Received: 29 April 2025/ Revised: 04 October 2025/ Accepted: 03 December 2025

ORIGINAL ARTICLE

Journal of Hacettepe University Physical Therapy and Rehabilitation

Investigation of Chronotropic Response and Exercise Intolerance in Colorectal Cancer Survivors

Mehmet Fatih SANVER[1*], Melda SAGLAM[2], Ebru CALIK[2], Saadettin KILICKAP[3], Naciye VARDAR YAGLI[2]

[1]Kütahya Health Sciences University, Vocational School of Health Services, Kutahya, Türkiye

[2]Hacettepe University, Faculty of Physical Therapy and Rehabilitation, Department of Cardiorespiratory Physiotherapy and Rehabilitation, Ankara, Türkiye

[3]Liv Hospital Ankara, Department of Medical Oncology, Ankara, Türkiye

*Corresponding author e-mail: mfsanver@gmail.com

ABSTRACT

Purpose: Advances in colorectal cancer (CRC) treatment have significantly increased patient survival rates. However, cancer-specific therapies can induce chronic adverse effects on the cardiovascular system, leading to various symptoms in survivors. The aim of this study was to investigate exercise capacity and cardiac responses to exercise in CRC survivors and compare them with healthy individuals.

Methods: The study included twenty-three CRC survivors (aged 18–65 years) and twenty-two age and sex-matched healthy individuals. All participants underwent a Cardiopulmonary Exercise Test (CPET). Physical activity level (SF-IPAQ) and fatigue severity (BFI) were assessed. The chronotropic index (CI) was calculated using the formula (HRpeak-HRrest)/(220-age)-(HRrest).

Results: Maximal oxygen consumption and the difference between resting heart rate and the peak heart (ΔHR) rate achieved during exercise were lower in CRC survivors compared to healthy individuals ($p<0.001$, $p=0.04$, respectively). CI was observed insufficient in 11 (47.83%) CRC survivors and 3 (13.64%) healthy individuals ($p=0.01$). Whereas physical activity level was similar between the groups ($p=0.10$), fatigue was more common in CRC survivors ($p<0.001$).

Discussion: Significant reduction in VO_{2peak}, the objective measure of exercise capacity, and the statistically higher prevalence of CI (CI<80%) in CRC survivors highlight a compromise in the cardiovascular system's functional reserve. We suggest that CI acts as a sensitive functional marker of subclinical cardiotoxicity induced by cancer treatments, pointing to an impaired cardiac autonomic response, rather than solely structural heart damage. These findings underscore the long-term need for routine screening of cardiac functional response in this growing population of survivors.

Key Words: Colorectal Neoplasms, Chronotropism, Cardiopulmonary Exercise Test, Oxygen Consumption, Fatigue.

INTRODUCTION

Although colorectal cancer incidence varies across countries, it is generally among the top three cancer types for both incidence and cancer-related mortality (1). A large proportion of cases and mortality can be prevented or reduced though regular screening and improved treatment methods (2). Following lifestyle changes and local-regional and systemic anti-cancer treatments after diagnosis, most cancer survivors encounter various early and late autonomic and physiological effects that increase morbidity and mortality (3). As a consequence of cancer and treatment-related cardiotoxicity, reduced cardiac responses and cardiorespiratory fitness may be observed in cancer patients and survivors (4, 5). The reduction in maximal oxygen consumption (VO_{2max}), which defines exercise capacity, in cancer survivors is complex and multifactorial (6). To objectively quantify functional status and reduced cardiorespiratory fitness, Cardiopulmonary Exercise Testing (CPET) is globally recognized as the gold standard for the integrated, comprehensive assessment of the body's response to stress in high-risk populations (7).

CPET provides crucial insight into the underlying mechanisms of functional limitation, particularly through the evaluation of dynamic cardiovascular responses to exercise (6). One of the most sensitive CPET-derived parameters is the heart rate (HR) response, which directly reflects the functional integrity of the cardiac autonomic nervous system (8). Chronotropic insufficiency (CI) is defined as the inability to sufficiently increase heart rate (HR) during and at the peak point of CPET (9). CI is a clinical manifestation of autonomic dysfunction, in which the balance between sympathetic and parasympathetic nervous systems is impaired, hindering the necessary cardiac output augmentation. Autonomic dysfunction, associated with decreased parasympathetic activity and increased sympathetic overload, elevates the risk of premature death by increasing cardiovascular stress and adversely affecting cardiac health (8). The presence of CI is a predictor of increased long-term cardiovascular risk and is associated with adverse prognosis (10). Changes in HR may initially not be perceived as a problem by cancer survivors, but their long-term effects can lead to increased daily fatigue and even risk for future cardiovascular events (10-12).

The decrease in VO_{2max} is complex and multifactorial. Central causes include subclinical cardiotoxicity and a potential reduced left ventricular function, often induced by chemotherapy. This cardiac damage directly impairs the heart's ability to increase stroke volume and, crucially, limits the maximal heart rate (HR_{peak}) response during exercise, leading to CI (13). Peripherally, treatments contribute to skeletal muscle atrophy, mitochondrial dysfunction, and endothelial dysfunction. These factors restrict the muscles' ability to efficiently utilize oxygen and are further compounded by autonomic imbalance (CI), which limits adequate blood flow and oxygen delivery during peak exertion (14). Thus, CI is a key but yet easily quantifiable, indicator of underlying cardiotoxicity and autonomic imbalance that contributes significantly to the observed decrease in VO_{2max} and, consequently, reduced exercise tolerance in this patient population.

Previous studies using CPET have identified chronotropic insufficiency as a potential indicator of cardiac dysfunction in various cancer populations (e.g., breast cancer, lymphoma). However, the specific characteristics of exercise capacity and cardiac responses, particularly chronotropic responses, to exercise in colorectal cancer survivors remain less understood. This comparison is aimed at revealing clinically significant differences by detecting and quantifying potential decrements in exercise capacity and cardiac responses, as well as the presence of autonomic dysfunction, in colorectal cancer survivors relative to a healthy reference point.

METHODS

Study Design

This case-control study included colorectal cancer survivors and age and gender matched healthy individuals. Participants were evaluated between November 2024 and March 2025. The patients with colorectal cancer under the routine follow-up of the medical oncology clinic of Liv Hospital Ankara were consulted for physiotherapy and rehabilitation. The evaluations were carried out at Hacettepe University Faculty of Physical Therapy and Rehabilitation. The study was approved by the Hacettepe University Faculty of Physical Therapy and Rehabilitation Research Ethics Committee on 24/10/2024 (approval number: FTREK24/97). The written informed consent was obtained from all participants.

Participants

Individuals aged 18-65 years who were at least three months post-surgery for colorectal cancer and who had completed radiotherapy and/or chemotherapy treatments were included in the study. The exclusion criteria for patients were brain metastasis, contraindication to exercise testing or the presence of cardiac disease. Healthy individuals with similar demographic and physical characteristics from the healthy relatives of the patients who applied to our faculty were taken as the control group. The inclusion criteria for healthy individuals were determined as not having a cardiovascular, neurological and/or genetic musculoskeletal system disease and not having an orthopedic or cognitive problem that prevents the tests from being performed.

Assessments

Demographic information of the participants, such as age, height, and weight were obtained before the evaluation. The type of cancer and the treatments received by the patietns were recorded. The short form of the International Physical Activity Questionnaire (SF-IPAQ) was used to determine the level of physical activity. The SF-IPAQ lists activities and asks for estimates of duration and frequency for each activity during the past week. Durations are multiplied by the MET value for each activity, and the results for all items are added together to form a physical activity score. A higher score in

MET-min/week indicates a higher level of physical activity. The various forms of the IPAQ have been accepted as a reliable and valid physical activity measurement tool in different populations, including cancer patients. Scores for walking, moderate, and vigorous activities are the sum of the corresponding item scores. Sitting questions are not included in the physical activity score. Its validity and reliability have been established in Turkish, and permission for its use has been obtained (15). The Brief Fatigue Inventory (BFI) was used for fatigue impact and severity assessment. The scale ranges from 0 (None) to 10 (Worst possible). A higher total BFI score indicates greater fatigue severity and/or a larger impact of fatigue on daily life. It is widely used and has been proven valid and reliable in the cancer population to measure the severity and impact of cancer-related fatigue quickly and effectively. The BFI consists of 10 questions. The form evaluates general fatigue levels (fatigue felt at the time of the interview, general fatigue experienced in the last 24 hours, and the worst fatigue level experienced in the last 24 hours) and the extent to which daily activities (general activity, mood, walking ability, life outside the home, communication with other people, joy of life) were affected by fatigue in the last 24 hours. Its validity and reliability have been established in Turkish, and permission for its use has been obtained (16). The CPET was used for chronotropic response and exercise capacity.

Cardiopulmonary Exercise Test (CPET)

CPET was used as the gold standard to evaluate cardiorespiratory fitness and cardiac chronotropic response to exercise. The tests were performed using a calibrated gas exchange system (Cosmed Quark CPET, Rome, Italy). This system allows for the simultaneous assessment of physiological parameters, including VO_{2max}, CO_2 production (VCO_2), lactate measurements, and continuous monitoring of HR responses via electrocardiogram (ECG), ensuring a safe and objective assessment method (17). A modified Bruce protocol with intermediate increments was used for CPET on a treadmill. The test was terminated when the subject reached volitional exhaustion (symptom-limited test) or when subject met one of the following criteria such as reaching ≥85% of the age-predicted HRmax, reaching a respiratory exchange ratio (RER) of ≥1.10, or the presence of clinical contraindications. The test was considered maximal if an RER of ≥1.10 was achieved (17). Resting heart rate (HRrest), the average heart rate recorded in a seated position prior to the initiation of the exercise test. Peak heart rate (HRpeak), the highest heart rate achieved at the point of test termination. Heart Rate Difference (ΔHR), calculated as the absolute difference between peak and resting heart rates (HRpeak − HRrest). Heart rate reserve (HRR), the difference between the age-predicted maximal heart rate (HRmax = 220 −Age) and the HRrest. Heart rate recovery at 1-minute (HRR1min), calculated as the difference between the heart rate recorded at the point of test termination and the heart rate recorded one minute after the cessation of exercise. HRR1min serves as an independent marker of cardiac autonomic nervous system function and vagal withdrawal (18). The chronotropic index was calculated from the formula (HRpeak - HRrest) / (220-age) - (HRrest). When the index was <80%, it was considered as chronotropic insufficiency (19). An index value below 80% signifies chronotropic incompetence, which means the heart fails to adequately increase its rate in response to the metabolic demands of exercise. CI is an indicator of cardiac autonomic dysfunction and is considered an important predictor of adverse cardiovascular outcomes and risk stratification, including in cancer survivors. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded at rest (baseline) and every 3 minutes during the test using a standard cuffed blood pressure sphygmomanometer. Changes in blood pressure (ΔSBP and ΔDBP) were calculated as the difference between peak and baseline values.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 26.0 (SPSS, Chicago, IL, USA) software. The conformity of the variables to normal distribution was analyzed visually (histograms and probability plots) and analytically (Shapiro-Wilk tests). Descriptive data for continuous variables that were approximately normally distributed were expressed as mean±standard deviation. For categorical variables, data were expressed as number (n) and percentage (%). For colorectal cancer survivors and control group, *Student t test* was used for the comparison of numerical variables that were determined to be normally distributed. In terms of categorical variables, *Chi-Square test* was used for colorectal cancer survivors and control group. The effect size (d=0.82) used for the sample size calculation was derived from a previous study by Cramer et al. investigating cardiovascular function and exercise capacity in colorectal cancer patients (20). This effect size was based on the difference in VO_{2max} values between the cancer survivors and the control group in their study. According to the calculation of the sample size to be included in the study, 5% type 1 error, two-way working power of at least 80 % and effect size is taken as 0.82 it was calculated that a total of 40 participants were required from 20 participants in each study arm.

RESULTS

In our study, 23 colorectal cancer survivors with a mean age of 52.09±11.66 years and 22 healthy individuals with a mean age of 47.82±10.29 years participated (p=0.201). The demographic characteristics between colorectal cancer survivors and healthy individuals were similar (p>0.05) except for height. The smoking history of colorectal cancer survivors and healthy individuals was similar (p=0.124) (Table 1).

Table 1. Demographic and clinical characteristics of colorectal cancer survivors and healthy individuals.

Variables	Colorectal cancer survivors (n=23)	Healthy individuals (n=22)	p
Age (year)	52.09±11.66	47.82±10.29	.201
Weight (kg)	74.96±11.49	81.18±10.99	.070
Height (cm)	168±8.46	172.82±5.61	**.030***
BMI (kg/m²)	26.7±4.95	27.09±2.71	.749
Smoking (package*year)	12.43±17.87	5.64±9.92	.124
Diagnosis (n)			
Colon CA	19	N/A	N/A
Rectal CA	4	N/A	N/A
Treatment (n)			
Chemotherapy	1	N/A	N/A
Surg.	5	N/A	N/A
Surg. and Chemo.	10	N/A	N/A
Surg. Chemo. and RT	7	N/A	N/A

kg: Kilogram, cm: Centimeter, m^2: Square meter, BMI: Body mass index, CA: Cancer, Surg.:Surgical, Chemo: Chemotherapy, RT: Radiotherapy, *Student t test p<0.05.

According to the IPAQ-SF, PA levels were similar in both groups (p>0.050). According to the BFI, the total fatigue score was found to be higher in colorectal cancer survivors compared to healthy individuals (p<0.05). Among the BFI subscales, scores of general activity, mood, walking ability, and work were found to be higher in colorectal cancer survivors (p<0.05) (Table 2).

Table 2. Physical activity level and fatigue impacts of colorectal cancer survivors and healthy individuals.

Variables	Colorectal cancer survivors (n=23)	Healthy individuals (n=22)	p
IPAQ-SF vigorous (MET min/week)	580.87±1484.21	333.33±721.04	0.492
IPAQ-SF moderate (MET min/week)	1202.61±1645.21	924.76±2155.48	0.631
IPAQ-SFwalking (MET min/week)	1747.57±1899.29	997.43±1008.15	0.114
IPAQ-SFtotal (MET min/week)	3531.48±2605.21	2258.52±2373.7	0.099
IPAQ-SFsitting (min/week)	339.13±164.42	300±135.5	0.397
Brief Fatigue Inventory			
Total score	31.64±21.66	16.14±11.25	**0.005***
General activity	2.26±2.56	0.59±1.14	**0.008***
Mood	2.57±2.87	0.91±2.02	**0.031***
Walking ability	2.26±2.67	0.73±1.45	**0.022***
Normal work	2.3±2.69	0.73±1.28	**0.017***
Relations with other people	1.48±2.17	0.5±1.14	0.067
Enjoyment of life	2.04±2.51	0.73±1.78	0.050

IPAQ-SF: International Physical Activity Questionnaire-short form, MET: Metabolic equivalent, *Student t test p<0.05.

Baseline test SBP were similar in the two groups (p=0.517), whereas post-test SBP were lower in colorectal cancer survivors (p=0.007). Diastolic blood pressure (DBP) levels were similar between the groups both baseline and post-test (p=0.907, p=0.239). In parallel with this situation, ΔSBP values was lower in colorectal cancer survivors compared to healthy individuals (p=0.010), while ΔDBP values was similar in both groups (p=0.151). According to the exercise test results, VO_{2peak} levels were lower in colorectal cancer survivors (p<0.001). HRrest was similar in both groups (p=0.681). HRR and HRR_{1min} were similar in both groups (p=0.201, p=0.383). ΔHR values was lower in colorectal cancer survivors (p=0.045) (Table 3). The reduced ΔHR was physiologically reflected in the HRpeak, which was numerically lower in colorectal cancer survivors (156.39±19.35 bpm) than in healthy individuals (165.55±15.04 bpm). Although the mean this difference did not reach statistical significance (p=0.084), the lower CI definitively captures the functional failure of the heart to adequately utilize its reserve capacity. The CI calculation explicitly normalizes the ΔHR to the predicted Heart Rate Reserve, making it a superior and more sensitive measure for detecting chronotropic impairment. Furthermore, HRR1min was found to be similar between the two groups (17.43±8.4 bpm vs. 19.59±8.00 bpm, p=0.383). While HRR1min is often used as a marker of vagal tone, the lack of difference, in contrast to the significant CI finding, suggests that the primary site of autonomic impairment in this group may be related to sympathetic activation failure during the exercise stress phase, rather than a delayed vagal reactivation after exercise. This finding underscores the importance of the CI as the most pertinent indicator of cardiotoxicity in colorectal cancer survivors.

Table 3. Cardiopulmonary exercise test results of colorectal cancer survivors and healthy individuals.

Variables	Colorectal Cancer Survivors (n=23)	Healthy individuals (n=22)	p
Baseline-test SBP (mmHg)	111.74±11.44	114.09±12.69	0.517
Post-test SBP (mmHg)	139.35±12.55	151.36±15.90	**0.007***
Baseline-test DBP (mmHg)	73.7±6.43	73.41±9.68	0.907
Post-test DBP (mmHg)	83.7±7.26	87.5±13.34	0.239
VO_{2peak} (ml/min)	1865.22±479.44	2476.59±521.5	**<0.001***
VO_{2peak}/kg (ml/kg/min)	24.84±5.15	30.77±7.08	**0.002***
$HR_{Resting}$ (bpm)	87.83±18.64	85.77±13.7	0.681
HR_{peak} (bpm)	156.39±19.35	165.55±15.04	0.084
HR_{peak} (%pred)	93.13±8.77	96.04±6.15	0.201
Chronotropic index	85.88±17.78	93.14±11.65	0.114
HRR_{1min} (bpm)	17.43±8.4	19.59±8.00	0.383
ΔHR (bpm)	68.56±18.40	79.77±17.95	**0.045***
ΔSBP (mmHg)	27.61±11.86	37.27±12.02	**0.010***
ΔDBP (mmHg)	10.00±8.12	14.09±10.54	0.151
HRR (bpm)	11.52±14.36	6.64±10.50	0.201

SBP: Systolic blood pressures, DBP: Diastolic blood pressures, VO_2: Oxygen uptake, %pred: percentage of predicted value, HR: heart rate, bpm: beats per minute, HRR: Heart rate reserve, HRR_{1min} :Heart rate recovery in the first minute after test, * Student t test p<0.05.

The categorical comparison of cardiac autonomic function status between the two groups is presented in Table 4. The Chi-Square test showed a significant difference in the prevalence of CI between colorectal cancer survivors and healthy controls. CI < 80% was presented in 11 of 23 colorectal cancer survivors (47.83%) but only in 3 of 22 healthy individuals (13.64%), indicating a statistically significant difference (p = 0.01). This finding strongly supports the hypothesis that colorectal cancer survivors, years after treatment, exhibit a higher rate of impaired cardiac autonomic response, a critical indicator of subclinical cardiotoxicity.

Table 4. Chronotropic index results of colorectal cancer survivors and healthy individuals.

Variables	Colorectal Cancer Survivors (n=23)	Healthy individuals (n=22)	p
Chronotropic index <80	11 (47.83%)	3 (13.64%)	**0.001***
Chronotropic index ≥80	12 (52.17%)	19 (86.36%)	**0.008***

* Chi-square test p<0.05.

DISCUSSION

The main findings of this study were that VO_{2peak}, the gold standard objective measure of cardiorespiratory fitness and exercise capacity, was significantly lower, and chronotropic insufficiency was more common in colorectal cancer survivors. VO_{2peak} precisely reflects the integrated maximal ability of the body to transport and utilize oxygen, whereas exercise tolerance is more broadly defined as the clinical ability to perform and sustain physical activity. A reduced VO_{2peak} is recognized as a primary physiological determinant and objective marker of poor exercise capacity and clinical exercise intolerance. Our findings, consistent with previous research, demonstrate a statistically significant reduction in maximal oxygen consumption and, consequently, reduced exercise capacity compared to healthy controls. Our finding that nearly half of the survivors (47.83%) exhibited CI, compared with only 13.64% of healthy controls (p=0.01), highlights a significant functional impairment of the cardiac response to exercise. We acknowledge that this study did not include clinical measures of structural cardiotoxicity (e.g., echocardiographic evidence of reduced ejection fraction). Therefore, we do not claim that CI is a direct clinical finding of cardiotoxicity in our patients. Instead, we propose that CI serves as a sensitive, functional surrogate marker of subclinical cardiotoxicity and/or autonomic nervous system dysfunction induced by cancer treatment. The association between chemotherapy and CI is well-established in cardiotoxicity literature. Agents commonly used in colorectal cancer treatment (such as 5-fluorouracil, platinum compounds, and anthracyclines, which may have been used in neoadjuvant settings) can cause direct myocardial damage and microvascular injury, leading to reduced cardiac output reserve (21). This damage may impair the functional capacity of the cardiac autonomic nervous system, either by affecting the sinus node directly or altering the sympathetic/parasympathetic balance. Since CI is defined as the heart's failure to increase its rate during exercise, it is a definitive functional sign of reduced cardiac reserve and, specifically, reduced sympathetic drive, which is the functional result of the cardiotoxic insult (7, 10). Therefore, we can strongly conclude that the significantly higher prevalence of CI in our patient group is a manifestation of residual subclinical cardiotoxicity following their cancer therapy, representing a compromised cardiovascular system that lacks the reserve capacity to meet the stress of maximal exertion.

Cardiotoxicity can manifest as heart muscle damage, arrhythmia, cardiac ischemia, or impaired vagal tone, indicating autonomic dysfunction (4). Studies have shown that chronotropic insufficiency is a predictor of adverse prognosis and increased cardiovascular morbidity (10). In our study, chronotropic insufficiency was presented in 13.64% of healthy individuals, while chronotropic insufficiency was seen in 47.83% of colorectal cancer survivors and the difference was found to be statistically significant. Existing literature also indicates an increase in resting HR among cancer patients (22). Furthermore, both SBP and HR responses to exercise were statistically lower in colorectal cancer survivors compared to healthy controls, consistent with previous findings of abnormal cardiac autonomic dysfunction in individuals treated for cancer (11). Although colorectal cancer survivors in our study exhibited a relatively higher resting HR compared to healthy individuals, this difference did not reach statistical significance.

The overall reduction in exercise capacity may not be solely attributed to cardiac factors. Cramer et al. suggested that the decrease in maximal oxygen consumption could be attributed to be a mild decrease in left ventricular ejection fraction, a significant decrease in heart rate variability, reduced in lean mass in the legs, a decrease in hemoglobin, endothelial dysfunction, and inflammatory activation (20). The blunted systolic blood pressure response (ΔSBP) observed in the survivor group further supports the notion of peripheral involvement, potentially indicating reduced systemic vascular function or underlying endothelial dysfunction that restricts blood flow to working muscles. Autonomic dysfunction, fatigue, and reduced ability to participate in physical activities requiring higher metabolic demands also contribute to the decrease in cardiovascular fitness (23).

Fatigue is one of the most common symptoms in cancer patients and survivors of cancer treatment (20). In our study, colorectal cancer survivors reported higher total scores on the Brief Fatigue Inventory, and a more significant impact of fatigue on general mood, work, and walking abilities. While previous studies have suggested that fatigue contributes to declines in quality of life and decreased physical activity levels, our findings show that physical activity levels (IPAQ) were similar between colorectal cancer survivors and healthy individuals (24, 25). This similarity physical activity finding, despite the high fatigue scores in survivors, warrants further context. The high Total MET scores suggest that this group may represent highly motivated individuals who are actively striving to meet or exceed recommended exercise guidelines to improve their prognosis and manage late effects. This intense motivation and adherence to a healthy lifestyle may mask the underlying objective deficits in VO_{2peak} and CI which were revealed by the objective CPET assessment. Exercise training has been recognized as safe, tolerable and effective for alleviating fatigue and improving cardiovascular fitness, body composition, physical function, strength and quality of life in patients with cancer (26). However, there is a risk of exercise overdose if exercise intensity is prescribed using only age-estimated maximum heart rate in patients with autonomic dysfunction, especially in cancer survivors (27). Our finding of high CI prevalence highlights the need for clinicians to use CPET-derived parameters, such as the ventilatory threshold or a CI-corrected HRpeak, to safely and effectively prescribe exercise intensity.

In conclusion, colorectal cancer survivors demonstrate significantly lower VO_{2peak} compared to healthy individuals. This impaired capacity is strongly associated with a high prevalence of CI, which is considered a functional indicator of subclinical cardiotoxicity. Our findings support the importance of screening for CI in post-cancer follow-up using routine CPET or simple heart rate parameters.

Limitations

The primary constraint of our study is the limited scope of autonomic function assessment. While we evaluated chronotropic response, resting heart rate, and maximal heart rate data, the lack of heart rate variability (HRV) data prevents a more comprehensive understanding of the cardiac autonomic response, particularly the balance between sympathetic and parasympathetic nervous system activity. Future studies, including HRV assessment, will yield better results in this regard. Another limitation stems from the reliance on self-reported questionnaires (SF-IPAQ and BFI) for physical activity and fatigue assessment. Self-reported physical activity, while practical, is prone to recall bias and may lead to an overestimation of actual activity levels, potentially explaining why the objective VO_{2peak} was low despite similar reported PA levels across groups. Finally, our exclusion criteria, specifically the exclusion of patients with pre-existing cardiac disease, may have led to the inclusion of a relatively healthier survivor group, potentially underestimating the true prevalence and severity of cardiotoxicity in the general population of colorectal cancer survivors.

The strength of our study, however, is that we assessed exercise intolerance with CPET, which remains the gold standard for measuring cardiorespiratory fitness.

CONCLUSION

Cancer survivors often demonstrate reduced exercise capacity and increased fatigue. One of the various reasons for this is inadequate cardiac response to exercise due to cardiotoxicity. Therefore, we recommend that patients in this group should be evaluated with cardiopulmonary exercise test, if possible, before exercise training and exercise plan should be made according to these results.

Author Contributions:

MFS: Conceptualization, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization. MS: Validation, Investigation, Writing – Review & Editing. EÇ: Writing – Review & Editing. SK: Resources, Methodology. NVY: Supervision, Project Administration, Methodology, Validation, Investigation.

Financial Support: The authors declare that they have no competing financial or non-financial interests directly or indirectly related to the work submitted for publication. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest: The author(s) state that there are no potential conflicts of interest concerning the research, writing, and/or publication of this article.

Ethical approval: This study was approved by Hacettepe University Faculty of Physical Therapy and Rehabilitation Research Ethics Committee on 24/10/2024 (FTREK24/97).

How to cite this article: Sanver M. F, Sağlam M, Çalık E, Kılıçkap S, Vardar Yağlı N. Investigation of Chronotropic Response and Exercise Intolerance in Colorectal Cancer Survivors. Journal of Hacettepe University Physical Therapy and Rehabilitation. 2026;4(1),14-21.

REFERENCES

1. Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. CA Cancer J Clin. 2023;73(3):233-54.
2. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018;68(1):31-54.
3. Toohey K, Pumpa KL, Arnolda L, Cooke J, Yip D, Craft PS, et al. A pilot study examining the effects of low-volume high-intensity interval training and continuous low to moderate intensity training on quality of life, functional capacity and cardiovascular risk factors in cancer survivors. PeerJ. 2016;4:e2613.
4. De Couck M, Gidron Y. Norms of vagal nerve activity, indexed by Heart Rate Variability, in cancer patients. Cancer Epidemiol. 2013;37(5):737-41.
5. Koelwyn GJ, Jones LW, Moslehi J. Unravelling the causes of reduced peak oxygen consumption in patients with cancer: complex, timely, and necessary. J Am Coll Cardiol. 2014;64(13):1320-2.
6. Bonsignore A, Marwick TH, Adams SC, Thampinathan B, Somerset E, Amir E, et al. Clinical, Echocardiographic, and Biomarker Associations With Impaired Cardiorespiratory Fitness Early After HER2-Targeted Breast Cancer Therapy. JACC CardioOncol. 2021;3(5):678-91.
7. Yoon SY, Oh J. Cardiovascular Autonomic Dysfunction Before and After Chemotherapy in Cancer Patients. J Clin Neurol. 2024;20(6):551-62.
8. Lakoski SG, Jones LW, Krone RJ, Stein PK, Scott JM. Autonomic dysfunction in early breast cancer: Incidence, clinical importance, and underlying mechanisms. Am Heart J. 2015;170(2):231-41.
9. Bertrand E, Caru M, Lemay V, Andelfinger G, Laverdiere C, Krajinovic M, et al. Heart rate response and chronotropic incompetence during cardiopulmonary exercise testing in childhood acute lymphoblastic leukemia survivors. Pediatr Hematol Oncol. 2021;38(6):564-80.
10. Paolillo S, Agostoni P, De Martino F, Ferrazzano F, Marsico F, Gargiulo P, et al. Heart rate during exercise: mechanisms, behavior, and therapeutic and prognostic implications in heart

failure patients with reduced ejection fraction. Heart Fail Rev. 2018;23(4):537-45.
11. Groarke JD, Tanguturi VK, Hainer J, Klein J, Moslehi JJ, Ng A, et al. Abnormal exercise response in long-term survivors of hodgkin lymphoma treated with thoracic irradiation: evidence of cardiac autonomic dysfunction and impact on outcomes. J Am Coll Cardiol. 2015;65(6):573-83.
12. Arab C, Dias DP, Barbosa RT, Carvalho TD, Valenti VE, Crocetta TB, et al. Heart rate variability measure in breast cancer patients and survivors: A systematic review. Psychoneuroendocrinology. 2016;68:57-68.
13. Ness KK, Plana JC, Joshi VM, Luepker RV, Durand JB, Green DM, et al. Exercise Intolerance, Mortality, and Organ System Impairment in Adult Survivors of Childhood Cancer. J Clin Oncol. 2020;38(1):29-42.
14. Vigo C, Gatzemeier W, Sala R, Malacarne M, Santoro A, Pagani M, et al. Evidence of altered autonomic cardiac regulation in breast cancer survivors. J Cancer Surviv. 2015;9(4):699-706.
15. Saglam M, Arikan H, Savci S, Inal-Ince D, Bosnak-Guclu M, Karabulut E, et al. International physical activity questionnaire: reliability and validity of the Turkish version. Percept Mot Skills. 2010;111(1):278-84.
16. Azak A, Çınar S. Lenfomalı (hodgkin ve non-hodgkin) hastalarda yorgunluk sendromu ve etkileyen faktörler. Turk J Hematol Oncol. 2005;15:78-83.
17. American Thoracic S, American College of Chest P. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211-77.
18. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. Ann Intern med. 2000;132(7):552-5.
19. Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA. 1999;281(6):524-9.
20. Cramer L, Hildebrandt B, Kung T, Wichmann K, Springer J, Doehner W, et al. Cardiovascular function and predictors of exercise capacity in patients with colorectal cancer. J Am Coll Cardiol. 2014;64(13):1310-9.
21. Viale PH, Yamamoto DS. Cardiovascular toxicity associated with cancer treatment. Clin J Oncol Nurs. 2008;12(4):627-38.
22. Grote S, Ricci JM, Dehom S, Modeste N, Sealy DA, Tarleton HP. Heart Rate Variability and Cardiovascular Adaptations Among Cancer-Survivors Following a 26-Week Exercise Intervention. Integr Cancer Ther. 2020;19.
23. Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. Ann Oncol. 2015;26(2):272-8.
24. Wagner LI, Cella D. Fatigue and cancer: causes, prevalence and treatment approaches. Br J Cancer. 2004;91(5):822-8.
25. Velthuis MJ, May AM, Koppejan-Rensenbrink RA, Gijsen BC, van Breda E, de Wit GA, et al. Physical Activity during Cancer Treatment (PACT) Study: design of a randomised clinical trial. BMC Cancer. 2010;10:272.
26. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. Med Sci Sports Exerc. 2019;51(11):2375-90.
27. Zimmerman A, Planek MIC, Chu C, Oyenusi O, Paner A, Reding K, et al. Exercise, cancer and cardiovascular disease: what should clinicians advise? Cardiovasc Endocr Me. 2021;10(2):62-71.