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Posttraumatic Stress, Posttraumatic Growth, and Heart Rate Variability Among Breast Cancer Survivors

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ABSTRACT

Introduction: Breast cancer as a life-threatening disease is the most frequent malignant disease among women all over the world. Resulting in post-traumatic stress disorder (PTSD) symptoms, breast cancer may also be related to positive changes like post-traumatic growth (PTG). The present study aims to evaluate heart rate variability (HRV) parameters among female survivors of breast cancer regarding its relationship with PTSD and PTG.

Method: Forty-three women with stage 1–2–3 breast cancer were recruited. Heart rate variability parameters were measured with a 24-hour ECG. Post-traumatic stress disorder checklist for DSM-5 (PCL-5) and Post-traumatic Growth Inventory (PTGI) were utilized to measure PTSD and PTG.

Results: The mean value of PCL-5 was 49.56; the mean value of PTGI was 71.56. Correlation analysis showed that PCL-5 was associated with SDNN (r=-0.310, p=0.043), LF (r=-0.349 p=0.022), and mean heart rate (r=0.396 p=0.009). Post-traumatic growth inventory scores were associated with LF/HF ratio (r=0.310 p=0.043). Linear regression analysis demonstrated that PCL-5 and PTGI scores predicted SDNN and mean heart rate.

Conclusion: PTSD and PTG symptoms are related to HRV parameters among female survivors of breast cancer. While PTSD symptoms are related to lower HRV and higher mean heart rate, PTG symptoms are associated with higher HRV and lower mean heart rate.

Keywords: breast cancer, heart rate, heart rate variability, post-traumatic growth, post-traumatic stress disorder

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INTRODUCTION

Breast cancer, as a life-threatening disease, is the most frequent malignant disease among women all over the world. According to the Cancer Reports of the World Health Organization, breast cancer has surpassed lung cancer to become the most common cancer, accounting for 12% of all new cases (1). As in many countries, the burden of cancer is also growing in Türkiye, and it is estimated that one of every four Turkish women diagnosed with cancer is breast cancer (1). Although the survival rate of breast cancer has increased day by day due to innovation and advances in treatment and diagnosis, it is a significant source of stress, having adverse impacts on every facet of women's lives (2,3). Post-traumatic stress symptoms are one of the most prevalent mental health problems among women with breast cancer (4,5). Despite those adverse effects, some patients also experienced positive changes after breast cancer diagnosis, which is widely known as post-traumatic growth (6,7). Research on the physiological effects of post-traumatic stress shows autonomic system dysfunctions. However, little is known about post-traumatic growth and sympathetic and parasympathetic activity.

Highlights

- **Breast cancer causes significant levels of traumatic stress.**
- **Many patients report positive changes after breast cancer.**
- **Traumatic stress is related to worse cardiac autonomous system functioning.**
- **Post-traumatic growth is related to better cardiac autonomous system functioning.**

Heart rate variability (HRV) is a practical measure of the sympathovagal balance of the autonomic nervous system, which indicates adrenergic stimulation. Heart rate variability is a late mediator of the physiology of the acute stress response through the hypothalamus-pituitary axis.

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Heart rate variability could be a significant clinical marker for mental and physical health outcomes (8). More clearly, decreases in HRV were found to be linked with cardiovascular disease (9), diabetes (10), and cancer (11). Kemp and Quintana proposed that chronic reduction in HRV will impair immune system functions and inflammation, which, in turn, will cause the above-mentioned physical health problems to emerge (8). Furthermore, a number of previous researches on the relationship between psychological well-being and HRV indicated that anxiety disorders (12), depression (13), and post-traumatic stress disorder (Moon et al., 2013) were associated with reduced HRV. The relationship between HRV and psychological distress was studied in some chronic physical health problems and their caregivers, and the findings of the studies were sparse. Whereas some studies did not find any significant relationship between HRV and psychological distress such as panic disorder, depression, anxiety, and post-traumatic stress symptoms (14,15), some of them revealed lower HRV was associated with psychological distress in patients with different chronic health problems (16). A few studies examining the association of HRV and PTG in different populations presented conflicting findings for this relation (17).

The present study aims to explore associations between HRV parameters and post-traumatic stress and post-traumatic growth among women with breast cancer.

METHOD

The present study has a cross-sectional design.

Participants

Women with breast cancer were recruited from the Oncology Clinic of Eskişehir Osmangazi University Faculty of Medicine. Researchers included the patients if they meet the following inclusion criteria: a) diagnosed with breast cancer in the past four years, b) having completed breast cancer surgery and (if advised) additional cancer treatments at least one month ago, c) having stage I-II-III breast cancer, d) getting the first and only breast cancer, e) aged between 20 and 65, f) having no cardiac disease or cardiac complications of chemotherapy and/or radiotherapy (examined by cardiologist). Exclusion criteria were determined as a) getting psychopharmacological treatment after breast cancer, b) having mental retardation, dementia, organic mental disorders, psychotic disorder, substance abuse, severe depression, anxiety disorder, or obsessive-compulsive disorder c) metastasis. Finally, 43 applicants participated in this study. The sample's age ranged between 28 and 64, and the mean was 45.56±7.85. Most participants were married (76.7%) and employed (60.5%). More participants had mastectomies (65.1%). Of these, 19 participants were diagnosed with stage II breast cancer (44.2%). Table 1 presents the characteristics of the sample.

Table 1. The characteristics of the study sample (n=43)

Age (M ± SD)	45.56±7.85
Education Level % (n)	
Elementary School	18.6% (8)
Secondary School	9.3% (4)
High School	32.6% (14)
University	39.5% (17)
Employment Status % (n)	
Working	60.5% (26)
Not working	39.5% (17)
Marital Status % (n)	
Married	76.7% (33)
Single	9.3% (4)
Divorced	14% (6)
Stage of breast cancer % (n)	
I	25.6% (11)
II	44.2% (19)
III	30.2% (13)
Type of surgery % (n)	
Mastectomy	65.1% (28)
Lumpectomy	34.9% (15)
Adjunct treatment % (n)	
Chemotherapy	74.4% (32)
Targeted therapy	16.3% (7)
Radiotheraphy	76.7% (33)

Measurement Tools

Sociodemographic and illness-related information form

The form aims to get the participants' related information. It covers age, educational level, marital status, employment status and illness-related information such as type of operation, stage of breast cancer, and adjuvant treatment.

Post-Traumatic Stress Disorder Checklist for DSM-5 (PCL-5)

Post-Traumatic Stress Disorder (PTSD) Checklist for Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Fifth Edition (PCL-5) (18) was used to evaluate the severity of post-traumatic stress symptoms over the last month. PCL-5 is scored on a 5-point scale ranging from 0 (not bothersome at all) to 4 (extremely bothersome). It has four subscales that cover the PTSD cluster of DSM-5:re-experiencing, avoidance, negative alterations, and hyper-arousal. It has 20 items and scored from 0 to 80. Higher scores obtained from the total scale indicate higher post-traumatic stress symptoms. The Turkish adaptation was conducted by Boysan et al. (19). The Turkish version exhibited good reliability scores. We used the total score of PCL-5, and internal consistency was found 0.91 in this study.

Post-traumatic Growth Inventory (PTGI)

PTGI, developed by Tedeschi and Calhoun in 1996, was used to evaluate post-traumatic growth (20). It consists of 21 items, and participants were asked to rate to what extend they experienced each following changes in their life as a result of breast cancer diagnosis on a 6-point Likert-type scale ranging from 0 (I did not experience this change) to 5 (I experienced this change to a very great degree). Higher scores indicate higher post-traumatic growth experienced. The Turkish version of PTGI was adapted by Dirik and Karanci (21). The Turkish version has three subscales: change in the relationship with others, change in the self, and change in the philosophy of life. Internal consistency of the total score of PTGI was found to be 0.94. We used the total score of this scale, and Cronbach's alpha was calculated as 0.91 in this study.

Heart Rate Variability (HRV)

Heart rate variability outcomes are selected regarding Schneider and Schwerdtfeger's study in 2020 as follows: 1) time-domain: root mean square of successive heartbeat (RMSSD), 2) time-domain: standard deviation of NN intervals (SDNN), 3) frequency-domain: high-frequency HRV (HF-HRV), 4) frequency-domain: low-frequency HRV (LF-HRV), 5) frequency-domain: low-frequency/high-frequency ratio (LF/HF), 6) heart rate (HR) (22).

Heart rate variability measurements were performed using a 24-hour ambulatory Holter ECG, which is the gold standard for measuring HRV (23).

Heart rate variability measurements were performed in the Cardiology Outpatient Clinic of Eskişehir Osmangazi University Hospital. During morning hours (between 08:30 and 11:00), patients applied to the Cardiology Clinic for 24-hour Holter ECG measurement. The device

utilized was a 3-channel digital holter recording device (BI9800TL+3, Biomedical Instruments Co., China).

The Holter monitor was applied for 24 hours and taken off the next day in the Cardiology Clinic. HRV parameters were evaluated by an experienced electrophysiologist cardiology consultant GOM.

Procedure

The Clinical Research Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine approved this study. Afterward, the researchers of the present study announced the study via posters at the various departments of the hospital, and also one of the researchers (oncologist) informed her patients about the study and collected the voluntary patients phone numbers to convey to Psychologist CYK and Psychiatrist IGYK. Psychologist CYK performed tele-interviews to determine if the applicant is eligible for the study. If tele-interview result is positive, applicants are invited for a face-to-face interview with Psychologist CYK and Psychiatrist IGYK. Fig. 1 demonstrates the flow diagram of the current study (See Fig. 1).

The face-to-face interview was organized with the participants in a quiet room of the psychiatry clinic. The researchers informed the study procedures with oral and written informed consent. After providing informed consent, Psychiatrist IGYK evaluated applicants regarding DSM-5 criteria (24). Eligible participants filled out the self-report questionnaires. Finally, the participants were directed to the cardiology clinic to be evaluated by Cardiologist GOM. If there was no cardiac disease and no complications of breast cancer treatments, the 24-hour Holter EKG procedure for HRV recording was performed.

Statistical Analysis

Statistical analysis was conducted using IBM Statistical Package for Social Sciences (SPSS) program version 23.0. Continuous data were presented as mean/SD, and categorical data was presented as prevalence. Cronbach alpha score was calculated for the internal consistency of each self-report measurement tool. Skewness and kurtosis were used to determine the normality of distribution. Two participants were excluded due to not meeting the normality assumptions of at least two or more HRV-based domains. Pearson correlation was conducted to test the study aim. Linear regression analysis tested the predictors of HRV and heart rate. *P* value <0.05 was considered to be statistically significant. Descriptive statistics of the study variables are presented in Table 2.

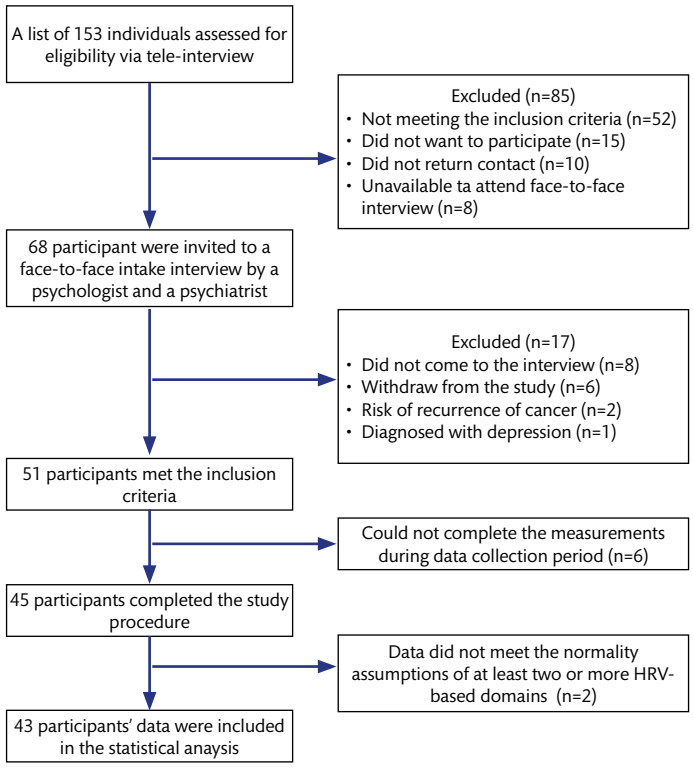

Figure 1. Flowchart of the study.

RESULTS

Following the aim of the study, Pearson correlation analysis was conducted (Table 3). Psychological variables of the study, namely post-traumatic stress symptoms and post-traumatic growth, were not associated with each other (r=0.061 p=0.697). PCL-5 scores were related to SDNN (r=-0.310, p=0.043), LF (r=-0.349 p=0.022), and heart rate (r=0.396 p=0.009). Post-traumatic growth scores were associated with LF/HF ratio (r=0.310 p=0.043). Additionally, the relationship between PTGI and SDNN and PTGI and heart rate was marginally significant (respectively r=0.298 p=0.052, r=-0.292 p=0.057) (Table 3).

Table 4 demonstrates multivariate linear regression analysis that used SDNN as the dependent variable. Post-traumatic growth scores are included since their correlation with SDNN showed a p-value lesser than 0.1. The model explained 19%.7 of SDNN variance (F=4.918 p=0.012).

Another variable that was correlated with both psychological outcomes was heart rate. A second model was tested using linear regression analysis. Table 5 shows predictors of heart rate. The model explained 25%.7 of heart rate variance (F=6.929 p=0.003).

Table 2. Mean, standard deviation, skewness, and kurtosis of the study variables (n=43)

Variables	Mean	Standard deviation	Skewness	Kurtosis
Psychological variables				
PCL-5	49.56	15.39	0.266	-0.832
PTGI	71.56	17.77	-0.110	-0.620
HRV parameters – 24 hours				
RMSSD	22.77	8.07	0.332	-0.263
SDNN	126.21	34.54	-0.063	-0.848
HF	186.21	131.90	1.342	2.589
LF	387.17	209.00	0.781	0.107
LF/HF ratio	2.79	1.59	0.490	-0.718
Heart rate	86.14	12.04	1.206	2.298

HF: high frequency; LF: low frequency; PCL-5: post-traumatic stress disorder checklist for diagnostic and statistical manual of mental disorders fifth edition; PTGI: post-traumatic growth inventory; RMSSD: root mean square of successive heartbeat; SDNN: standard deviation of NN intervals.

Table 3. Pearson's correlation analysis of post-traumatic stress, post-traumatic growth, and HRV parameters

	PCL-5	PTGI
PCL-5	-	
PTGI	0.061	-
RMSSD	-0.220	-0.021
SDNN	-0.310*	0.298
HF	-0.047	-0.136
LF	-0.349*	0.170
LF/HF ratio	-0.046	0.310*
Heart rate	0.396**	-0.292

**p<0.01, *p<0.05.
HF: high frequency; LF: low frequency; PCL-5: post-traumatic stress disorder checklist for diagnostic and statistical manual of mental disorders fifth edition; PTGI: post-traumatic growth inventory; RMSSD: root mean square of successive heartbeat; SDNN: standard deviation of NN intervals.

In addition to the above-mentioned relationship between PTSD and reduced HRV, there is evidence of HRV being a risk factor and a prognostic factor for PTSD. Minnasian et al. demonstrated that baseline low HF-HRV was related to PTSD diagnosis (31). Soder et al. asserted that baseline HRV may predict PTSD treatment outcomes in patients with comorbid substance use disorder (32).

The novelty of the present work is that it demonstrates that post-traumatic growth was related to a high LF/HF ratio, and post-traumatic growth predicted high SDNN and low mean heart rate. De Vincenzo et al. researched the relationship between HRV and PTG among ovarian cancer survivors, finding that the LF/HF ratio was negatively related to PTG (17). That contradicts the findings of the present study. The contrast may stem from HRV measuring methods; De Vincenzo et al. utilized a 5-minute measurement; on the other hand, the present study measured

Table 4. Predictors of SDNN

	B	p	95% Confidence interval	
			Lower	Upper
PCL-5	-0.740	0.025	-1.384	-0.096
PTGI	0.619	0.030	0.061	1.177

PCL-5: post-traumatic stress disorder checklist for diagnostic and statistical manual of mental disorders fifth edition; PTGI: post-traumatic growth inventory.

Table 5. Predictors of heart rate

	B	p	95% Confidence Interval	
			Lower	Upper
PCL-5	0.325	0.004	0.109	0.541
PTGI	-0.215	0.025	-0.402	-0.028

PCL-5: post-traumatic stress disorder checklist for diagnostic and statistical manual of mental disorders fifth edition; PTGI: post-traumatic growth inventory.

DISCUSSION

The present study found that traumatic stress symptoms were related to lower SDNN, lower LF, and higher heart rate. Post-traumatic growth was related to a higher LF/HF ratio. Additionally, SDNN and heart rate were predicted by post-traumatic stress symptoms and post-traumatic growth.

Traumatic stress severity was related to low HRV and higher mean heart rate in the present study. Both factors are related to dysregulated stress systems. Post-traumatic stress affects the hypothalamus-pituitary-adrenal axis and the autonomic nervous system, resulting in low HRV and high heart rate, correlatively with existing knowledge (22,25,26). de Faria Cardoso et al. researched the relationship between PCL-5 scores and HRV of women following pregnancy loss, finding a positive association between SDNN and PCL-5, and no relationship between heart rate and PCL-5 scores (27). Since the present study demonstrated a positive link between mean heart rate and PCL-5 scores, the discrepancy may be related to the heart rate measurement method. Short-term measurements may not be enough to detect changing heart rates during the day. Many research utilized short-term HRV measurement. However, Dennis and colleagues studied PTSD and HRV with 24-hour ECG monitoring, they found out that PTSD symptom severity was related to lower SDNN, HF, and LF (28).

Mäder et al. showed a positive relation between heart rate response and PCL-5 scores among trauma survivors (29). On the other hand, this study by Mäder et al. found no connection between resting HRV and PTSD, claiming that this may be a result of not measuring HRV during sleep (29,30).

HRV in 24 hours (17). Additionally, HRV parameters may show non-linear patterns (22). A meta-analysis study by Schneider and Schwerdtfeger put forward the previous research on LF/HF ratio and PTSD, which showed significant heterogeneity (22).

LF/HF ratio is higher among individuals with PTSD than among healthy controls (22). Sandoz et al. uncovered that LF/HF ratio was lower among women with a high risk of childbirth-related PTSD (33). The present results showing that higher PTG is related to a higher LF/HF ratio may be interpreted as women with high PTG had better autonomous nervous system functioning. Post-traumatic growth was not related to PTSD in correlation analysis. However, previous research on PTG and PTSD reveals that they may not be in a linear relationship but a curvilinear association (34). Without any traumatic stress, PTG does not occur (34). Ongoing high traumatic stress may reduce PTG (35). Post-traumatic growth and PTSD have complicated effects on the autonomous nervous system and HRV. The results of the present work may be interpreted as that PTG has the potential to relieve adverse effects of PTSD on the autonomous nervous system.

The mean PCL-5 scores of the participants were 49.56, which was high since scores above 33 show probable PTSD (36). Breast cancer is related to significant levels of psychological distress. That is related to breast cancer having the potential to be a fatal disease and breasts being overvalued regarding female sexuality under patriarchal views of society.

Heart rate variability parameters in the present study varied between normal ranges (37). The present study excluded women with cardiac

diseases, women receiving chemotherapy at the time of recruitment, women with cardiac complications of chemotherapy, and women with additional physical diseases. Thus, normal values were expected. The authors of the present study underline that even in a sample with high traumatic stress, HRV parameters stay in the normal interval. Further studies may reveal critical HRV and 24-hour heart rate cut-off scores for PTSD.

Heart rate variability and 24-hour heart rate can be used as a biomarker of psychological adjustment for breast cancer. Furthermore, previous research on various psychological interventions, such as supportive therapies, relaxation programs, and cognitive behavioral therapies in many chronic illnesses, revealed that HRV could be improved through these interventions (38–40). However, the use of HRV in psychiatry is still in its infancy. Thus, combining psychological measurements with reliable physical measurements, such as HRV, in assessing individuals and the efficiency of the treatments could provide a better understanding for clinicians and physicians.

Bourla et al. proposed using technology to monitor PTSD symptoms (25). Heart rate variability parameters and 24-hour heart rate can be measured with many devices, such as smartwatches. Including those data in patient visits may improve service quality. Detecting PTSD and psychological distress and treating it with supporting-based therapies will contribute to the patient's well-being. Considering none of the participants were admitted to mental health services despite their high levels of traumatic stress symptoms, physiological measurements may help clinicians detect psychological distress.

Strengths and limitations

Previous research demonstrated biological differences between females and males regarding HRV (41). Thus, the present study recruiting only females is its strength. The present study utilized a 24-hour EKG Holter to measure HRV, the gold standard. Additionally, the participants were examined by a cardiology consultant to eliminate any conflicting cardiologic situations.

Dennis et al. underlined that PTSD has many behavioral comorbidities like smoking, drinking alcohol, problems with eating and obesity, and changes in sleep patterns, putting forward that the relationship between HRV reduction and PTSD may arise because of those behavioral factors (28). The present study evaluated the participants regarding acute psychiatric disorders, including eating and sleeping disorders and alcohol use disorders. However, we did not cover smoking as a study variable, which might be a limitation. No participant had alcohol or substance use disorder.

The study recruited participants during the COVID-19 pandemic. That came along with many obstacles in reaching potential participants face-to-face. The present study did not recruit healthy controls to compare, which might be a limitation. Besides, we had no male participants to compare; however, breast cancer is a disease mostly affecting women.

The participants of the current study had higher education levels compared to over 25 female population of Türkiye in 2022 (42). That limits the finding's application to the general population since both PTSD and PTG are related to education level (34,43).

Another limitation of the present study is that diagnosing with breast cancer is a psychological distressing factor, however its treatment may result in physiological stress and cardiac complications, which can affect HRV domains. That problem was tried to overcome by cardiological examination of the study participants. Even so, the results of the present study need to be replicated in psychologically distressed populations without physical diseases. Future studies may focus on those individuals.

Additionally, future studies may evaluate the effect of diseases that are not gender-specific in male and female samples.

In conclusion, PTSD and PTG symptoms are related to HRV parameters among female survivors of breast cancer. While PTSD symptoms are related to lower HRV and higher mean heart rate, PTG symptoms are associated with higher HRV and lower mean heart rate. Post-traumatic growth has a potential to alleviate psychological trauma's adverse effects on autonomous nervous system.

Ethics Committee Approval: The Clinical Research Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine approved this study (17.06.2021, decision no: 33).

Peer Review: Externally independent.

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