in BCS ($p<0.05$), indicating autonomic dysfunction. Pulmonary function tests revealed reduced FEV1, FVC, FEV1/FVC ratio, FEF25%–75%, and PEFR in BCS ($p<0.05$), suggesting impaired respiratory health. CRF was also diminished, with a significantly lower VO_2 max in BCS compared to controls (31.2 ± 13.1 ml/kg/min vs. 37.4 ± 11 ml/kg/min, p=0.041). Furthermore, the Ruffier Dickson Index (RDI) was significantly higher in BCS than in controls (5.8 ± 2.2 vs. 4.6 ± 1.3, P=0.009), indicating reduced cardiovascular fitness and recovery efficiency after physical exertion. However, no significant differences were observed in carotid intima–media thickness (CIMT) or blood pressure parameters between the groups. A statistically significant association was found in RDI categories between groups ($\chi^2 = 6.554$, P=0.038), indicating a difference in RDI grading distribution between healthy controls and breast cancer survivors.

Conclusion: Breast cancer survivors are at increased risk of impaired cardiac autonomic and pulmonary functions, likely as a result of the adverse effects of chemotherapy and radiotherapy. These findings highlight the need for comprehensive post–treatment monitoring and targeted rehabilitation strategies to mitigate cardiopulmonary risks and enhance the quality of life of these individuals.

Keywords: Autonomic nervous system, Baroreflex sensitivity, Breast cancer survivors, Carotid intima–media thickness, Cardiorespiratory fitness, Pulmonary function, Ruffier–Dickson Index (RDI).

Corresponding Author: Rajalakshmi Rajasegaran, Associate Professor, Department of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry – 605006, India.

Introduction

Breast cancer remains a global health scare, accounting for nearly one in every eight diagnoses of malignancy worldwide. It summed up to an alarmingly large total of 2.3 million cases and was the most common malignancy in women in the year 2020[1]. Representing about a fourth of all cancers in females, the burden of breast cancer has only been growing, with a particular rise in developing nations.

Despite the ever–increasing rates of manifestation, the rates of mortality associated with breast cancer have been decreasing, dropping by about 40 percent from the 1980s[2,3]. This decrease is primarily due to the advancements in early detection techniques and advanced therapies aimed at curing the disease[4]. However, recent studies have highlighted a potential association between breast cancer treatments and subsequent cardiovascular and pulmonary complications, suggesting a complex interplay between the therapeutic strategies of chemotherapy and radiotherapy[5,6].

It is hypothesized that alterations in protein synthesis or suppression, energy metabolism, ultrastructural changes, and apoptosis can act as potential contributors to cardiac complications in patients treated for breast cancer[7]. Similarly, sufficient evidence indicates that radiation–induced pulmonary toxicity can be primarily attributed to mechanisms such as direct tissue injury, DNA damage, and the synthesis of reactive oxygen species[8].

With respect to the management of early–stage breast cancer, current adjuvant treatment modalities have been identified to be linked to an array of cardiovascular effects. These effects can be direct, such as cardiac dysfunction, or indirect, manifesting as detrimental cardiovascular disease (CVD) risk factors[9]. Presently, the assessment of the cardiovascular consequences of cytotoxic treatments in oncology is predominantly based on alterations in the resting left ventricular ejection fraction (LVEF).

Recent studies indicate that adjuvant treatments for breast cancer survivors (BCS) may negatively impact the functioning of the cardiac autonomic nervous system with heightened activity of the sympathetic nervous system and diminished responsiveness of the parasympathetic nervous system[10], which in turn increases cardiovascular morbidity and mortality. The extent of mediastinal radiation and the amount of radiation exposure to the heart and coronary vessels are proposed as possible reasons for the increased cardiovascular risk in these individuals.

Baroreflex sensitivity (BRS) provides a more nuanced measure of the interaction between vascular and autonomic control, indicating how well the Autonomic Nervous System (ANS) adapts to fluctuations in blood pressure. In cancer survivors, chemotherapy and radiation have been associated with ANS dysfunction, which could also lead to impaired BRS. Similarly, there are also reports on the increase in the carotid artery intima thickness (CIMT) due to the formation of carotid plaques following chronic chemotherapy[11]. However, data on the impact of breast cancer treatment modalities on BRS and CIMT of breast cancer survivors is very limited.

Cardiorespiratory Fitness (CRF) is recognized as a reliable indicator of both cardiovascular health and overall mortality risk. In breast cancer survivors, CRF often declines due to treatment–related fatigue and reduced physical activity. Evaluating the CRF will provide insights into the cancer survivors' capacity for physical exertion and the overall efficiency of their cardiopulmonary systems, which are deemed essential for overall health and quality of life[12].

Knowledge regarding baroreflex sensitivity, vascular status, and cardiorespiratory fitness of breast cancer survivors is limited with respect to the Indian scenario. Hence, this study was done to address this lacuna wherein the parameters mentioned above were assessed in breast cancer survivors and were compared with those in healthy women.

Methodology

This cross–sectional analytical study was conducted from February to April 2024 in the Department of Physiology in collaboration with the Departments of Pulmonary Medicine, Neurology, and Medical Oncology at the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), a tertiary care hospital in Southern India, after obtaining approval from the Institutional Ethics Committee for Observational Studies (JIP/IEC–OS/315/2023). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki. The study details were explained, and written informed consent was obtained from all the study participants. Flyers were used to recruit the participants.

The study involved two groups (Test and Control Group), and the participants for both groups were recruited as per the following inclusion and exclusion criteria:

Inclusion criteria for the Test group:

Breast cancer survivors (BCS) aged between 30–60 years who had completed their curative therapy for breast cancer two to three years back and on conventional follow–up hormone therapy at the Regional Cancer Centre (RCC) under the Department of Medical Oncology.

Inclusion criteria for the Control group:

Age and BMI matched healthy females working in the Institutional campus who consented to participate in the study were included.

Exclusion criteria for both groups:

BCS / females

- with medical comorbidities such as diabetes, hypertension, cardiovascular disease, stroke, hepatic, renal, and endocrine disorders
- undergoing yoga or any relaxation therapies
- with active respiratory tract infections

Sample size calculation:

The sample size was estimated using the statistical formula for comparing two independent means. With an anticipated mean difference in BRS between BCS and healthy females as 6.9 ms/mmHg and a standard deviation of 10, the sample size was estimated at a 5% level of significance and 80% power[13]. The estimated sample size was 33 in each group. Although the sample size was also estimated to assess the difference in vascular status and cardiorespiratory fitness, estimation with BRS yielded the highest sample size and was considered.

Sampling technique: Consecutive sampling

Recording of study parameters:

1. Assessment of anthropometric parameters and blood pressure (BP):

The participant's height and weight were measured. Blood pressure was recorded using an automated BP apparatus after 5 minutes of rest in the sitting posture.

2. Assessment of Baroreflex sensitivity (BRS):

BRS was measured using the Finapres machine, based on the principle of measurements of finger arterial pressure with the volume clamp technique of Penaz and the physiocal criteria of Wesseling[14]. The participant was made to rest in the supine position for 10 minutes, during which the brachial cuff, finger cuff, and height sensors were connected for continuous beat–to–beat blood pressure and heart rate monitoring. After 10 minutes of recording, the BRS value was computed from systolic blood pressure and pulse interval by the cross–correlation method.

3. Assessment of Vascular Status:

The vascular status was assessed by measuring the Intima–media thickness (IMT) of the left and right common carotid arteries using a GE Logiq P6 with a 10–MHz linear–array transducer. Following standard procedures, the common carotid artery was identified using B Mode, and an ideal longitudinal image of the far wall was frozen. About 1 cm proximal to the dilatation of the carotid bulb, the edges of the transition zones between lumen–intima and media–adventitia were traced, and single measurements were obtained on each side.

3. Assessment of Pulmonary Functions:

The pulmonary functions were assessed using the computerized Spirometer SPIROLAB III. The participants were asked to perform at least three forced expiratory maneuvers at intervals of 2 minutes. The best of the three readings was taken as their actual value. FEV1/FVC, FEF25%–75%, and peak expiratory flow rate (PEFR) were assessed.

4. Assessment of Cardiorespiratory Fitness (CRF):

Cardiorespiratory fitness (CRF) was assessed using the Ruffier–Dickson test (45–second squat test) and VO_2 max. The Ruffier–Dickson Index (RDI) evaluates cardiovascular efficiency and autonomic recovery, with higher values indicating reduced efficiency. VO_2 max measures maximal oxygen uptake, reflecting aerobic capacity and overall cardiorespiratory fitness.

Ruffier–Dickson test (45–second squat test):

The initial heart rate (P1) of the study participants was noted after 5 minutes of rest in a sitting posture using a pulse oximeter. Then, they were asked to perform 30 squats in 45 seconds in synchrony with a metronome. The squatting involved bending the knees to a 90–degree angle, maintaining the back straight, and arms extended forward. Heart rate (HR) was noted immediately after the squats (P2), and a third reading of HR (P3) was recorded after a recovery period of one minute.

The Ruffier Dickson Index (RDI) was calculated as follows[15]:

$$RDI = [(P2–70) + 2 (P3–P1)] / 10$$

Depending on the RDI values, the participant's CRF was graded as poor (RDI ≥ 11), fair (RDI 6–10), and good (RDI ≤ 5).

The **VO_2 max** was calculated using the following formula[16]:

$$VO_2 \text{ max} = 3.0143 + 1.1585 \times \text{sex} - 0.0268 \times (P1/\text{height}) + 118.7611 \times [(P2–P3)/\text{age}^3]$$

In this formula, sex was coded as 0 for women and 1 for men.

The participant's CRF was classified as poor, fair, good, excellent, and superior based on the VO_2 max normalized for age.

If any of the study parameters mentioned above were found to be abnormal, the study participants were referred to respective physicians for further evaluation and management.

Statistical Analysis

The data was entered into an Excel datasheet, and SPSS Version 16.0 was used for the statistical analysis. Quantitative variables are expressed as mean with standard deviation (if normally distributed) or median with interquartile range (if non–normally distributed). The distribution of categorical variables is expressed as frequency and percentages. The comparison of BRS, vascular status, pulmonary functions, and cardiorespiratory fitness of BCS and healthy women is done using the Independent student's t–test or Mann–Whitney U test based on normality. The association between VO_2 grading and Ruffier–Dickson Index (RDI) categories with group classification (healthy controls vs. breast cancer survivors) was assessed using the Chi–square test. All statistical analyses were carried out at a 5% significance level, and p–values < 0.05 were considered significant.

Results

Thirty–three breast cancer survivors (BCS) who had completed their curative therapy for breast cancer two to three years prior and were on hormone therapy were included in the test group. Thirty–three age and BMI–matched healthy women were included in the control group (Table 1).

Systolic, diastolic, and mean arterial pressure were not significantly different between the test and control groups. The Baroreflex sensitivity (BRS) was significantly low among the BCS compared to the healthy controls (Table 2). The assessment of right and left carotid intima–media thickness (CIMT) revealed no significant differences between the groups (Table 2). The results of the pulmonary function tests revealed a significant reduction in FEV1, FVC, FEV1/FVC%, FEF 25%– 75%, and PEFR among breast cancer survivors compared to healthy controls (Table 2). The Ruffier–Dickson Index (RDI) was significantly high, while the VO_2 max was significantly low in the test group compared to the control group (Table 2).

Among the control group, 10 (30.3%) had superior and 1 (3%) had excellent VO_2 grading. In the test group, 5 (15.2%) had superior and 4 (12.1%) had excellent VO_2 grading. There was no statistically significant association in VO_2 grading between the groups (P=0.132) (Table 3). Among the controls, 22 (66.7%) had good, and 11 (33.3%) had a fair RDI category. In the test group, 12 (36.4%) and 20 (60.6%) had good and fair RDI. A statistically significant association was found in RDI between groups ($\chi^2 = 6.554$, P=0.038) (Table 4).

Discussion

In this study, 33 female breast cancer survivors (test group), aged between 30 to 60 years, satisfying the inclusion and exclusion criteria, were recruited in the test group. These participants were matched for BMI and age against a group of 33 healthy controls (control group) recruited from within the Institutional campus. The subject's autonomic function was assessed by baroreflex sensitivity, vascular status by carotid intima–media thickness (CIMT), pulmonary function by pulmonary function test, and cardiorespiratory fitness by Ruffier–Dickson index and VO_2 max.

This study, with findings in line with the results of studies by Vigo et al. and Frye et al.[13,17] demonstrates a significantly low BRS among breast cancer survivors compared to healthy controls, suggesting the presence of vagal impairment or autonomic dysfunction in these individuals. This decrease in BRS can be attributed to abnormalities in the central autonomic system, as explained by Goldstein et al.[18], and plausibly to direct damage inflicted on afferent neuron axons and Schwann cells by taxane–based chemotherapies such as paclitaxel and docetaxel as stated by Argyriou et al.[19]. Additionally, thoracic irradiation has been associated with afferent baroreflex failure, leading to impaired baroreflex sensitivity and cardiovascular dysregulation[20]. When compared to the general healthy population, individuals receiving chemotherapy, especially in the thoracic area, exhibit unfavourable cardiopulmonary vascular alterations and

Parameters	Control Group Median (IQR)	Test Group Median (IQR)	P–value
Age (years)	40 (38,45.5)	40 (38,45.5)	0.647
BMI (Kg/m^2)	20.8 (18.7,23.2)	21.2 (18.1,23.2)	0.513

Table 1: Characteristics of study participants

Values are expressed as median (IQR). Mann–Whitney U–test – P; P<0.05 was considered statistically significant. BMI – Body Mass Index.

Parameters	Control Group	Test Group	P–value
SBP (mmHg)	120.3 (110.1,135.6)	127.2 (114.8,140.6)	0.290
DBP (mmHg)	77.8 (72,80.9)	79.8 (71.8,90)	0.273
MAP (mmHg) #	93 ± 10.4	96.7±13.8	0.223
BRS (ms/mmHg)	13.4 (9.8,20.9)	7.6 (6.1,11.8)	0.003*
RCIMT (mm)	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.259
LCIMT (mm)	0.1 (0.1,0.1)	0.1 (0.1,0.1)	0.540
FEV1 (L) #	1.8 ± 0.3	1.6 ± 0.4	0.003*
FVC (L)	2.1 (1.9,2.3)	1.8 (1.6,2.1)	0.040*
FEV1/FVC (%)	87.8 (85.3,90)	84.5 (77.4,87.5)	0.001*
FEF 25%–75% (L)	2.3 (2,2.9)	1.9 (1.6,2.3)	0.002*
PEFR (L/sec)	5.1 (4.2,5.5)	4.1 (3.7,4.7)	0.001*
RDI#	4.6 ± 1.3	5.8 ± 2.2	0.009*
VO_2 max (ml/kg/min) #	37.4 ± 11	31.2 ± 13.1	0.041*

Table 2: Differences in study variables among healthy controls (Control group) and breast cancer survivors (Test group)

Values are expressed as median (IQR) – Mann Whitney U test – P, P<0.05 was considered statistically significant. #Values are expressed as mean ± SD – Independent Student T–test – P, P<0.05 was considered statistically significant.

SBP – Systolic blood pressure, DBP – Diastolic blood pressure, MAP – mean arterial pressure, BRS – Baroreflex sensitivity, RCIMT – Right carotid artery intima–media thickness, LCIMT – Left carotid artery intima–media thickness, FEV1 – Forced expiratory volume in one second, FVC – Forced vital capacity, FEF – Forced expiratory flow, PEFR – peak expiratory flow rate, RDI – Ruffier Dickson Index, VO2 max – maximal oxygen consumption.

VO_2 max Grading	Control Group Frequency (percentage)	Test Group Frequency (Percentage)	Chi–square value	P–value
Superior	10 (30.3)	5 (15.2)	7.081	0.132
Excellent	1 (3)	4 (12.1)		
Good	5 (15.2)	1 (3)		
Fair	1 (3)	1 (3)		
Poor	16 (48.5)	22 (66.7)		

Table 3: Association of VO_2 max grading between healthy controls (Control group) and breast cancer survivors (Test group)

Values are expressed in frequency (percentage). P–value <0.05 is considered significant.

RDI Category	Control Group Frequency (Percentage)	Test Group Frequency (Percentage)	Chi–square value	P–value
Good	22 (66.7)	12 (36.4)	6.554	0.038*
Fair	11 (33.3)	20 (60.6)		
Poor	0	1 (3)		

Table 4: Association of RDI grading between healthy controls (Control group) and breast cancer survivors (Test group)

Values are expressed in frequency (percentage). P–value <0.05 is considered significant. RDI– Ruffier Dickson Index

lower BRS, which could exacerbate the long–term risk of cardiovascular disease morbidity and mortality in breast cancer survivors.

Pulmonary function tests (PFTs) serve as a valuable tool in detecting early lung damage and changes in lung function in breast cancer patients, which may result from chemotherapy and radiation therapy. The study by Tuğral et al.[21] demonstrated a significant decline in Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1) from baseline to the completion of chemotherapy and radiotherapy in breast cancer patients. In concordance with these findings, our study revealed that the breast cancer survivors exhibited a notable decrease in FVC, FEV1, Forced Expiratory Flow at 25%–75% (FEF 25%–75%), and Peak Expiratory Flow Rate (PEFR), a measure of respiratory muscle function, generalized airways obstruction, patency of smaller airways, and an index of patency of airways respectively when compared to the healthy controls. According to Jaén et al.[22], radiation therapy initially induces harm to alveolar cells, resulting in acute inflammation termed radiation pneumonitis. Over time, sustained inflammation, fueled by cytokines and chemokines released by multiplying leukocytes and lymphocytes, can cause irreversible alterations like radiation fibrosis. This latter stage is marked by reduced lung segments and ongoing breathing difficulties due to compromised gas exchange. Chemotherapy compounds this progression by intensifying oxidative stress and immune–related damage to lung tissue with its cytotoxic properties. Over time, these pathological changes culminate in diminished values of pulmonary function parameters, as observed in this study.

The maximum amount of oxygen that an individual can consume is called maximal O_2 consumption or VO_2max, which is an indicator of cardiovascular fitness. In this study, a low VO_2 max was observed in breast cancer survivors compared to healthy controls. In addition, the values of the Ruffier Dickson Index (RDI) also indicated low cardiorespiratory fitness and endurance among breast cancer survivors. The mechanisms behind these findings could be due to the chemoradiation–induced cardiotoxicity leading to damage of cardiomyocytes, a reduction in left ventricular ejection fraction, decreased oxygen diffusive conductance in skeletal muscles, and alterations in the microvascular and/or mitochondrial function of skeletal muscles in breast cancer survivors on adjuvant therapy. These changes significantly influence the exercise capacity and endurance of these individuals[23]. Furthermore, breast cancer survivors (BCS) often experience a decline in physical activity, which can lead to obesity and further reduce cardiorespiratory fitness.

In individuals diagnosed with breast carcinoma, varying reports highlight the occurrence of atherosclerotic complications. Radiation exposure promotes atherosclerosis through mechanisms including oxidative stress, endothelial dysfunction, inflammatory and procoagulant alterations, and radiation–induced genetic instability, leading to cellular senescence and vascular aging[24]. In this study, the CIMT of BCS and healthy controls were not significantly different, a finding contradictory to the results published by Melichar et al. [25]. This could be attributed to the limited sample size of our study and the variations across drug regimens in chemotherapy.

Clinical Implications

The findings of this study underscore the profound and long–lasting impact of chemotherapy and radiotherapy on the cardiopulmonary and autonomic health of breast cancer survivors (BCS). The autonomic dysfunction evidenced by BRS decline in the Breast cancer survivor group predisposes them to cardiovascular risks, thus highlighting the necessity of routine BRS evaluation and other autonomic markers as part of survivorship care to detect and manage early signs of cardiovascular complications.

Similarly, the diminished pulmonary function elicited by reduced FEV1, FVC, and other lung parameters emphasizes the importance of incorporating pulmonary function tests into regular follow–up protocols in an attempt to minimize long–term morbidity and improve the quality of life among these survivors.

Furthermore, the reduced cardiorespiratory fitness (CRF) indicated by lower VO_2 max and higher Ruffier–Dickson Index scores points to the need for targeted rehabilitation programs aimed at enhancing physical activity and endurance to counteract the cardiotoxic effects of cancer treatments.

Together, these findings highlight the need for a comprehensive, multidisciplinary approach to survivorship care intended to effectively address the interconnected cardiopulmonary and autonomic challenges faced by Breast cancer survivors.

Limitations and Future Directions

This study, while providing valuable insights into the cardiopulmonary and autonomic health of breast cancer survivors (BCS), has certain limitations that warrant consideration.

The cross–sectional design of our study, while documenting associations between adjuvant therapies and negative health outcomes, precludes the establishment of causal relationships. This warrants further exploration

in the form of longitudinal assessments to determine the progression of cardiopulmonary and autonomic dysfunction, enabling us to arrive at a definitive understanding of the causation of the observed effects.

The study's relatively small sample size may limit the generalizability of the findings. Future studies should aspire to include a larger and more diverse cohort to capture variations across different demographics, treatment regimens, and stages of breast cancer at treatment initiation.

Additionally, the reliance on the specific assessment tools utilized, such as the Ruffier–Dickson Index and pulmonary function tests, while robust as outlined in the methods section, could be complemented by more comprehensive evaluations, including advanced imaging techniques and molecular biomarkers, thus enabling a deeper understanding of the mechanisms underlying the observed changes in hopes of identifying novel therapeutic targets.

Despite these limitations, this study lays a strong foundation for exploring personalized interventions to mitigate long–term adverse effects. Structured exercise programs, dietary modifications, and pharmacological strategies may be promising avenues for improving survivorship outcomes. The findings of this study highlight the importance of developing multidisciplinary approaches that prioritize the long–term well–being of breast cancer survivors.

Conclusion

Reduction in baroreflex sensitivity, pulmonary functions and cardiorespiratory fitness predispose breast cancer survivors to an increased risk of cardiac and pulmonary complications. Hence, early cardiopulmonary risk detection and the development of tailored interventions would enhance the long–term well–being of breast cancer survivors.

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Ethical statement

This study was approved by the Institute's Research Monitoring Committee and the Institute Ethics Committee of the Jawaharlal Institute of Postgraduate Medical Education and Research (JIP/IEC–OS/315/2023). All participants provided written informed consent after receiving detailed information about the study's objectives, procedures, potential risks, and benefits. They were also given the opportunity to ask questions before participation.

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Declaration of Conflicting Interest

The authors declare that they have no competing interests.

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