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Differences and effects on heart rate variability regarding time-domain parameters and frontal QRS-T angle in irritable bowel syndrome with diarrhea or constipation

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Abstract

Aim: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder associated with autonomic nervous system (ANS) abnormalities. The primary aim is to examine heart rate variability (HRV) in IBS patients and identify differences between diarrhea (IBS-D) and constipation-predominant (IBS-C) subtypes with time-domain (T-D) parameters linked to parasympathetic nervous system (PNS) activity using 24-hour Holter electrocardiography (ECG). The secondary aim is to determine if ANS dysregularities affect frontal QRS-T angle f(QRS-T) and ECG features.

Material and Methods: The patients with palpitation symptoms who had a 24-hour Holter ECG evaluation at our clinic from January 2019 to December 2022 were reviewed retrospectively. Twenty-five patients with IBS-D, 25 with IBS-C, and 50 healthy controls were included.

Results: According to univariate logistic regression, the PR interval, 24-hour minimum heart rate (minHR), rMMSSD, pNN50, and SDNN index are predictors of IBS. In multivariate logistic regression analysis, only the 24-Hour minHR and SDNN index remained significant as an independent predictor of IBS. Based on the Scatter-Plot, 12% of the variation in the 24-hour minHR was connected to the SDDN index. IBS had a moderate negative association with minHR and SDNN index, a weak negative correlation with rMMSSD and pNN50, and a weak positive correlation with PR interval. The IBS predictability of the PR interval, 24-Hour minHR, rMMSSD, pNN50, and SDNN index was also determined using ROC analysis.

Discussion: We found that T-D parameters were adversely affected in IBS, irrespective of subtype. PR intervals were longer in IBS than controls; however, the f(QRS-T) angle did not differ between the subtypes.

Keywords

Irritable Bowel Syndrome, Frontal Qrs-T Angle, Time-Domain Parameters, Electrocardiography, Ambulatory Holter Electrocardiography

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Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by recurring abdominal pain and alteration of bowel movement (constipation, diarrhea) in the absence of detectable organic causes with routine clinical examination [1,2]. Although the prevalence is difficult to know studies have reported it approximately 13.8% in women and 9.4% in men [2-4]. The complicated etiology of IBS is primarily characterized by abnormalities of microbiota-gut–brain interaction [1,2]. Furthermore, stress exacerbates digestive symptoms [2,5]. Autonomic nervous system (ANS) disorders, defined by decreased parasympathetic nervous system (PNS) activity, can be the disease's defining characteristic. Studies have also shown that sympathetic nervous system (SNS) activity may increase [2,4,6].

Heart rate variability (HRV) can be utilized to analyze autonomic activity in response to GI functions and to discover reduced gut-brain connections [2]. Using data from peak-to-peak or RR intervals, the time interval between successive R peaks in an ECG signal, the time-domain (T-D) parameters assess the degree of variability in heart rate (HR). The mean root square of the sequential differences in RR intervals (rMMSSD), the percentage of successive RR intervals that differ by greater than 50 ms (pNN50), and standard deviations of the RR interval (SDRR) are the samples of T-D parameters, which are directly affected by PNS activity. Other T-D parameter samples like the average and the mean of NN intervals for each 5-min section of a 24-hour recording (SDANN and SDNN index, respectively) SDNN index may also be influenced by SNS activity [2,4,7]. Additionally, frequency domains (F-D) and non-linear (N-L) parameters can also show ANS activity (The sympathetic index (SI), low-frequency (LF), and high-frequency (HF) bands regarding spectral analysis, the length of the minor axis of the fitted eclipse on the Poincare Plot of RR intervals (SD1), the length of the major axis of the fitted eclipse on the Poincare Plot of RR intervals (SD2), the autonomic balance (SD2/SD1)) [2,4,8,9].

The majority of studies that have examined the association between HRV and IBS have focused on F-D features. However, the recording times in these investigations vary, and there are both 24-hour and short-term recordings [2,4,10-12]. Only a few research studies investigate the association between time domain-related factors and IBS. Some studies compared IBS with pain type and severity, and some compared IBS with depression or anxiety [13]. Heitkemper M et al's study, which includes only the female gender, found changes in T-D parameters in only severely symptomatic IBS subgroups [14]. Lee et al. only compared constipated or diarrhea-predominant IBS types (IBS-C and IBS-D, respectively) regarding RR interval variation [15]. Although other research in the literature was searched, as far as we know, no study could be found that compared IBS-C and IBS-D subtypes regarding T-D parameters in both genders [14-16]. Since autonomic dysfunction in IBS is mainly associated with decreased PNS activity, our study's primary aim is to evaluate HRV in IBS patients regarding T-D parameters mainly associated with PNS activity, using 24-hour Holter ECG recordings to investigate possible differences between IBS-C and IBS-D.

ANS disturbances impact the electrical features of the heart; injury to the PNS results in repolarization dispersion with SNS activity predomination [17]. The frontal QRS-T (f(QRS-T)) is the angle, which is an indicator of heterogeneity in ventricular repolarization, between the spatial axes of ventricular depolarization and repolarization [18,19]. Increases in the f(QRS-T), as a measure of cardiac autonomic function, have been observed in patients with type 2 diabetes and cardiac autonomic neuropathy [17,20]. However, as far as we know, no study evaluated the f(QRS-T) angle in IBS disease. Therefore, our study's secondary aim is to investigate whether ANS dysregularities cause a change in f(QRS-T) angles and standard electrocardiographic (ECG) characteristics in IBS patients.

Material and Methods

In our study, patients who presented to our clinic with palpitation and underwent 24-hour rhythm Holter examination between January 2019 and December 2022 were retrospectively analyzed via our hospital information system. Among these patients, patients diagnosed with IBS for the first time in the gastroenterology department were included in the study. Then, patient groups were classified into diarrhea and constipation-predominant types by reference to the clinical examination notes of the gastroenterology department. Finally, these patients were compared with a healthy control group of age- and sex-matched patients with a 24-hour rhythm Holter evaluated in our hospital and without pathology. A total of 50 IBS patients, 25 diarrhea-predominant, 25 constipation-predominant, and 50 controls were included in our study. Patients with a history of cardiovascular disease, inflammatory bowel disease, obstructive sleep apnea, gastrointestinal surgery, chronic renal and liver failure, thyroid diseases, anemia, cardiac arrhythmia, and taking medications that could interfere with HRV, such as beta-blockers, antihistaminic agents, antipsychotics, or antidepressants were excluded from our study. Our study was conducted within the ethical standards of the Declaration of Helsinki. Bilecik Seyh Edebali University Ethics committee approved our study with E-10333602-050.04.01-181790 decision number dated 18.5.2023.

Irritable Bowel Syndrome Diagnosis

Due to Rome IV criteria, IBS symptoms should appear at least six months before diagnosis and persist for at least three months [1]. IBS is divided into four subtypes: IBS-C, IBS-D, mixed bowel habits (IBS-M), and IBS without subtype. The Bristol stool form scale is used to classify irregular bowel motions [21]. In IBS-C, more than one-fourth (25%) of bowel movements are Bristol Stool Scale Type 1 (Separate hard lumps, like nuts) and Type 2 (Sausage-shaped, but lumpy), and less than one-fourth (25%) are Type 6 (Fluffy pieces with ragged edges, a mushy stool), and Type 7 (Watery, no solid pieces, entirely liquid). However, in IBS-D, more than one-fourth (25%) of bowel movements are in Bristol Stool Scale Types 6-7, and less than one-fourth (25%) are Types 1-2 [1,21].

Only the IBS-C and IBS-D subgroups were evaluated and compared to demonstrate the difference between the study groups more clearly, independent of confounding factors. Mixed

and unclassified IBS patients were excluded from our study.

Electrocardiographic Analysis

HR, PR interval, QRS width, and QT duration were evaluated from the standard 12-lead recording ECGs (10 mV/mm and 25 mm/s paper speed) at rest. The Bazett formula (QT/√RR) measures the corrected QT (QTc) interval. All data regarding parameters are obtained from ECG automatic analysis report. The f(QRS-T) was computed as the absolute difference value between the frontal plane QRS and T axes from the automated ECG reports. If f (QRS-T) was higher than 180°, the difference of 360° and f(QRS-T) was used instead [22]. In our investigation, no patients had 2nd or 3rd-degree AV blocks, bundle branch blocks, atrial fibrillation, or pacing rhythm.

24-Hour Holter ECG Analysis

To evaluate T-D parameters relating to HRV, a 24-hour Holter ECG with a 12-channel digital recorder (Cardioline, Cube Software, Italy) was utilized. The evaluation includes at least 22-hour-long records of acceptable quality for evaluation. Patients were excluded if they did not meet these criteria. T-D HR variability indices rMMSSD, pNN50, SDRR, and SDNN index were obtained automatically from the reports with Cube program software. Also, total heartbeat, minimum HR, maximum HR, and heart rate distribution width (HRD is accepted and calculated as maximum HR minus minimum HR) were obtained from automatic 24-hour Holter reports.

Statistics

The IBM SPSS Statistics 25.0 software was used. The Shapiro-Wilk and Kolmogorov-Smirnov tests were utilized to evaluate if numerical variables followed the normal distribution. Numerical variables' mean and standard deviation were provided. If the normal distribution was achieved, the independent samples t-test was used to compare the two groups regarding numerical variables. The Mann-Whitney U test was used if it was not. Numerals (n) and percentages (%) indicate categorical variables. The association between categorical variables was examined using Pearson's Chi-square and Fisher's Exact tests. The power of parameters predicting IBS was evaluated with univariable and multivariable analyses. The odds ratio (OR) and 95% confidence interval (CI) were calculated. In addition, the cut-off values were subjected to ROC (Receiver Operating Characteristic) analysis. The Youden index was used to determine the cut-off value. Descriptive data for regularly distributed continuous variables were expressed as mean and standard deviation (SD). $p < 0.05$ value was accepted as the significance level for all hypotheses. The Forest-Blot graphic displays IBS predicting factors. Also, the Scotter-Dot graph illustrates the link between the SDNN index and minimum HR.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The number of females in the IBS patient group accounted for 70%. There were no statistically significant differences in demographic or clinical characteristics between the IBS and control groups and between IBS subtypes (all p- values >0.05). Regarding ECG parameters, the only difference between the IBS and healthy controls, the PR interval is significantly higher in favor of IBS (PR: 156.0±26.3 ms, 145.0±18.8 ms, respectively; p=0.018). Nevertheless, no differences were obtained between IBS subtypes (all p-values >0.05).

Regarding the 24-Hour Holter ECG parameters, total heartbeat (102891±10127, 113569±17704, respectively; <0.001), minimum HR (44.7±8.1, 51.7±8.4, respectively; <0.001), rMMSD (25.9±10.8 ms, 38.4±24.7 ms, respectively; p=0.018), pNN50 (6.7±5.2 ms, 11.1±9.8 ms, respectively; 0.039), and the SDNN index (75.0±19.3 ms, 86.5±14.8 ms, respectively; 0.001) were significantly lower in IBS patients than in healthy controls. In

Table 1. Comparison of Demographic, Clinical Characteristics, Electrocardiographic, and 24-Hour Holter

Parameters	1. IBS (n=50)		2. Control (n=50)	p (a-b)	p (1-2)
	a) IBS-D (n=25)	b) IBS-C (n=25)			
Age, mean±SD	38.7±10.5	43.0±10.6	39.8±14.2	0.161	0.698
Female, n, (%)	17 (68)	18 (72)	32 (64)	0.758	0.523
BMI, kg/m², mean±SD	27.2±3.5	26.3±4.0	27.5±3.2	0.398	0.327
Syst. BP, mmHg, mean±SD	126±8	129±6	125±8	0.125	0.274
Diast. BP, mmHg, mean±SD	75±5	73±5	74±5	0.077	0.801
Smoker, n (%)	10 (40)	13 (52)	15 (30)	0.395	0.099
Electrocardiographic Parameters					
HR, n, mean±SD	78.4±14.2	72.0±13.9	75.9±12.0	0.117	0.792
PR interval, ms, mean±SD	156.0±24.1	156.0±28.9	145.0±18.8	1.000	0.018
QRS width, ms, mean±SD	89.6±9.5	90.8±14.6	91.8±12.3	0.742	0.523
QT duration, ms, mean±SD	373.0±25.8	380.4±29.9	371.6±27.5	0.352	0.363
QTc duration, ms, mean±SD	405.1±17.7	401.9±20.3	399.5±17.4	0.556	0.273
F(QRS-T) Angle, mean±SD	31.5±19.6	31.2±20.1	25.7±19.8	0.955	0.156
24-Hour Holter (Time-Domain) ECG parameters					
Minimum HR, n, mean±SD	45.1±8.3	44.2±8.0	51.7±8.4	0.719	<0.001
Maximum HR, n, mean±SD	134.1±8.6	130.8±11.9	137.1±16.9	0.265	0.104
Mean HR, mean±SD	81.1±9.4	77.5±7.7	81.6±14.9	0.149	0.347
HRD width, mean±SD	89.0±13.7	86.5±16.6	85.3±19.5	0.568	0.491
rMMSSD, ms, mean±SD	27.2±9.3	24.6±12.2	38.4±24.7	0.397	0.031
RRSD, ms, mean±SD	129.4±34.4	128.9±23.0	133.9±34.7	0.946	0.461
pNN50, ms, mean±SD	7.1±5.4	6.4±5.0	11.1±9.8	0.633	0.039
SDNN index, ms, mean±SD	75.4±20.4	74.6±18.6	86.5±14.8	0.886	0.001

IBS: Irritable bowel syndrome, IBS-D: Diarrhea predominant IBS, IBS-C: Constipation predominant IBS, Syst: Systolic, Diast: Diastolic, HR: Heart rate, f(QRS-T): Frontal QRS-T, HRD: Heart rate Distribution, rMMSSD: Mean root square of the sequential differences in RR intervals, RRSD: standard deviations of the RR interval, pNN50: the percentage of successive RR intervals that differ by greater than 50 ms, SDNN index: the mean of NN intervals for each 5-min section of a 24 h recording

Table 2. Univariable - Multivariable Regression and Spearman's Correlation Analyses for Determine Predictor of Irritable Bowel Syndrome

Parameters	Univariate Analysis		Multivariate Analysis		Spearman's Correlation	
	OR (95% CI)	p	OR (95% CI)	p	rho	p
PR interval	1.022 (1.003-1.041)	0.022	1.018 (0.996-1.040)	0.105	0.241	0.016
Minimum HR	0.906 (0.861-0.954)	<0.001	0.904 (0.853-0.958)	0.001	-0.367	<0.001
rMMSSD	0.961 (0.934-0.988)	0.004	0.981 (0.938-1.027)	0.422	-0.217	0.030
pNN50	0.925 (0.871-0.982)	0.010	0.955 (0.862-1.058)	0.379	-0.208	0.038
SDNN index	0.960 (0.934-0.986)	0.003	0.967 (0.936-0.998)	0.037	-0.352	<0.001

OR: Odds ratio, CI: Confidence interval, HR: Heart rate, rMMSSD: Mean root square of the sequential differences in RR intervals, pNN50: the percentage of successive RR intervals that differ by greater than 50 ms, SDNN index: the mean of NN intervals for each 5-min section of a 24 h recording

Table 3. Comparison of Demographic, Clinical Characteristics, Electrocardiographic, and 24-Hour Holter

Parameters	Cut-Off	AUC	95%CI	p	Sensitivity	Specificity
PR interval	147.0	0.639	0.530-0.748	0.016	56%	66%
Minimum HR	35.5	0.288	0.186-0.390	<0.001	90%	8%
rMMSSD	22.5	0.375	0.262-0.488	0.031	62%	32%
pNN50	3.5	0.380	0.270-0.490	0.039	70%	26%
SDNN index	101.5	0.297	0.194-0.400	<0.001	10%	88%

AUC: Area under the curve, CI: Confidence interval, HR: Heart rate, rMMSSD: Mean root square of the sequential differences in RR intervals, pNN50: percentage of successive RR intervals that differ by greater than 50 ms, SDNN index: mean of NN intervals for each 5-min section of a 24 h recording

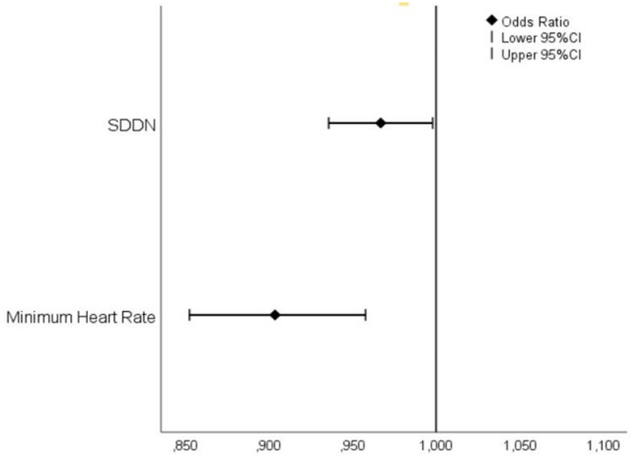

Figure 1. Forest-Plot Diagram Showing the Association Between Minimum Heart Rate and SDDN Index Parameters and Irritable Bowel Syndrome

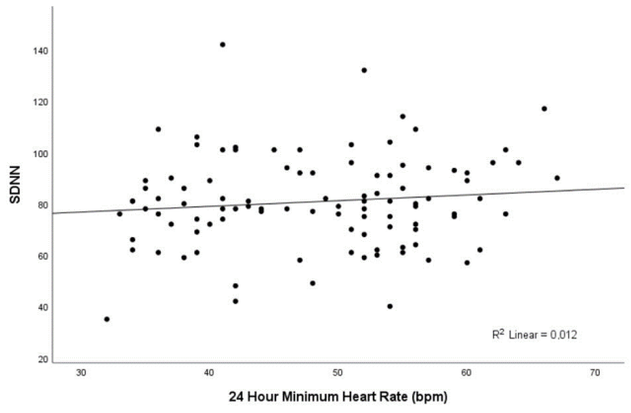

Figure 2. Scatter-Plot Diagram Showing the Correlation Between Minimum Heart Rate and SDDN Index

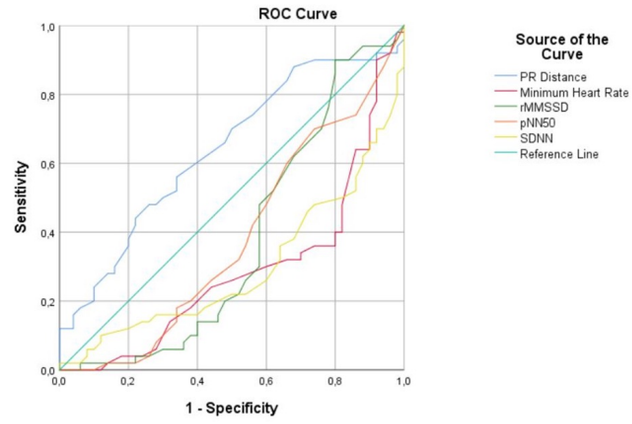

Figure 3. ROC Curve Analysis

addition, these parameters tended to be lower in IBS-C than in IBS-D, but there was no significant difference among the IBS subtypes (all p-values >0.05). Comparison of demographic, clinical characteristics, ECG, and 24-hour Holter ECG parameters are summarized in Table 1.

In univariate logistic regression, PR interval, minimum HR, rMMSSD, pNN50, and SDNN index were lower in the IBS group than in the healthy control group (p=0.022, p<0.001, p=0.004, p=0.010, and p=0.003; respectively). Multivariate logistic regression analysis also showed that minimum HR (odds ratio: 0.904, 95% confidence interval [CI]: 0.853-0.958, p=0.001) and SDNN index (odds ratio: 0.967, 95% CI: 0.936-0.998, p=0.037) are independent predictors of IBS (Figure 1 - Forest-Blot diagram). Moreover, 12% of the 24-hour minimum heart rate variation was related to the SDDN index (Figure 2 - Scatter-Plot Diagram). Spearman's correlation analysis is also shown in Table 2.

ROC Curve analysis results are shown in Table 3 and Figure 3.

Discussion

IBS is a common disorder with ANS abnormalities, which is observed more frequently in the PNS. Our study aimed to identify the potential differences in the T-D HRV parameters that more accurately reflect the PNS in the studies conducted [2,4,6,7]. In our study, both genders were included, and IBS-D and IBS-C were compared separately. Our study showed no significant difference between the two subtypes; nevertheless, several T-D parameters were significantly lower in the IBS group. In addition, this study examined the f(QRS-T) angle, an indication of cardiac autonomic function, for the first time in patients with IBS (p=0.955).

IBS is more common in women, and it has been demonstrated that the number of female patients seeking therapy is up to 2.5 times that of male patients [22]. Similar to the literature, in our study the proportion of female patients was higher than that of male patients, accounting for 70% of the study population.

We could not find a study that evaluated the essential electrocardiographic characteristics (PR interval, QRS width, and QT duration) in IBS patients. Only significant ECG difference, the PR time of IBS patients was greater than that of the healthy control group (156.0±26 ms, and 145.0±18 ms, respectively; p=0.018). In a study examining the effects of obesity on arrhythmias and the autonomic nervous system, the PR length was shown to be longer in class 3 obese individuals with a mean age of 34 and a female gender percentage of around 78% than in the control group (163 ± 20, 151 ± 20, respectively; p<0.001). This study stated that the ANS involvement was primarily in the SNS [23]. The PR interval is also highly affected by the ANS. SNS activation decreases the PR interval, whereas PNS activation increases the PR interval [24]. In IBS patients, the length of the PR may have been influenced by the degree of PNS and SNS involvement and the balance between them. In 2014, Duraklioglugil ME et al. found that T-D parameters, SDNN index (51±12 ms, 62±18, respectively; p=0.010), and rMMSSD (28±9 ms, 38±15, respectively; 0.002) were significantly lower in the IBS group (n=30) compared to controls (n=30). In this study, there were no comparisons regarding IBS subtypes [12]. In the study by Heitkemper M et al., which included only female

gender, PNS activity was much lower in the IBS-C subgroup, whereas ANS balance was significantly higher. Subgroups of women with IBS differ in ANS function as determined by 24-hr HRV; however, only women with severe symptoms exhibit these changes (Parameters: SD5 min, SDANN, SD-24 hr, rMMSSD, pNN50) [17]. Jarrett ME et al. reported that a history of anxiety and depressive disorders is related to decreased PNS in women with IBS and healthy controls. In addition, they stated that additional research is required to determine if lower PNS affects the pain and stool pattern changes observed in individuals with IBS [24]. Similar to the Duraklioglugil ME et al. study, the rMMSSD and SDNN index were lower in the IBS group than in the control group in our study. The pNN50 parameter was likewise lower in the IBS group than in the controls, similar to the Heitkemper M et al.'s study. Furthermore, we analyzed both male and female genders, and this situation was revealed independently of the symptoms.

Burr RL et al. stated in a review that 24-hour minimum HR was negatively correlated with general T-D HRV measures (approximately 70% of the variance in the HRV variable can be predicted from the minimum HR) [25]. Our study found that minimum HRs were significantly lower in IBS than in healthy controls. In our study, only 12% of the 24-hour minimum HR variation was related to the SDDN index. The concomitant pain symptoms, symptom severity, and potential vagal involvement in outpatient clinic applications may have contributed to the findings of our study regarding 24-Hour minimum HR and PR interval.

By comparing the T-D parameters across the most prevalent IBS-D and IBS-C types and including patients of both genders, our study will contribute to future studies and help complete the missing pieces in the subject. In our study, as stated in our article's introduction, T-D parameters significantly affected by PNS were evaluated. Our results show how important it is to evaluate both SNS, PNS activity, and the ANS balance with T-D, F-D, and N-L parameters in future multi-center studies.

Limitations

The retrospective nature, the relatively small number of patients, and the absence of information about the pain status and intensity of the patients at the time of admission can be assessed as study limitations.

Conclusion

As a result of univariate logistic regression, PR interval, 24-Hour minimum heart rate, rMMSSD, pNN50, and SDNN index are predictors for IBS. Nevertheless, in multivariate logistic regression analysis, 24-Hour minimum HR and the SDNN index are independent predictors of IBS. Due to scatter-plot analysis, 12% of the 24-hour minimum heart rate variation was related to the SDDN index. A weak positive correlation between IBS and PR interval, a weak negative correlation between IBS and rMMSSD, pNN50, and a moderate negative correlation between IBS and minimum HR and SDNN index were obtained. In addition, in ROC curve analysis, predictability results of the PR interval, 24-Hour minimum HR, rMMSSD, pNN50, and SDNN index for IBS were obtained.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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