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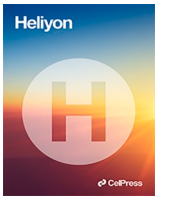

Research article

Increased stress burden and electrodermal reactivity in bladder cancer patients in comparison to healthy controls

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ABSTRACT

The purpose of our study was to assess specific physiological parameters associated with stress responses in bladder cancer (BCa) patients compared to healthy individuals. By examining the transition from a supine to a sitting position, representing a mild physiological load, we investigated the changes in autonomic nervous system (ANS) activity as reflected by alterations in these parameters, indicating shifts in ANS regulation, using non-linear heart rate variability (HRV) parameters (0V%, 2UV%, parasympathetic and sympathetic nervous system – PNS and SNS indices), modified heart rate acceleration (ACmod) and deceleration capacities (DCmod), heart rate (HR), electrodermal activity (EDA), and also their correlations with perceived stress score. Our findings showed that BCa patients (n = 38) exhibited elevated resting HR, heightened SNS index, and increased EDA compared to their healthy counterparts (n = 47), indicating a notable physiological stress burden. The 0V% parameter showed a positive association with the SNS index, ACmod, HR, and EDA parameters, while displaying a negative correlation with the PNS index, DCmod and 2UV%. These non-linear HRV parameters, such as 0V% and 2UV%, offer nuanced insights into the complexities of heartbeat dynamics and autonomic regulation. After the transition from supine to sitting positions, BCa patients displayed higher EDA responses, indicating heightened stress reactivity and ANS sensitivity. These physiological distinctions persisted even when we did not prove differences in the levels of perceived stress between the studied groups. In conclusion, our study emphasizes the significance of identifying cancer patients at risk of ANS dysregulation, paving the way for tailored stress management strategies.

1. Introduction

Bladder cancer (BCa) is the most common malignancy of the urinary tract and ranks as the 12th most common type of cancer diagnosed globally for both sexes combined [1]. Urothelial bladder cancer limited to the mucosa (NMIBC - non-muscle-invasive BCa) is

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diagnosed in 75 % of cases [2]. It is characterized by frequent recurrences (with a 5-year recurrence rate of 50–70 %) and a high risk of disease progression (with a 5-year progression rate of 10–30 %) [3]. Advanced age (>65 years), male sex, smoking history, obesity, and other metabolic influences have been identified as demographic and clinical factors associated with increased risk of BCa initiation and progression [4].

In addition to surgical intervention, there are multiple therapeutic approaches to prevent disease progression and recurrences, such as BCG immunotherapy or intravesical chemotherapy. However, the risk of BCa recurrence or progression is not negligible and represents a significant burden on society, currently impacting the most developed communities worldwide [5]. BCa is the most expensive malignancy to treat from diagnosis to death and financial toxicity, or the excess financial difficulties caused by treatment, has a significant impact not only on patient well-being but also on oncologic outcomes [6].

One of the factors that could play a role in the disease progression is psychological stress and its effects via the autonomic nervous system [7]. Chronic stress contributes to cancer initiation and progression by influencing virtually all cancer hallmarks. Both experimental and clinical studies indicate that an imbalanced autonomic nervous system (ANS) plays a role in shaping the trajectory of tumorigenesis [7].

It has been proven that higher levels of psychological stress are associated with higher mortality in patients with colorectal cancer and prostate cancer [8], as well as increased lung cancer mortality [9]. Additionally, it has been revealed that the stress associated with a cancer diagnosis, along with the anxiety and fear regarding the consequences of the disease and its treatment on life and health, leads to a worse prognosis in breast cancer patients [10].

Lower heart rate variability (HRV), often accompanied by sympathetic predominance, indicates autonomic dysregulation [11,12]. Conversely, enhanced HRV supports an effective autonomic-cardio-respiratory equilibrium, facilitating energy conservation for regenerative processes during and post-treatment phases [11]. While several studies have shown altered HRV patterns in breast cancer patients [12–14], this phenomenon has yet to be comprehensively elucidated in patients with bladder tumors.

Linear HRV parameters alone are no longer considered sufficient for comprehensive assessing autonomic control and activity during short-time series commonly observed in exercise physiology [15–18]. Non-linear indices provide the means to investigate the intricate and multifaceted fluctuations arising from the complex interplay of variables related to hemodynamics, electrophysiology, humoral factors, and the regulations of both the ANS and CNS [19,20]. Beside other non-linear approaches, symbolic dynamics (as suggested by Porta et al.) may be used, providing reliable non-respiratory-associated parameters to detect ANS activity modulations in laboratory physical activity settings [16,21]. In a study by Majerova et al., non-linear parameters demonstrated greater sensitivity than linear methods in breast cancer patients, suggesting that non-linear indices may more effectively capture the complexity, irregularity, and dynamic characteristics of the HRV signal [12]. Symbolic dynamics involves converting sequences of RR intervals into discrete symbols based on predefined levels of variation. Two of these parameters, 2UV% and 0V%, characterize distinct facets of heartbeat dynamics. The 2UV% parameter indicates the percentage of sequences containing three heart periods with two dissimilar variations, thereby offering insights into cardiovagal modulation. Conversely, the 0V% parameter, denoting zero variation, reflects HR fluctuations modulated by sympathetic activity. This method allows for a detailed analysis of how different levels of variation in RR intervals correspond to specific autonomic modulations, enhancing our understanding of ANS activity in different physiological states [22,23].

Neuroimaging studies suggest links between HRV and subcortical regions like hypothalamus and amygdala, as well as ventromedial prefrontal cortex, which are associated with stress responses [24]. Psychological stressors, like cancer-related fear, can lead to individual autonomic variations, potentially involving increased sympathetic activation and vagal withdrawal [25,26].

Electrodermal activity (EDA) represents changes in the electrical conductance of the skin and serves as a measure of sympathetic neuronal activity [27]. Physiological changes in HRV and electrodermal activity are influenced by various factors, including fluctuations in blood pressure, respiration, thermoregulation, circadian rhythms, and emotional and behavioral responses [20,28]. It is well established that increased HR and EDA, measured as skin conductance level and/or non-specific skin conductance responses, can function as markers of physiological arousal and responses to internal and external stimuli [29].

Our work aimed to compare the basal levels of physiological stress indicators in bladder cancer patients and healthy individuals, as well as to identify the differences in these studied variables under mild physiological load. The physiological responses were evaluated in supine and sitting position, monitoring both positions using simultaneous electrocardiogram (ECG) and electrodermal activity recordings. This analysis included an exploration of the intricate interrelationships among selected HRV parameters known to be associated with the sympathetic and parasympathetic branches of ANS, including HR, symbolic dynamics parameters 0V%, and 2UV% [30,31], as well as indices of sympathetic nervous system activity (SNS, ACmod) and parasympathetic nervous system activity (PNS, DCmod) from Kubios software. We included symbolic dynamics with the intention of assessing whether its parameters 0V% and 2UV %, could better reflect subtle changes connected with mild physiological load than the linear (ACmod, DCmod) or mixed (SNS, PNS index) parameters derived from Kubios analysis. Methodological and physiological differences between ACmod, DCmoc, 0V% and 2UV% and other autonomic markers such as PNS and SNS index are described more detail in the methods. In addition, electrodermal activity, as measured by the overall mean of skin conductance level and count of non-specific skin conductance responses, was examined.

The second aim was to establish correlations between levels of psychological stress, gauged through the use of the Perceived Stress Scale questionnaire (PSS-10), and the selected HRV parameters and EDA.

2. Methods

2.1. Participants and study design

The study employed a cross-sectional comparative data collection design. A total of 85 participants aged 18 years and older were recruited between November 2021 and February 2023. Among these, 38 were patients undergoing transurethral resection (TUR) for a bladder tumor at the Urology Clinic of St. Cyril and Methodius Hospital in Bratislava, Slovakia. The study also included 47 healthy controls who were recruited from the local community and assessed at the Institute of Immunology, Faculty of Medicine, Comenius University in Bratislava.

The patient cohort comprised individuals with pathologically diagnosed urothelial papillary carcinoma of the bladder, encompassing a range of disease stages spanning from pTa to pT3 and CIS, and grades from low to high. These patients had undergone TUR as their primary therapeutic intervention. Exclusion criteria included individuals diagnosed with diabetes mellitus, heart conditions such as coronary artery disease, left ventricular hypertrophy, valvular heart disease, or those with a cardiac pacemaker implant. Additionally, participants with other oncology diseases, those taking cardiac glycosides, anti-arrhythmic drugs, selective serotonin reuptake inhibitors, or atropines were excluded. Individuals with incomplete electrodermal data, poor ECG quality, or those exhibiting more than 10 percent ectopic beats were also excluded. After the data were collected, one participant from healthy controls group was excluded due to using antipsychotic medication. The analysis was performed with 84 participants. Ethical approval for the study (125/2021) was obtained from the Ethics Committees of both the Hospital of St. Cyril and Methodius and Comenius University in Bratislava. Written informed consent was obtained from all individuals who participated in the study. The research was carried out according to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.2. Collection of clinical and psychological data

2.2.1. HRV data

ECG recordings for HRV were obtained from both patients and healthy participants during a resting period. This recording spanned a sequence of postures, including 5 min in the supine position, followed by 5 min of sitting. Data acquisition was conducted using a Bittium Faros 180 ECG device (Bittium Biosignals Ltd, Finland), with two electrodes placed at the right first and left fifth intercostal spaces at the midclavicular line. Before electrode placement, the skin area was prepared with ethanol. A sampling rate of 1000 Hz was employed for capturing the electrical signal.

To extract R–R intervals, measured in milliseconds (ms), the Kubios HRV Premium Version 3.5.0 software (Kubios Oy, Finland) automatically identified the R peak of the QRS complex within the ECG signal and subsequently analyzed the HRV parameters. The assessment of ANS balance and activity encompassed the analysis of variation, acceleration and deceleration capacity of HR and the exploration of non-linear parameters derived from symbolic dynamics (0V%, 2UV%), as well as HRV indices including the SNS tone index and PNS tone index. These approaches quantified the degree of variability in the time intervals between consecutive heartbeats. The symbolic dynamics parameters, specifically 2UV% and 0V%, characterize cardiovagal and sympathetic modulation, respectively. R software was used to convert RR intervals into a series of symbols and classify patterns in symbolic dynamics. The core principle involves spreading the chosen RR sequence over a fixed number of predefined levels, which are thresholds based on the magnitude of change between consecutive RR intervals. This transformation generates short patterns that are classified according to the direction of variation of the successive RRs (e.g. 2UV% and 0V%), and their rates of occurrence are evaluated, allowing to study short-term HRV pattern behavior [21].

Deceleration capacity (DC) of heart rate is a measure of cardiac parasympathetic modulation as it captures the lengthening of RR interval within 2–4 successive beats. Acceleration capacity (AC) of heart rate captures the opposite, i.e. shortening of RR interval within few successive beats. In this work, the deceleration and acceleration capacity of the heart rate is evaluated using modified indices (DCmod, ACmod), which should better capture the instantaneous deceleration and acceleration of the heart rate compared to the originally proposed parameters [32,33].

The PNS and SNS tone indices provide estimations of ANS activity relative to normal resting values. Calculated using linear and non-linear methodologies, these indices assess the complexity and variability of RR intervals within the time series. The calculation involves generating a Poincaré plot, which is a scatter plot of RR intervals against subsequent RR intervals, and subsequently quantifying specific features linked to the asymmetry of Poincaré plot indices, such as SD1, SD2, SD1/SD2 ratio, or approximate entropy. Additionally, normal values for Mean RR, RMSSD, and stress index contribute to the computation of PNS and SNS indices. The PNS index reflects vagal influence, resulting in a decrease in HR and an increase in HRV. Conversely, the SNS index indicates an elevation in HR and a reduction in HRV [32,34,35].

From a methodological perspective, ACmod and DCmod focus on short-term heart rate changes, capturing immediate autonomic responses through the analysis of instantaneous acceleration and deceleration of the heart rate. These modified indices provide a more precise measurement of short-term autonomic modulation compared to traditional linear HRV indices [36,37]. In contrast, the 0V% and 2UV% parameters from symbolic dynamics emphasize the patterns of RR interval sequences, reflecting sympathetic and cardiovagal modulation, and the non-linear aspects of heart rate dynamics [30]. Physiologically, ACmod and DCmod offer detailed insights into rapid autonomic adjustments, while the PNS and SNS indices provide a broader view of sustained autonomic balance and overall ANS tone, with the PNS index indicating vagal influence and the SNS index reflecting sympathetic dominance [34]. These differences highlight the complementary nature of these measures, while ACmod and DCmod offer detailed insights into transient autonomic responses, the PNS and SNS indices provide a comprehensive assessment of sustained autonomic regulation and balance

over time.

2.2.2. Electrodermal activity

EDA was assessed during the ECG recording. This assessment utilized the eVu-TPS (Triple-Physiology sensor) device, which was positioned on the middle finger of the participant's non-dominant hand. To prevent skin drying, which could compromise the electrodermal activity signal, neither ethanol nor conductive gel was utilized for skin preparation. The TPS sensor was Bluetooth-paired with a laptop running the BioGraph Infiniti software, developed by Thought Technology Ltd. in Canada, which facilitated the analysis of the recorded data. The sampling rate for electrodermal activity was set at 32 Hz. The software calculated statistical parameters of electrodermal activity, namely the mean of skin conductance level (SCL) (measured in microsiemens, μS), and the number of non-specific skin conductance responses (nsSCR). A comprehensive manual review was conducted to identify and eliminate any conspicuous artifacts from the skin conductance data.

2.2.3. Psychological assessment

We measured perceived stress via the PSS-10 scale [38]. This scale assesses experienced stress using 10 items which refer to the participants' experiences of life as unpredictable, uncontrollable, and overwhelming. Some of the items are reverse-scored. The resulting PSS scores range from 0, indicating an absence of perceived stress, to 40, indicating a heightened level of stress [38].

2.3. Statistical analysis

Demographic and clinical features were concisely outlined through descriptive statistics, comprising means accompanied by their corresponding standard deviations (SD). For frequency data, these features were expressed as counts with associated percentages (%).

Table 1
Descriptive statistics in patients with bladder cancer and healthy controls.

	Whole sample (n = 84)	Bladder cancer (n = 38)	Healthy (n = 46)
General			
Age (years), (M, SD)	63.38 (11.67)	64.74 (9.79)	62.26 (13.02)
Gender (n, % of women)	33 (39.29 %)	14 (36.84 %)	19 (41.30 %)
BMI (M, SD)	27 (4.28)*	28.08 (4.98)	26.10 (3.40)
Perceived stress (PSS)	15.37 (5.74)	15.95 (5.50)	14.89 (5.95)
Study variables (supine)			
Heart rate (M, SD)	65.54 (10.86)*	68.61 (11.61)	62.99 (9.60)
HRV - 0V% (M, SD)	26.78 (13.33)	28.15 (14.60)	25.64 (12.23)
HRV - 2UV% (M, SD)	16.55 (9.13)	17.15 (10.72)	16.06 (7.66)
DCmod ms (M, SD)	26.60 (21.13)	24.27 (19.76)	28.53 (22.22)
ACmod ms (M, SD)	−25.47 (16.59)	−24.05 (15.81)	−26.63 (17.29)
PNS index (M, SD)	−0.38 (1.04)	−0.62 (1.06)	−0.19 (0.98)
SNS index (M, SD)	1.24 (1.69)*	1.68 (1.82)	0.88 (1.50)
Skin conductance level (M, SD)	1.34 (0.93)	1.55 (1.23)	1.18 (0.52)
Non-specific skin conductance response count (M, SD)	3.57 (6.71)*	5.68 (9.06)	1.83 (2.95)
Study variables (sitting)			
Heart rate (M, SD)	70.95 (11.34)	72.79 (13.36)	69.44 (9.23)
HRV - 0V% (M, SD)	33.75 (14.70)	35.91 (16.37)	31.96 (13.07)
HRV - 2UV% (M, SD)	14.81 (9.24)	14.34 (9.36)	15.19 (9.22)
DCmod ms (M, SD)	20.78 (14.77)*	16.70 (9.04)	24.16 (17.59)
ACmod ms (M, SD)	−20.77 (13.57)*	−17.51 (9.83)	−23.47 (15.61)
PNS index (M, SD)	−0.86 (0.86)	−1.03 (0.93)	−0.71 (0.78)
SNS index (M, SD)	1.91 (1.94)	2.24 (2.29)	1.64 (1.58)
Skin conductance level (M, SD)	1.82 (1.32)*	2.18 (1.67)	1.53 (0.85)
Non-specific skin conductance response count (M, SD)	11.96 (12.97)*	17.00 (15.22)	7.79 (8.99)
Study variables (delta)			
Heart rate (M, 95%CI)	0.09 [0.07; 0.10]*	0.06 [0.04; 0.08]	0.11 [0.08; 0.13]
HRV - 0V% (M, 95%CI)	0.73 [0.34; 1.12]	0.97 [0.17; 1.77]	0.53 [0.27; 0.80]
HRV - 2UV% (M, 95%CI)	−0.01 [-0.14; 0.12]	−0.12 [-0.27; >-0.01]	0.08 [-0.13; 0.29]
DCmod ms (M, SD)	−0.09 [-0.24; - 0.05]	−0.22 [-0.31; −0.14]	0.01 [-0.24 - 0.26]
ACmod ms (M, SD)	−0.1 [-0.21; 0.01]*	−0.22 [-0.30; −0.13]	0 [-0.20; 0.19]
PNS index (M, 95%CI)	0.10 [-0.50; 0.70]	0.12 [-0.23; 0.46]	0.09 [-0.98; 1.56]
SNS index (M, 95%CI)	−1.59 [-5.36; 2.17]	0.52 [-0.27; 1.31]	−3.34 [-10.18; 3.50]
Skin conductance level (M, 95%CI)	0.34 [0.27; 0.41]*	0.42 [0.30; 0.53]	0.28 [0.20; 0.35]
Non-specific skin conductance response count (M, 95%CI)	3.38 [2.43; 4.34]	4.23 [2.43; 6.03]	2.68 [1.80; 3.56]

Note: BMI = body mass index; DCmod = Modified deceleration capacity of heart rate; ACmod = Modified acceleration capacity of heart rate; PSS = perceived stress scale; PNS = parasympathetic nervous system; SNS = sympathetic nervous system; HRV = heart rate variability; SCL = skin conductance level. Deltas for study variables are calculated as for example: $\Delta_{HR} = \frac{(HR_{sitting} - HR_{supine})}{HR_{supine}}$. The same formula was applied for all the other variables except nsSCR, where a constant 1 was added to the denominator to avoid dividing by 0. *$p \leq 0.05$ is considered significant.

Independent group comparisons were conducted using the Welch *t*-test, allowing for the evaluation of differences between the groups. To measure linear correlations between parameters in both supine and sitting positions, we computed the two-sided 95 % confidence interval for the Pearson correlation coefficient. Comparisons of bladder cancer patients and the healthy group in HRV and skin conductance in both supine and sitting positions were performed using two-way ANOVAs, with body position (supine or sitting) as repeated measures. The dataset underwent analysis employing the software JASP 0.15 (JASP Team, 2021)., in conjunction with IBM SPSS Statistics 21. Hypotheses tests were conducted with a type I error rate of 0.05 regarded as indicative of statistical significance.

3. Results

The entire sample included 84 people (33 women), with a mean (SD) age of 63.38 (11.67) years, ranging from 31 to 86 years. The mean (SD) BMI was 27 (4.28), ranging from 18.8 to 39.1. Among these participants, 38 had been diagnosed with bladder cancer and 46 were healthy controls. Table 1 shows the descriptives of the main study variables for both cancer patients and healthy controls.

Among all variables, patients with cancer had higher levels of BMI $t(63.24) = 2.08$; $p = 0.04$; $d = 0.46$; 95%CI [0.02; 0.90], higher levels of supine HR $t(71.79) = 2.38$, $p = 0.02$; $d = 0.52$; 95%CI [0.09; 0.96], a higher supine SNS index $t(71.98) = 2.17$, $p = 0.03$; $d = 0.48$; 95%CI [0.04; 0.92], higher skin conductance level in the sitting position $t(52.68 = 2.17$; $p = 0.03$; $d = 0.49$; 95%CI [0.05; 0.92], and more nsSCR in sitting position $t(57.45) = 3.28$; $p < 0.01$; $d = 0.74$; 95%CI [0.28; 1.18]. As the data in nsSCR were strongly positively skewed, non-parametric Mann-Whitney test was used for sensitivity analysis. In sitting position, the results were comparable to parametric test ($p < 0.01$), however, in supine position the results differed, as $t(43.50) = 2.52$; $p = 0.02$; $d = 0.57$; 95%CI [0.12; 1.02], while the non-parametric test resulted in $p = 0.05$.

On the contrary, healthy participants in siting position had higher values of modified deceleration capacity index (DCmod) $t(69.69) = -2.50$; $p = 0.01$; $d = -0.52$; 95%CI [−0.07; −0.96], and lower values of modified acceleration capacity index (ACmod) $t(76.98) = 2.13$; $p = 0.04$; $d = -0.45$; 95%CI [−0.89; 0.00]. The difference between patients and controls in perceived stress were not significant $t(80.93) = 0.84$; $p = 0.40$; $d = 0.18$; 95%CI [−0.25; 0.61].

Tables 2 and 3 display correlations between the main study variables in the supine and sitting positions. The HRV parameter of 2UV % correlated positively with the PNS index and DCmod in supine position and inversely with the HRV parameter of 0V%, HR, SNS index and ACmod in supine. As expected, perceived stress correlated positively with HR and the SNS index and negatively with the PNS index. Finally, the HRV parameter of 0V% correlated positively and significantly with the SNS index, nsSCR, ACmod and HR in the supine and also with the mean SCL in the sitting position, and negatively with 2UV%, DCmod and the PNS index in both positions. In the sitting position, there was also a significant mean SCL correlation with 0V%.

When examining the main study objective – the difference of studied variables between patients and healthy controls in the changes from supine to sitting positions we used a two-way ANOVA with body position (supine or sitting) as repeated measures. Here we present the results of the original model without covariates.

The summary of the main effects of group (bladder cancer patients/healthy controls) and position (supine/sitting) as well as the position × group interactions, is as follows: For HR, there was a significant main effect of position: $F(1, 82) = 107.87$, $p < 0.01$, $\eta_p^2 = 0.57$, and interaction between position and group: $F(1, 82) = 4.93$, $p = 0.03$, $\eta_p^2 = 0.06$. For 0V%, there was only a main effect of position: $F(1, 82) = 20.72$, $p < 0.01$, $\eta_p^2 = 0.20$, while the interaction was not significant $F(1, 82) = 0.22$, $p = 0.64$. For 2UV%, neither the main effects (data not shown) nor the interaction $F(1, 82) = 0.93$, $p = 0.34$, were significant. For HRV PNS and SNS indices, there was only a main effect of position (PNS: $F(1, 82) = 57.21$, $p < 0.01$, $\eta_p^2 = 0.41$; SNS: $F(1, 82) = 50.32$, $p < 0.01$, $\eta_p^2 = 0.38$). Finally, for mean SCL, we found a main effect of position: $F(1, 82) = 70.12$, $p < 0.01$, $\eta_p^2 = 0.46$; a main effect of group: $F(1, 82) = 4.59$, $p = 0.03$, $\eta_p^2 = 0.05$; and the interaction of both factors: $F(1, 82) = 5.57$, $p = 0.02$, $\eta_p^2 = 0.06$. For nsSCR count, we found a main effect of position: $F(1, 82) = 72.63$, $p < 0.01$, $\eta_p^2 = 0.47$; a main effect of group: $F(1, 82) = 12.0$, $p < 0.01$, $\eta_p^2 = 0.13$; and the interaction of both factors: $F(1, 82) = 6.96$, $p = 0.01$, $\eta_p^2 = 0.08$. However, due to strong positive skew in the nsSCRdata, we performed sensitivity analysis with ranks, which did not support the interaction effect: $F(1, 82) = 0.62$, $p = 0.43$. In the case of the DCmod and ACmod indices, we revealed only a main effect of position: $F(1, 82) = 10.75$, $p < 0.01$, $\eta_p^2 = 0.12$; resp. $F(1, 82) = 12.18$, $p < 0.01$, $\eta_p^2 = 0.13$.

In the sensitivity analysis, we also repeated the analysis with BMI as a covariate. This led to different results in following variables. The interaction between body position and group was no longer significant for HR. Instead, the interaction of body position and BMI was significant $F(1, 81) = 9.87$, $p < 0.01$, $\eta_p^2 = 0.11$, indicating BMI as potential confounding factor. Also, interaction between body position and BMI was observed in SNS index, $F(1, 81) = 4.40$, $p = 0.04$, $\eta_p^2 = 0.05$. The results of this sensitivity analysis and a comparison with the original results of the two-way ANOVAs are shown in the supplementary materials available at:
https://osf.io/5y2ag/?view_only=b8f77449c2a3448386f0a372d160f465.

Hence, only for HR and mean SCL were the patterns of changes from supine to sitting different between the groups. Therefore, we looked closer at the group differences in these two interactions, as shown in Figs. 1 and 2.

Bladder cancer patients show overall higher HR, mean SCL, and nsSCR (see Figs. 1 and 2). To compare the reactivity from the supine to the sitting position, we compared the increase in these variables[2] between patients and healthy controls. The increase from supine to sitting position is lower in patients only for HR: $t(80.87) = -3.04$, $p < 0.01$, $d = -0.66$, 95%CI [−1.10, −0.21]; while for SCL and ACmod the increase from supine to sitting position is higher in cancer patients than in healthy controls. SCL: $t(65.10) = 2.03$, $p =$

[2] Represented as delta value corrected for values in supine position: $\Delta_{HR} = \frac{(HR_{sitting} - HR_{supine})}{HR_{supine}}$. The same formula was applied for all the other variables except nsSCR, where a constant 1 was added to the denominator to avoid dividing by 0.

Table 2
Correlation matrix of variables in the supine position, Pearson correlation, and 95%CI.

	PSS	HR	0V%	2UV%	PNS	SNS	SCL mean	nsSCR count	DCmod
Perceived stress (PSS)	–								
Heart rate (HR)	**0.25 [0.03; 0.44]**	–							
0V%	0.11 [-0.10; 0.32]	**0.46 [0.28; 0.62]**	–						
2UV%	0.01 [-0.20; 0.22]	**−0.36 [-0.53; −0.15]**	**−0.75 [-0.83; −0.63]**	–					
PNS index	**−0.27 [-0.45; −0.05]**	**−0.89 [-0.92; −0.83]**	**−0.57 [-0.70; −0.41]**	**0.45 [0.26; 0.61]**	–				
SNS index	**0.28 [0.07; 0.47]**	**0.84 [0.76; 0.89]**	**0.46 [0.27; 0.61]**	**−0.23 [-0.43; −0.02]**	**−0.87 [-0.91; −0.81]**	–			
SCL mean	−0.05 [-0.26; 0.16]	**0.38 [0.18; 0.55]**	0.21 [-0.01; 0.41]	−0.20 [-0.40; 0.01]	**−0.30 [-0.48; −0.09]**	**0.23 [0.01; 0.42]**	–		
nsSCR count	0.03 [-0.18; 0.25]	**0.36 [0.16; 0.54]**	**0.29 [0.06; 0.46]**	−0.21 [-0.40; 0.01]	**−0.31 [-0.49; −0.11]**	**0.23 [0.02; 0.44]**	**0.69 [0.55; 0.78]**	–	
DCmod	**−0.26 [-0.45; −0.04]**	**−0.48 [-0.63; −0.29]**	**−0.47 [-0.62; −0.28]**	**0.24 [0.03; 0.43]**	**0.79 [0.70; 0.86]**	**−0.69 [-0.79; −0.56]**	−0.09 [-0.30; 0.13]	−0.14 [-0.34; 0.08]	–
ACmod	0.21 [-0.01; 0.40]	**0.50 [0.32; 0.65]**	**0.53 [0.36; 0.67]**	**−0.30 [-0.48; −0.09]**	**−0.81 [-0.87; −0.72]**	**0.74 [0.62; 0.82]**	0.13 [-0.09; 0.33]	0.17 [-0.04; 0.37]	**−0.95 [-0.97; −0.93]**

Table 3
Correlation matrix of variables in the sitting position, Pearson correlation, and 95%CI.

	PSS	HR	0V%	2UV%	PNS	SNS	SCL mean	nsSCR count	DCmod
Perceived stress (PSS)	–								
Heart rate (HR)	0.17 [-0.04; 0.37]	–							
0V%	−0.03 [-0.24; 0.19]	**0.38 [0.18; 0.55]**	–						
2UV%	0.01 [-0.20; 0.23]	**−0.37 [-0.54; −0.17]**	**−0.56 [-0.69; −0.39]**	–					
PNS index	−0.18 [-0.38; 0.03]	**−0.89 [-0.92; −0.83]**	**−0.44 [-0.60; −0.25]**	**0.43 [0.24; 0.59]**	–				
SNS index	**0.22 [<0.01; 0.41]**	**0.78 [0.68; 0.85]**	**0.30 [0.09; 0.49]**	−0.08 [-0.29; 0.13]	**−0.81 [-0.87; −0.71]**	–			
SCL mean	−0.02 [-0.23; 0.19]	**0.39 [0.19; 0.56]**	**0.26 [0.05; 0.45]**	−0.19 [-0.39; 0.03]	**−0.33 [-0.51; −0.13]**	0.21 [>-0.01; 0.41]	–		
nsSCR count	0.02 [-0.20; 0.23]	**0.34 [0.14; 0.52]**	**0.21 [<0.01; 0.41]**	−0.12 [-0.32; 0.10]	**−0.31 [-0.49; −0.11]**	0.21 [>-0.01; 0.41]	**0.80 [0.71; 0.87]**	–	
DCmod	−0.12 [-0.33; 0.10]	**−0.33 [-0.51; −0.12]**	**−0.33 [-0.51; −0.13]**	0.10 [-0.11; 0.31]	**0.67 [0.53; 0.77]**	**−0.61 [-0.73; −0.46]**	−0.10 [-0.30; 0.12]	−0.14 [-0.34; 0.08]	–
ACmod	0.11 [-0.11; 0.32]	**0.38 [0.18; 0.55]**	**0.39 [0.20; 0.56]**	−0.13 [-0.33; 0.09]	**−0.70 [-0.79; −0.57]**	**0.65 [0.51; 0.76]**	0.15 [-0.07; 0.35]	0.17 [-0.05; 0.37]	**−0.97 [-0.98, −0.96]**

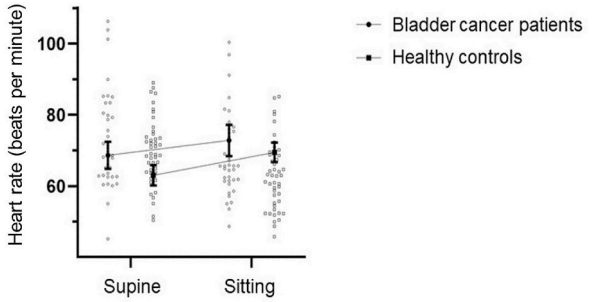

Fig. 1. Comparison of heart rate in the supine and sitting positions between bladder cancer patients and healthy controls.

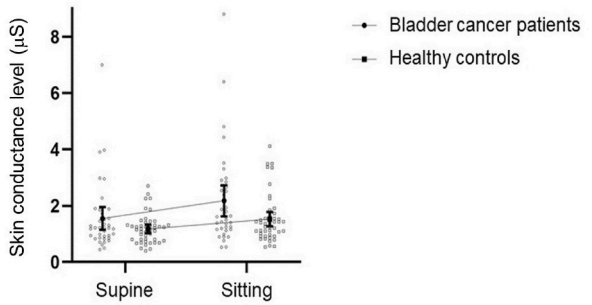

Fig. 2. Comparison of skin conductance level in the supine and sitting positions between bladder cancer patients and healthy controls.

0.04, d = 0.45, 95%CI [0.01, 0.89]; ACmod: t(60.69) = −2.04, p = 0.05, d = −0.42, 95%CI [−0.86, 0.03].

4. Discussion

The objective of this study was to assess the basal levels of physiological stress indicators in bladder cancer patients and healthy individuals, as well as the differences in studied variables between patients and healthy controls during the transition from a supine to a sitting position, which represented a mild physiological load. Nonlinear and time domain HRV parameters associated with sympathetic and parasympathetic modulation, such as symbolic dynamics 0V%, 2UV%, ACmod, DCmod and PNS and SNS indices from Kubios software, were selected. Porta et al. demonstrated that the two mentioned non-linear symbolic indexes provide a compelling alternative to linear spectral indexes for assessing cardiac autonomic modulation from short-term HRV [39]. Additionally, perceived stress was determined to explore its relationship with the studied parameters.

The key findings revealed elevated resting HR, a heightened SNS index, and increased skin conductance among bladder cancer patients compared to their healthy counterparts in both the supine and sitting positions. This may indicate an increased physiological stress load in bladder cancer patients. However, this difference in physiology did not correspond to the perceived stress, which was comparable in both studied groups. Even though patients subjectively perceived comparable levels of stress to healthy controls, their physiology showed a difference in terms of HR and EDA. A possible explanation is that under chronic stress, a person can become accustomed to and perceive this long-term strain as a „normal condition“. The perceived stress scores in both patients and healthy controls in our sample were in the normal range for PSS [40]. Similarly, another study that measured distress BCa patients using a distress thermometer showed moderate levels of subjective distress in patients, on average [41]. It has also been demonstrated that brief subjective measures of stress may not strongly correlate with physiological stress measures [42], a pattern that is consistent with our own data. Thus, there might be measurable physiological stress effects that are not detected through self-report measures. That's why we introduced a minimal physiological stress condition by measuring the signals in both supine and sitting positions. For HRV parameters 0V%, ACmod, PNS, DCmod and SNS indices, there was only a main effect of position, not an interaction. For 0V%, ACmod and the SNS index, the change from the supine to sitting position had a positive effect, while for the PNS index and DCmod, it had a negative effect. This aligns with the assumption that 0V% and ACmod reflects sympathetic modulation, while 2UV% and DCmod reflects parasympathetic modulation [20,22,43,44]. However, our results do not show any additional value of using symbolic dynamic parameters to those derived from Kubios such as ACmod, DCmod or SNS and PNS indices.

Porta et al. and Cysarz et al. also described the association between the enhancement of cardiac sympathetic modulation and the reduction of vagal modulation during sympathetic activation, resulting in an increase in the 0V% and a decrease in the 2UV% parameters [30,31]. Their findings align with our correlations observed in the supine position: the non-linear symbolic dynamics 2UV% parameter correlated positively with the PNS index, DCmod and inversely with 0V%, ACmod, HR, and the SNS index. As expected, perceived stress correlated positively with HR and the SNS index and negatively PNS index, DCmod. The positive correlation of the

HRV parameter 0V% with the SNS index, ACmod, nsSCR, and HR, as well as its negative correlation with 2UV%, DCmod and the PNS index, supports the findings of other studies suggesting an association of the 0V% index with sympathetic activity [16,22,45]. Additionally, in the sitting position, mean SCL also correlated positively with the 0V% index. This correlation only approached statistical significance in the supine position, reflecting the predominance of the PNS in the supine position.

On the other hand, for the two main physiological measures of the sympathetic autonomic nervous system activation, namely mean SCL and HR, we found a main effect of position, a main effect of group, and the interaction of both factors. This means that these parameters differed significantly between bladder cancer patients and healthy individuals and also differed significantly in the supine and sitting positions. Interestingly, healthy controls had lower basal levels (in the supine position) of both HR and mean SCL compared to patients, and these levels increased in the sitting position, reaching approximately the same level as the baseline level (supine position) of bladder cancer patients. This suggests that patients had basal stress levels within the same range as healthy individuals under the physiological stress imposed by the change of position to a sitting one.

Moreover, in patients, we observed a higher increase in mean SCL compared to healthy controls, indicating that they may have a higher stress reactivity. Although the total change of HR in bladder cancer patients was lower than that in healthy individuals, the final level (in the sitting position) was also higher than that of healthy controls. The lower change in HR can be explained by its higher basal levels, taking into consideration that the overall extent of HR change in mild stress conditions shows a narrower range than mean SCL, which can rise more markedly. The higher HR in cancer patients can also reflect decreased fitness of their organism caused by the disease itself, but together, increased EDA and HR suggest a higher stress load.

Of particular note is that we also observed higher nsSCR as a phasic component of EDA in bladder cancer patients, suggesting their higher ANS sensitivity. However, it should be noted that this result, when considered alongside the findings of the sensitivity analysis, revealed a reliable effect only in the sitting position. In an older study, Andresen reported nsSCR as more indicative of anxiety-related arousal than of behavioral inhibition [46]. In a prospective clinical study [47], the authors found that SCR in the immediate aftermath of trauma predicts the subsequent development of chronic post-traumatic stress disorder (PTSD). PTSD can develop in 10–20 % of individuals who are exposed to a traumatic event. People with PTSD can exhibit hypervigilance, an elevated state of constantly assessing potential threats around them. Since approximately 60 % of the population experiences at least one traumatic stressor in their lifetime, the elevated electrodermal spontaneous fluctuations observed in our study could reflect either hypervigilance in bladder cancer patients, who also have to cope with anxieties related to their diagnosis and treatment, or SNS instability expressed by their electrodermal pattern [48].

A population-based American study [49] found that more than one-fourth of 2000 NMIBC survivors had PTSD symptoms. Another study [50] reported that NMIBC survivors experienced cancer-related uncertainty, and PTSD symptoms mediated the effect of uncertainty on their quality of life (QOL). Collectively, comorbidities, cognition-general concerns, uncertainty, and PTSD symptoms had strong negative effects on the QOL of NMIBC survivors. In addition, cancer patients have to cope with anxieties related to their prognosis, potential recurrence/progression, and treatment-associated problems. All of this can contribute to higher levels of stress load and may influence survival, even if not perceived by patients. Our study, which shows a significant increase in basal levels of EDA and HR in BCa patients compared to healthy individuals, supports the findings of others, highlighting the importance of developing interventions for BCa supportive care. Furthermore, a recent pre-clinical study [51] showing that chronic unpredictable mild stress could affect the growth of bladder cancer in nude mice also suggests the need for interventions addressing chronic psychological stress as a possible therapeutic strategy for bladder cancer.

In conclusion, while our study demonstrates physiological alterations in parameters associated with stress responses in bladder cancer patients, the clinical relevance of these changes warrants further consideration. Future research should aim to establish clear associations of these changes with pathological reference values and patient outcomes. Such efforts can then justify the implementation of targeted stress-management interventions, such as bio-/neuro-feedback, psychotherapy, MBSR (mindfulness-based stress reduction), and vagal stimulation, for the identification and management of ANS dysregulation in this patient population. These approaches have the potential to ameliorate the stimulatory impact of the SNS, thereby reducing the recurrence and progression of cancer, while also mitigating additional side effects, anxiety, and the associated costs of additional treatment [1].

4.1. Study limitations

An important consideration in this study is the diversity among subjects in various variables, including age, heart rate, BMI, and health status, as well as additional influences including individual fitness, respiratory patterns, and emotional states. Each of these variables can exert an impact, spanning from minor to substantial, on both HRV and skin conductance measurements, as well as the implications regarding ANS modulation. Furthermore, the data for nsSCR exhibited a strong positive skew, necessitating additional sensitivity analysis alongside the originally planned analysis. Another potential limitation is the absence of blood pressure measurements in both positions. It was not feasible to measure blood pressure due to the need to minimize physiological stress and limit it solely to the change in position. From the standpoint of subjective stress measure, it could be argued that the PSS scale is too brief and general, further investigation using more detailed measures of stress and coping in cancer patients is desirable in further research. To maintain the fidelity of data interpretation, it is necessary to consider the contextual circumstances underpinning data collection and the inherent diversity in subject characteristics.

Brief Commentary.

Background

This study investigates physiological stress responses of bladder cancer (BCa) patients compared to healthy individuals during the transition from a supine to a sitting position. By analysing heart rate, nonlinear heart rate variability and electrodermal activity, the study uncovers notable differences in ANS modulation and stress reactivity.

Translational significance

The observed physiological changes indicate increased parameters associated with stress responses in patients, despite similar perceived stress levels to healthy individuals. Future research should explore the impact of these changes on patient outcomes. Understanding the nuances of stress responses is essential for optimizing stress management interventions and improving patients' well-being.

Authorship agreement

All authors have read the journal's authorship agreement.

CRediT authorship contribution statement

I. Mikolaskova: Data curation, Investigation, Writing – original draft. **M. Zvarik:** Data curation, Formal analysis, Methodology. **P. Hesko:** Data curation, Formal analysis. **M. Kopcova:** Formal analysis, Writing – original draft, Formal analysis, Writing – original draft. **Y. Gidron:** Formal analysis, Methodology, Writing – review & editing. **J. Rajcani:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **L. Hunakova:** Conceptualization, Funding acquisition, Project administration, Writing – original draft. **B. Kollarik:** Project administration, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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