

A Pilot Study Using a Smartwatch to Search for Biomarkers of Heart Rate Variability in Active Ulcerative Colitis

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Keywords

Inflammatory bowel disease · Ulcerative colitis · Heart rate variability · Wearable smart watch · Autonomic nervous system

Abstract

Introduction: Autonomic imbalance has been reported to correlate with clinical remission in patients with ulcerative colitis (UC). This study evaluated heart rate variability (HRV), a potential digital biomarker, in patients with active UC using a smartwatch that is easy to handle. **Methods:** Patients with active UC were recruited for this prospective study. The patients' HRV was measured via the Fitbit Inspire2™ linked via Bluetooth to their smartphone. HRV during nighttime sleep was obtained from continuous data. Patients were required to input the Simple Clinical Colitis Activity Index (SCCAI) score once daily by the application on their smartphones for 3 months. **Results:** Nine patients with UC

were included. In clinically active disease, SCCAI scores showed a weak inverse relationship with parasympathetic activity, differences of successive R-R pulse intervals (RMSSD) ($r = -0.44$, $p < 0.0001$), high frequency (HF) ($r = -0.42$, $p < 0.0001$), and total autonomic nervous activity, low frequency (LF) ($r = -0.43$, $p < 0.0001$). Receiver operating characteristic analysis indicated that the RMSSD, HF, and LF were significantly higher in patients with active UC. Meanwhile, LF showed the most correlation with severity for bowel urgency scores. **Conclusion:** Longitudinal nighttime HRV recorded using a smartwatch is associated with disease activity in patients with active UC. In particular, RMSSD and HF, which are indices of the parasympathetic nervous system, have been suggested as potential digital biomarkers for UC.

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Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract and includes Crohn's disease and ulcerative colitis (UC) [1]. Although the detailed etiology of IBD remains unclear, genetic and environmental factors, including gut microbiota, diet, stress, and smoking, collectively promote abnormal immune responses, leading to intestinal inflammation [2]. Several reports have suggested that the brain-gut axis may influence the pathogenesis of IBD. Brain-gut axis alterations are associated with the dysfunction of the autonomic nervous system (ANS), which is connected to the central nervous and digestive systems [3]. In particular, the relative trends in parasympathetic suppression and sympathetic dominance have been studied in patients with IBD [4]. While it is clear that inflammation within the intestinal wall affects visceral sensory perception via the central nervous system, signals from the brain to the gut are also important for altering the course of IBD progression [5]. Further, UC commonly presents with symptoms including abdominal pain, rectal bleeding, stool frequency, and bowel urgency (BU) which is the sudden or immediate need for a bowel movement and with substantial negative impacts on quality of life [6]. Concerning the causes of BU it has been reported that negative emotions, such as anxiety and stress, enhance visceral sensitivity by the brain-gut axis [7].

A definite reflection of the central nervous system is heart rate variability (HRV), which is quantified as the continuous oscillation of the R-R interval between normal heartbeats [8, 9]. HRV is used to assess autonomic dysfunction in various inflammatory diseases including gastrointestinal diseases. In patients with irritable bowel disease (IBS), it is advisable to include HRV measurements to monitor the effectiveness of interventions in IBS therapy and assess autonomic changes [10]. Similarly, HRV has been studied in patients with IBD as an indicator of clinical course. Although traditionally measured by electrocardiography [11], longitudinal measurements of the ANS using a disposable medical device called the VitalPatch™ were reported in 2021 to correlate with disease activity in UC and predict relapse [8]. However, this study included patients in remission; therefore, its efficacy during the induction phase for remission is not yet clear. Therefore, we investigated whether HRV was an objective indicator of disease activity in patients with active UC. Moreover, in this process, the goal was to demonstrate the effectiveness of HRV measurements on smart-

watches, which are used on a daily basis rather than special medical devices, and to explore digital biomarkers that are simple and easy to handle.

Materials and Methods

Study Design

This was a 3-month prospective correlational study; participants' HRV was measured using a wearable device during the study period, and the clinical symptom scale was measured using a smartphone application.

Study Samples

Patients with UC attending the Tokai University Hospital (Isehara, Kanawa, Japan) and Shiga University of Medical Science Hospital (Otsu, Shiga, Japan) were enrolled in this prospective study. Eligible subjects were patients with active UC aged 20–65 years, defined as a Simple Clinical Colitis Activity Index (SCCAI) score >2, were included in the study. Patients were excluded if they were pregnant, had a history of colon surgery, had a pacemaker or defibrillator, or were treated with medications that may affect the ANS or cardiovascular system. Clinical remission was defined as SCCAI score ≤2. Data regarding patients' age, sex, body mass index, disease duration, disease location, and medications were collected.

Survey of Clinical Disease Activity

Surveys were conducted throughout the study period to assess the clinical activity. A brief description of the surveys is as follows. The patients were required to input their SCCAI score once daily by downloading a specialized application (Sasaeru Note™, Arteryx, Japan) to their smartphones. The SCCAI measures the clinical symptoms of UC activity, including quantification of bowel frequency during the day and night, fecal urgency, presence of blood in the stool, general well-being, and presence of extracolonic manifestations [12]. Clinical remission was defined as score 0–2, mild activity as 3–5, moderate as 6–11, and severe as 12 or more [12]. The BU score was based on the Urgency of defecation in the SCCAI, defined as score 0 (no urgency), 1 (hurry), 2 (immediately), and 3 (incontinence) [12].

Wearable Monitoring Device

Patients' HRV was measured via the Fitbit Inspire2™ (Google Fitbit, CA, USA) linked to the smartphone via Bluetooth. The HRV consists of time- and frequency-domain components. Time-domain analysis was performed using the root mean square of successive differences

Table 1. Baseline demographics of patients at enrollment

	Cohort (N = 9)			
		±SD	min	max
Age, years, median	37	12.8	27	62
Sex (men)	4			
Age at UC diagnosis, years, median	31.0	9.1	24	40
Disease duration, years, median	6.4	5.9	1.6	22.1
Disease activity, SCCAI, median	4	1.7	3	8
Disease extent				
E1	3			
E2	2			
E3	4			
Smoking history				
Never	5			
Former	3			
Current	1			
Medical history				
Hyperuricemia	1			
Pneumothorax	1			
Epilepsy	1			
Appendicular cancer	1			
Extraintestinal complications				
Arthritis	3			
Erythema nodosum	1			
Medications				
Mesalamine	8			
Azathioprine or mercaptopurine	1			
Prednisolone	1			
Budesonide	1			
Prebiotics	3			
Vedolizumab	1			
Baseline laboratory values				
WBC, /μL, mean	6.6	1.8	3.6	10.2
Hb, g/dL, mean	13.7	1.6	9.7	15.4
PLT, /μL, mean	25.4	6.8	16.6	36.4
Alb, g/dL, mean	4.1	0.5	2.7	4.7
Erythrocyte sedimentation rate, mm, mean	8	4.9	3	19
CRP, mg/dL, mean	0.13	0.1	0.1	0.4
LRG, μg/mL, mean	11.7	2.5	8.6	17.1

(RMSSDs), which was calculated based on inter-beat interval data in milliseconds. The frequency domain was analyzed by separating the HRV into the low-frequency (LF) band (0.04–0.15 Hz), high-frequency (HF) band (0.15–0.4 Hz), and LF-HF power (LFHF). RMSSD and HF power are associated with parasympathetic (vagal) activity, while LF mainly represents total autonomic nervous activity [13, 14]. The LF/HF ratio is used to indicate the extent of sympathetic regulation of the instantaneous heart rate [15]. In the Fitbit Inspire2™ capability, HRV is acquired during

sleep of at least 3 h. Since almost 100% of the data acquired is during the nighttime, the nighttime sleep period was used for the analysis data.

Statistical Analysis

All analyses were performed using the GraphPad Prism software (version 10; GraphPad Software, Inc., San Diego, CA, USA). The HRV data were generated using box plots (median, Tukey's test). Differences between the two groups were compared using the Mann-Whitney U test (nonparametric).

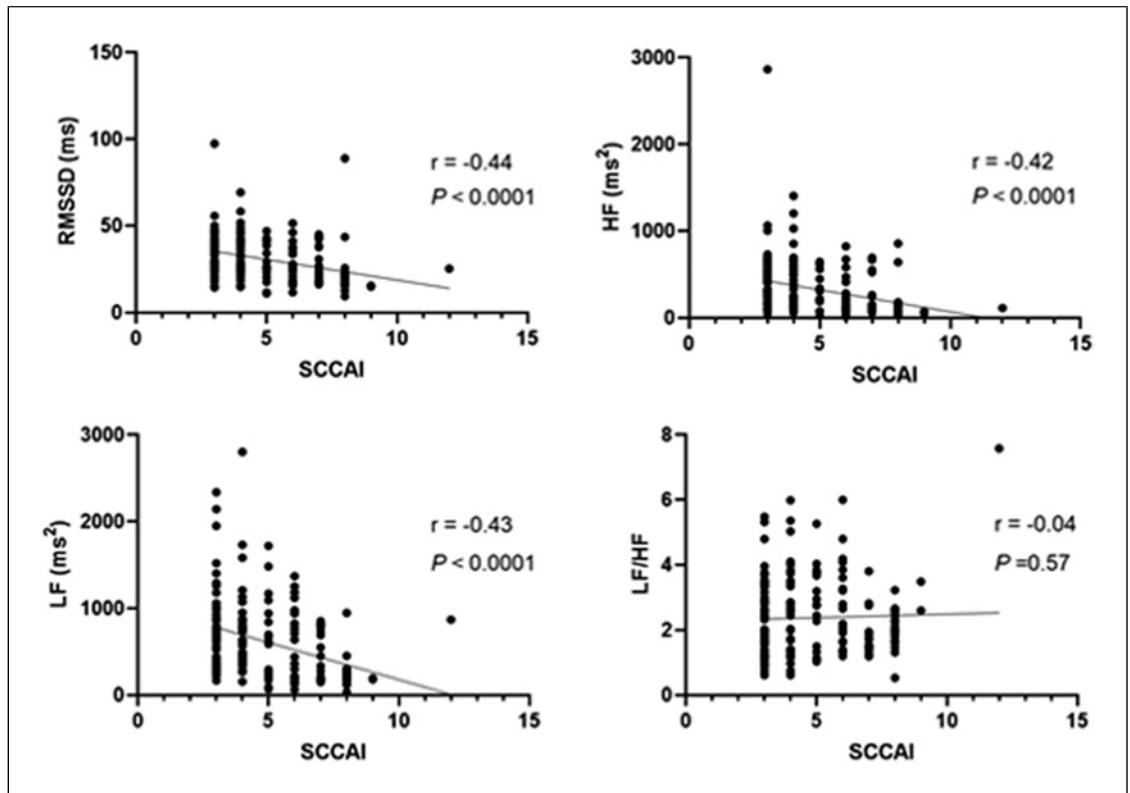


Fig. 1. Correlation between heart rate variability and SCCAI in clinically active disease in UC patients. In clinically active disease (187 points), SCCAI scores showed a weak inverse relationship with RMSSD ($r = -0.44$, $p < 0.0001$), HF ($r = -0.42$, $p < 0.0001$), and LF ($r = -0.43$, $p < 0.0001$). There was no correlation between

the LF/HF ratio and SCCAI ($r = -0.04$, $p < 0.57$). Statistical analyses were performed using Spearman's rank correlation coefficients. SCCAI, Simple Clinical Colitis Activity Index; RMSSD, root mean square of successive differences of RR intervals; LF, low frequency; HF, high frequency.

All levels of significance were set at $p < 0.05$ (*), < 0.01 (**), < 0.001 (***), and < 0.0001 (****). Correlations between each HRV index and the SCCAI or BU score were analyzed using Spearman's rank correlation coefficient (r). Receiver operating characteristic (ROC) curves and the corresponding area under the curve (AUC) were used to evaluate the performance of the prediction model on the test data. The ROC curve is a graphical representation of test characteristics, with sensitivity on the y -axis and 1-specificity on the x -axis, over all possible cut-off points for defining positive and negative test results. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Baseline Demographics of Patients at Enrollment

Nine patients were enrolled in the study (Table 1). The median age at enrollment was 37 years and 44% of the patients were men. The median duration of UC was

6 years at the time of inclusion. The median age of onset was 31 years. All the patients were Asian. Three patients had a history of smoking, and one patient was currently smoking. Four patients had a history of extensive UC, and three patients had a history of arthritis as an extra-intestinal complication. There were no overlapping cases of IBS and UC. The median SCCAI score for clinical activity at the time of inclusion was 4. Two patients had a history of at least one steroid use. Only one patient was on a biological agent at enrollment (vedolizumab). The median C-reactive protein and leucine-rich $\alpha 2$ glycoprotein levels were 0.13 mg/dL and 11.7 μ g/mL, respectively.

HRV and Disease Activity in Clinically Active Disease

To evaluate the usefulness of the biomarkers, this study assessed the correlation between the SCCAI entered by the patient during daytime and HRV during nighttime sleep on the same day. The HRV-SCCAI pairing was able to pick up 736 points in 9 patients. Of the 736 points, 187

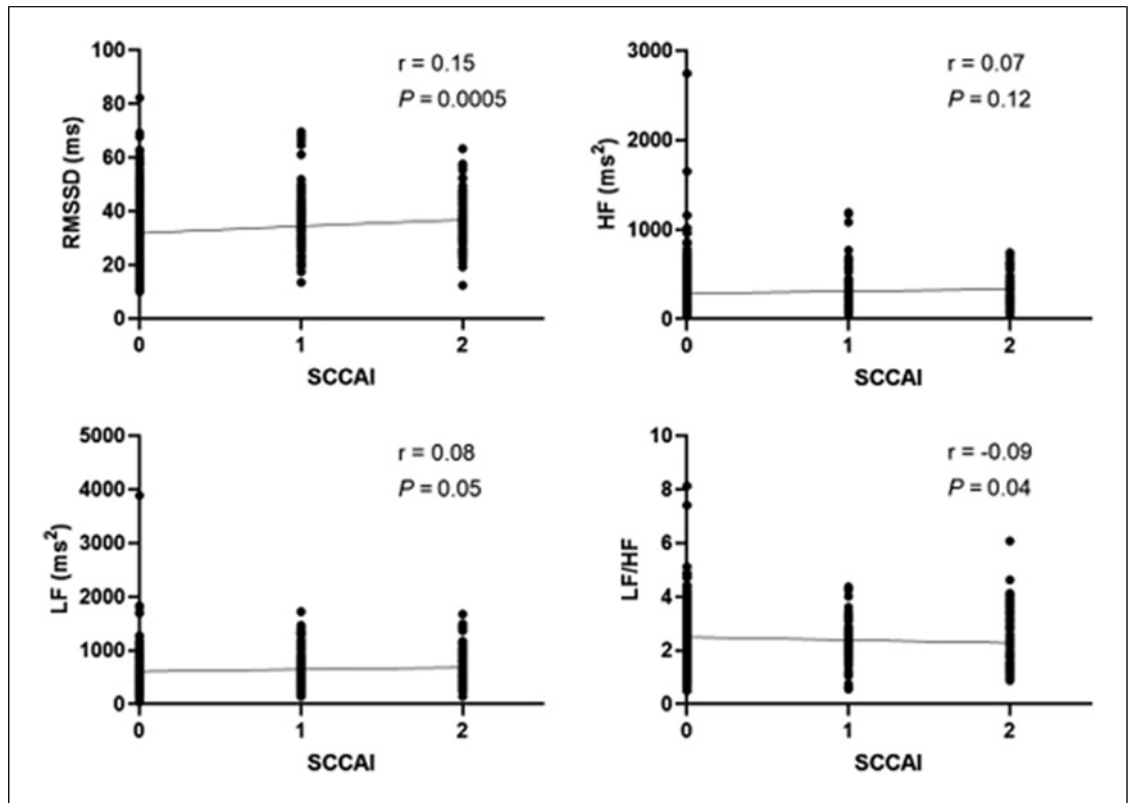


Fig. 2. Correlation between heart rate variability and SCCAI in the clinical remission of UC patients. In the clinical remission phase (552 points), all HRV indices showed no correlation with the SCCAI (RMSSD [$r = 0.14$, $p < 0.0005$], HF [$r = 0.07$, $p < 0.12$], LF [$r = 0.08$, $p < 0.05$], and LF/HF ratio [$r = -0.09$, $p < 0.04$]).

Statistical analyses were performed using Spearman's rank correlation coefficients. SCCAI, Simple Clinical Colitis Activity Index; HRV, heart rate variability; RMSSD, root mean square of successive differences of RR intervals; LF, low frequency; HF, high frequency.

were from data on patients with clinically active disease (SCCAI > 2) and 552 were data on patients with clinical remission (SCCAI ≤ 2). In clinically active disease, SCCAI scores showed a weak inverse relationship with RMSSD ($r = -0.44$, $p < 0.0001$), HF ($r = -0.42$, $p < 0.0001$), and LF ($r = -0.43$, $p < 0.0001$), as determined using Spearman's rank correlation coefficient. Contrarily, there was no correlation between LF/HF ratio and SCCAI ($r = -0.04$, $p < 0.57$) (Fig. 1). Thus, during the active phase, the SCCAI inversely correlated with the parasympathetic index. However, it did not correlate with the sympathetic index.

HRV and Disease Activity in Clinical Remission

Next, a comparison was performed between disease activity level and HRV, which was recorded at 552 points from the patients with clinical remission. RMSSD ($r = 0.14$, $p < 0.0005$), HF ($r = 0.07$, $p < 0.12$), LF ($r = 0.08$, $p < 0.05$), and the LF/HF ratio ($r = -0.09$, $p < 0.04$) showed no

correlation with SCCAI (Fig. 2). Unlike the active phase, the SCCAI did not correlate with the ANS index in clinical remission.

Differences between Remission and Active Disease by HRV

Next, we compared the differences in the HRV indices between clinically active disease and remission. RMSSD and LF/HF ratio were significantly lower in active disease than in remission; however, HF and LF did not differ between the two conditions (Fig. 3a). Because the LF/HF ratio did not correlate with SCCAI in active disease and remission (Fig. 1, 2), RMSSD was considered the first candidate digital biomarker for the evaluation of clinically active disease and remission. ROC analysis was used to evaluate the effectiveness of each marker in classifying or diagnosing the two conditions of the disease. The AUC was calculated to determine the optimal cut-off value for this model (0.5 = pure random

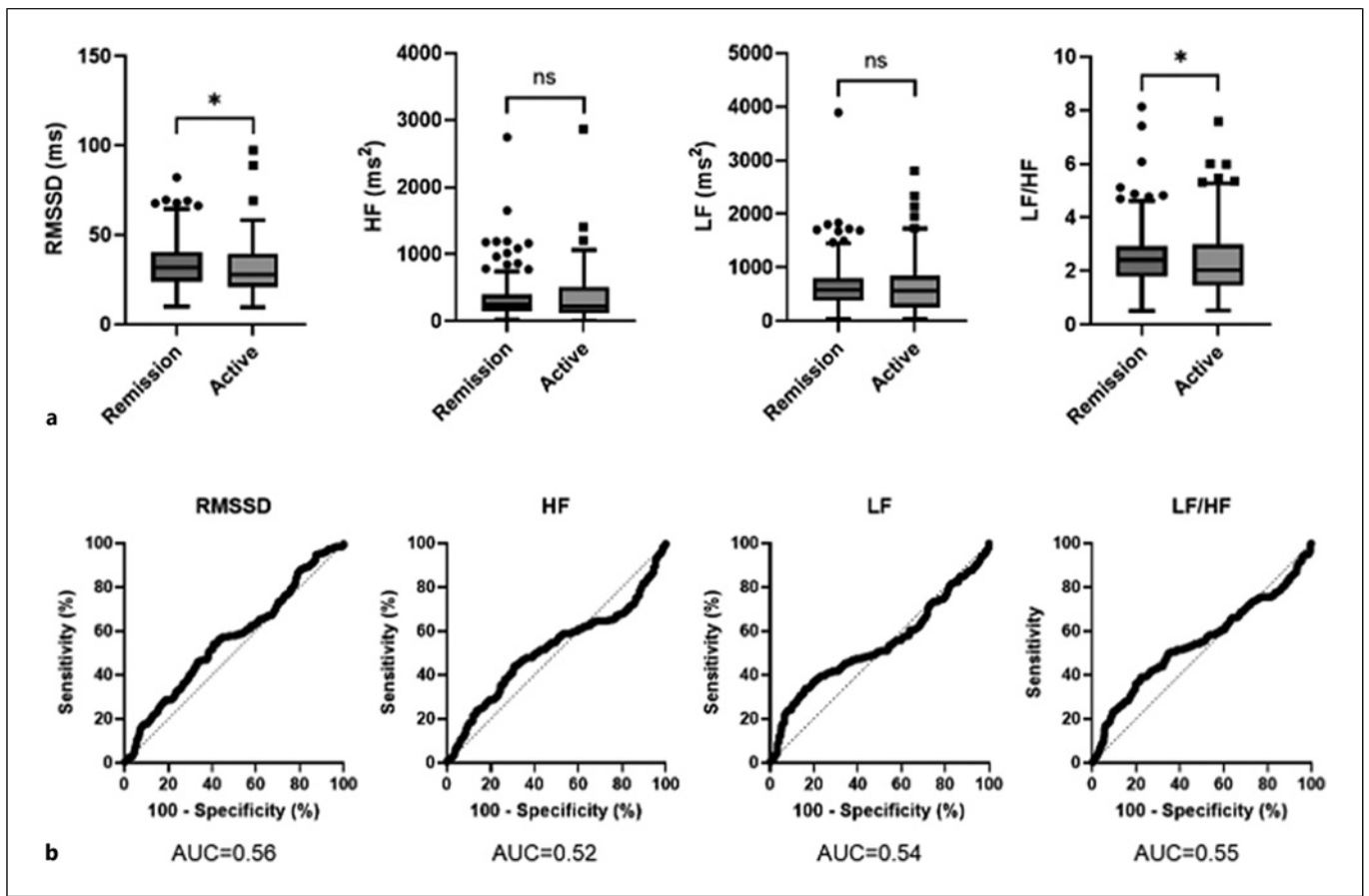


Fig. 3. Comparison of heart rate variability between clinically active disease and remission of UC patients. **a** RMSSD, and LF/HF ratio were significantly lower in the active phase than in the remission phase; however, HF and LF were not different between these two phases. * $p < 0.05$, Mann-Whitney U test. **b** Results from the ROC analyses for each HRV index, with the corresponding AUCs. RMSSD, Root Mean Square of Successive Differences of RR intervals; LF, low frequency; HF, high frequency.

prediction, 1 = full identification) [16]. It is interpreted that tests with an area under the ROC curve greater than 0.9 have high accuracy, 0.7 to 0.9 have moderate accuracy, 0.5 to 0.7 have low accuracy, and below 0.5 is the result of chance [17]. The horizontal coordinates represent specificity, and the vertical coordinates represent sensitivity. The AUC of RMSSD was 0.56, suggesting that this index has a weak predictive effect on UC clinical activity (Fig. 3b).

Comparison of Two Groups: Moderate-Severe and Mild Disease in HRV

In this study, due to the small number of hospitalized patients who needed intensive treatment, there were less severe cases defined as SCCAI ≥ 12 . To further examine its function as a marker of clinical course, a two-group comparison of moderate-to-severe and mild disease was

performed to make an indicative assessment by treatment course. These results indicate that RMSSD, HF, and LF were important for identifying clinical course improvements in patients with UC (Fig. 4a). In contrast, there was no significant difference in the LF/HF ratio between patients with moderate-to-severe and mild disease. The results from the ROC analyses for each HRV index and RMSSD showed an AUC value of 0.73, cut-off value of 24.3, sensitivity of 63.4%, and specificity of 81.0%. HF also showed an AUC value of 0.72, cut-off value of 154.9, specificity of 66.2%, and sensitivity of 81.0%; LF also showed an AUC value of 0.75, cut-off value of 335.8, specificity of 66.2%, and sensitivity of 83.5%, indicating moderate accuracy (Fig. 4b; Table 2). The parasympathetic index was also valid for discriminating between more-than-moderate and mild disease.

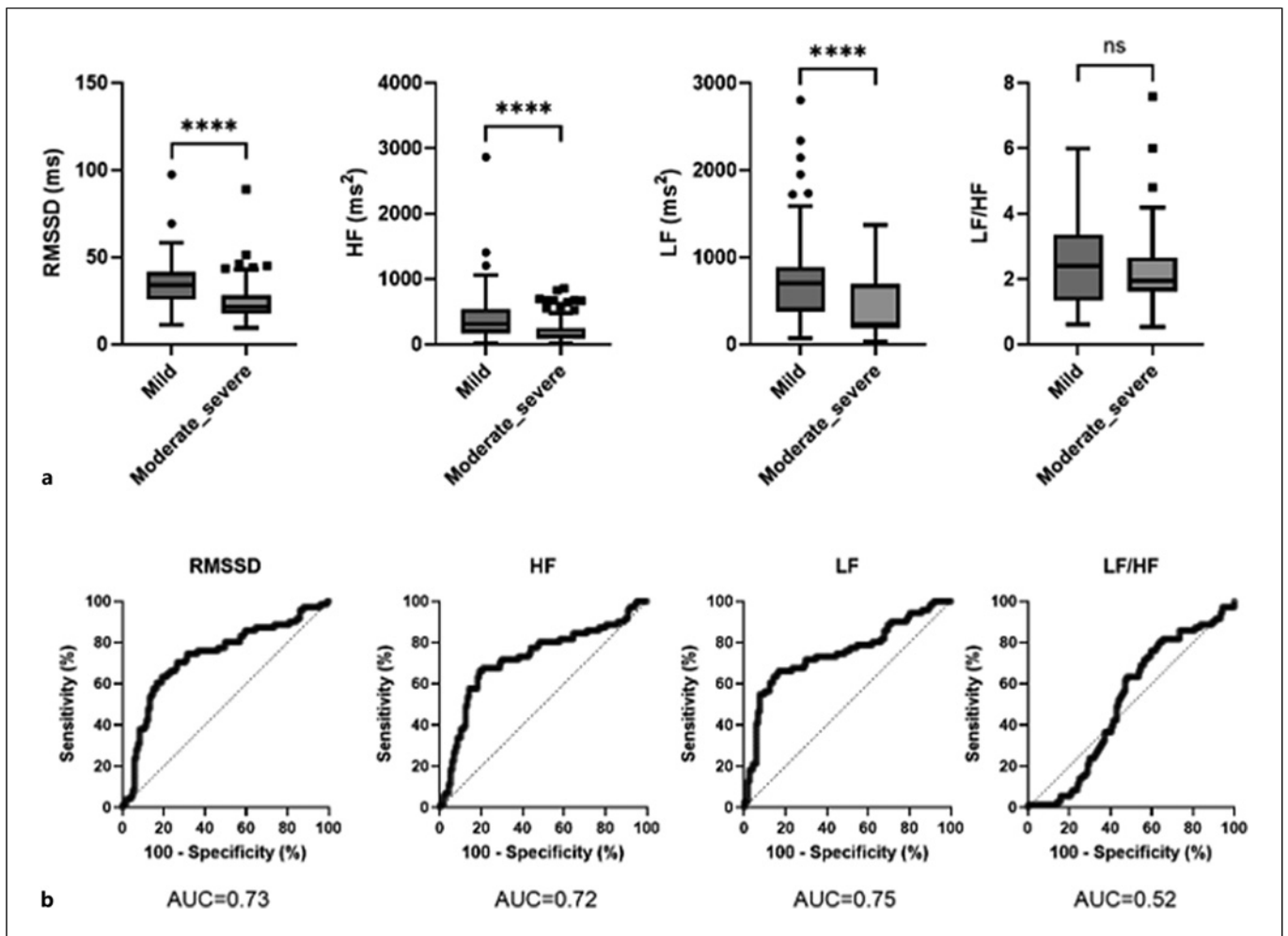


Fig. 4. Comparison of heart rate variability between moderate-severe and mild disease in UC patients. **a** RMSSD, HF, and LF were significantly higher in moderate-severe than in mild disease. **** $p < 0.0001$; ns, not significant by Mann-Whitney U test. **b** Results from the ROC analyses for each HRV index, with the corresponding AUCs. RMSSD showed an AUC value of 0.73, cut-off value of 24.3, sensitivity of 63.4%, and specificity of

81.0%. HF also showed an AUC value of 0.72, cut-off value of 154.9, specificity of 66.2%, and sensitivity of 81.0%. LF also showed an AUC value of 0.75, cut-off value of 335.8, specificity of 66.2%, and sensitivity of 83.5%, which indicated moderate accuracy. HRV, heart rate variability; RMSSD, root mean square of successive differences of RR intervals; LF, low frequency; HF, high frequency.

Comparison of BU and HRV

As indicated in the introduction, BU, which is known to be related to the brain-gut axis, has a significant impact on the quality of life of UC patients. Thus, we investigated whether HRV is related to BU scores. First, a two-group comparison was performed between BU negative (0) with BU positive (1–3). In these results, only LF were significantly higher in the case of BU positive than in the BU negative (Fig. 5a; online suppl. Table 1; for all online suppl. material, see <https://doi.org/10.1159/000543295>). Further, we investigated a two-group comparison was performed

between mild BU (0–1) with moderate-to-severe BU (2–3). Interestingly, these analyses were also showed LF was clearly higher in the case of moderate-to-higher BU than in the mild BU (Fig. 5b). And HF was also higher in the case of moderate to higher BU than in the mild BU. The results from the ROC analyses for LF showed an AUC value of 0.75, cut-off value of 694.5, sensitivity of 83.3%, and specificity of 63.3% and HF showed an AUC value of 0.70, cut-off value of 551.0, sensitivity of 50.0%, and specificity of 87.7% (Fig. 5c; Table 3). In conclusion, LF was potentially most related to BU among the HRV measures.

Table 2. Comparison of two groups: moderate-severe and mild disease in HRV in ROC analysis

Variable	AUC (95% CI)	Cut-off value	Sensitivity, % (95% CI)	Specificity, % (95% CI)
RMSSD	0.73 (0.66–0.81)	24.3	63.4 (51.8–73.6)	81 (73.1–87.0)
HF	0.72 (0.64–0.80)	154.9	66.2 (54.6–76.1)	81 (73.1–87.0)
LF	0.75 (0.67–0.83)	335.8	66.2 (54.6–76.1)	83.5 (75.8–89.0)
LF/HF	0.52 (0.43–0.60)	2.8	80.3 (69.6–87.9)	36.4 (28.3–45.2)

RMSSD, root mean square of successive differences of RR intervals; LF, low frequency band; HF, high frequency band.

Discussion

This prospective study showed that longitudinally assessed HRV, particularly the nighttime vagal index, including the RMSSD and HF index, was inversely correlated with UC disease activity. In previous reports, including systematic reviews, HRV and the ANS have been associated with gastrointestinal diseases, such as IBS or IBD [3, 18]. There was a significant difference between patients with IBD and healthy controls in the time-domain HRV, and especially a significant decrease in HF measurements, which is known as one of the vagal indices [19]. There are several suspected causes of the reduced parasympathetic activity in patients with IBD. First, chronic gut inflammation directly affects the ANS. Inflammatory cytokines such as tumor necrosis factor- α and interleukin-6 can influence the nervous system and disrupt autonomic balance [20]. Specifically, inflammation can activate the sympathetic nervous system, which is responsible for stress responses, and suppress the parasympathetic nervous system [21]. Inflammation, pain, and stress can suppress the function of the parasympathetic nervous system, impairing relaxation and digestive functions [22]. This suppression can lead to irregular bowel movements and the worsening of digestive symptoms.

Second, the gut-brain axis, which refers to the cross-talk communication between the gut and brain, may be disrupted by gut inflammation. The gut-brain axis involves bidirectional and continuous interactions that inform the molecular, cellular, and functional status [23]. It has been suggested that the brain-gut axis may influence the pathogenesis of IBD [24]. When the vagal nerve is activated, acetylcholine is stimulated and the

release of acetylcholine suppresses the production of inflammatory cytokines [25]. Inflammatory mediators may affect the nervous system and impair parasympathetic nervous system function, thereby disrupting the balance of ANS. The sensory fields of the gut afferent vagal neurons are equipped with receptors that sense inflammatory modulators in the intestinal microenvironment [26]. Third, alterations in the gut microbiota can influence the interactions between the gut and the ANS in IBD. Imbalances in the gut microbiota can contribute to inflammation, which in turn may lead to a reduction in parasympathetic nervous system activity. Furthermore, peripheral regulatory T cells in the gut, which are essential for gut immune tolerance, are regulated not only by the gut microbiota but also by the vagal reflex [27]. Remarkably, dysbiosis precedes changes in CNS immunity, causing intestinal permeability and triggering neuro-inflammatory symptoms, suggesting that dysbiosis promotes humoral signaling of inflammatory factors across the gut-brain axis [25, 28].

Although several pieces of evidence were generated in this manner, this study has some critical points. First, we were able to achieve results using a smartwatch, which is not a medical device. In a systematic review, HRV was recorded on ECGs over periods ranging from 5 min to 24 h [3, 11, 29]. Hirten et al. [18] reported that a disposable medical device called the VitalPatchTM could be used to successfully obtain HRV in patients with UC. The evaluation of the correlation between HRV and disease activity levels through means other than medical devices in this study is a favorable step toward practical applications in the future.

The results of this study showed a clear correlation among the patients with active UC. In particular, when a

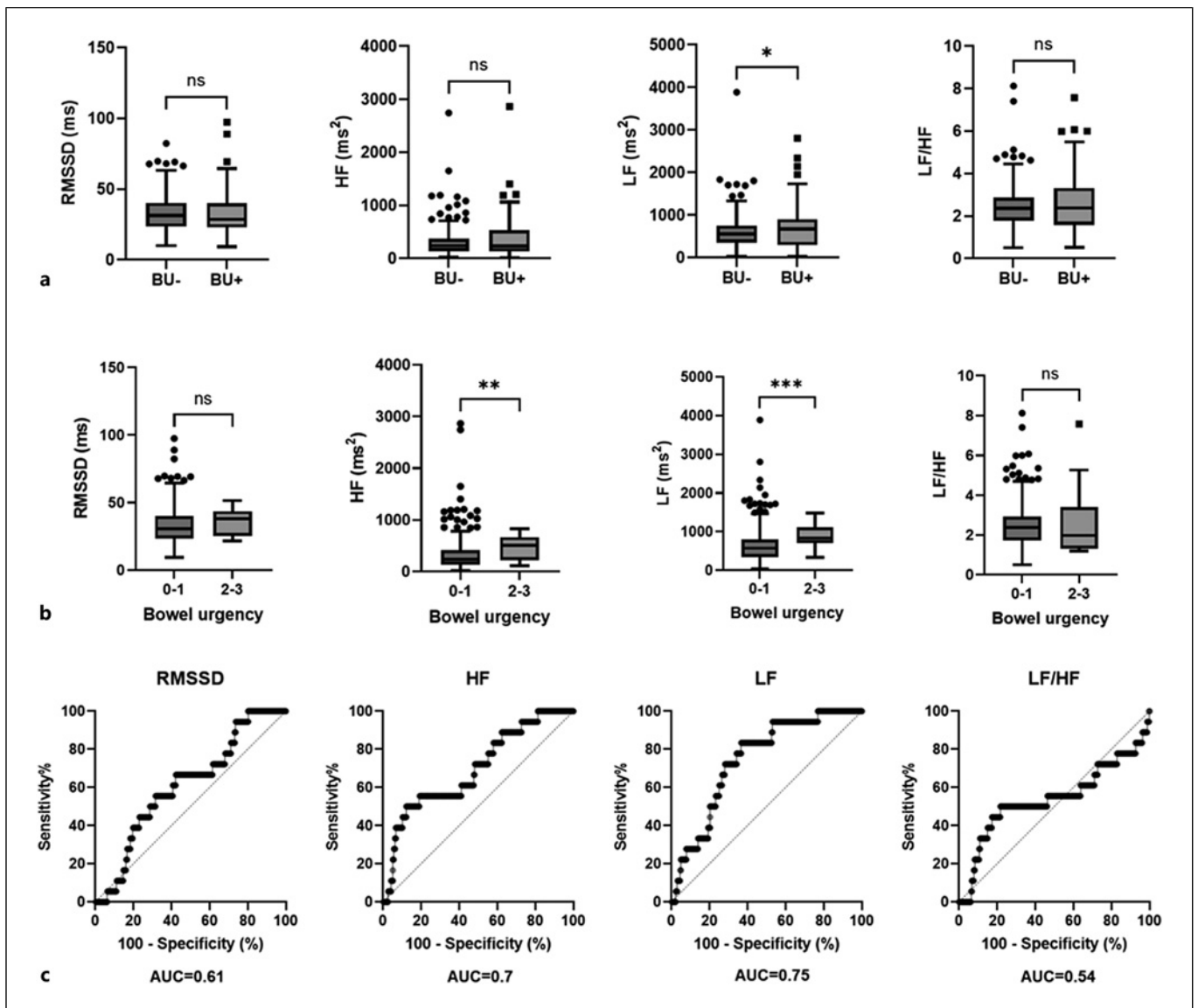


Fig. 5. Comparison of BU and heart rate variability. **a** LF were significantly higher in the case of BU positive (1–3) than in the BU negative (0). * $p < 0.05$; not significant by Mann-Whitney U test. **b** LF and HF were significantly higher in the case of moderate-to-higher BU (2–3) than in mild BU (0–1). ** $p < 0.01$; *** $p < 0.001$; ns, not significant by Mann-Whitney U test. **c** The results from the ROC analyses for LF showed an AUC

value of 0.75, cut-off value of 694.5, sensitivity of 83.3%, and specificity of 63.3% and HF showed an AUC value of 0.70, cut-off value of 551.0, sensitivity of 50.0%, and specificity of 87.7%. BU, bowel urgency; HRV, heart rate variability; RMSSD, root mean square of successive differences of RR intervals; LF, low frequency band; HF, high frequency band; ns, not significant.

new medication is administered to the patient with active IBD treated as an outpatient, conventional biomarkers are evaluated several weeks in advance. The results of this study allow real-time HRV measurement, which may help simplify the prediction of treatment efficacy.

Finally, we found that the most correlated with BU symptoms was LF among HRV measures. The LF/HF

ratio is commonly used to indicate the degree of sympathetic activity, but some reports described that LF alone also reflects the sympathetic nervous system [30]. Interestingly, RMSSD, parasympathetic index, which was highly correlated in SCCAI, was not associated with BU symptoms. Namely, UC disease activity and BU may be different pathogenesis at least in the functioning of the

Table 3. Comparison of two groups: mild and moderate to severe BU in HRV in ROC analysis

Variable	AUC (95% CI)	Cut-off value	Sensitivity, % (95% CI)	Specificity, % (95% CI)
RMSSD	0.61 (0.50–0.73)	33.7	66.7 (43.8–83.7)	57.8 (54.2–61.3)
HF	0.70 (0.57–0.82)	551.0	50.0 (29.0–71.0)	87.7 (85.1–89.9)
LF	0.75 (0.66–0.84)	694.5	83.3 (60.8–94.2)	63.3 (59.7–66.7)
LF/HF	0.54 (0.37–0.71)	1.7	50 (29.0–71.0)	78.2 (75.1–81.1)

RMSSD, root mean square of successive differences of RR intervals; LF, low frequency; HF, high frequency.

ANS. More in-depth research is needed to clarify this matter, which could potentially further improve the quality of life of UC patients.

Our study had several limitations. The sample size for this study was nine. This small sample size may have allowed the outliers to affect the analysis. Although this was a pilot study because of the small budget, we believe that the results of this study will lead to further large-scale research designs. In addition, HRV at night was applied to avoid the influence of daytime activity as much as possible; however, other factors, such as smoking and alcohol consumption, were not restricted.

However, it is very worthwhile that in a prospective study design, continuous HRV could be measured in patients with active UC using a nonmedical device. We look forward to future research in this area.

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Statement of Ethics

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study design was reviewed and approved by the Medical Ethics Committees of Tokai University

(23R-004) and Shiga University Medical School (RC2023-063). Written informed consent was obtained from all participants before their inclusion in the study. The privacy of participants was completely protected by anonymization.

Conflict of Interest Statement

There are no conflicts of interest to declare.

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Author Contributions

The authors’ responsibilities were as follows: J.I. conceived and designed the study, performed the data collection, performed the statistical analysis, and wrote the manuscript; M.O. conceived and designed the study, collected the data, and performed the statistical analysis; M.S., A.N., Y.H., T.U., H.S. (Hiroaki Suzuki), E.T., M.M. (Makiko Monma), M.F., R.D., N.K., H.S. (Haruhiko Sato), M.M. (Masashi Matsushima), and T.K. contributed to data collection; T.M., H.S., N.I., and A.B. contributed to data analysis; Y.N., A.A., and H.S. (Hidekazu Suzuki) conceived and designed the study and supervised the data collection. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding authors.

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