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Preliminary Study on Establishing a Heart Rate Variability-based Method for Objectively Evaluating Bone Metastasis Pain

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Abstract. *Background/Aim: The aim of this study was to establish an objective evaluation method for pain due to bone metastasis, based on heart rate variability (HRV). Patients and Methods: In this prospective study, patients who underwent radiotherapy for painful bone metastases were enrolled. Pain was assessed using a numerical rating scale (NRS), and anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS). Autonomic and physical activities were evaluated by measuring HRV using a wearable device. NRS, HADS, and R-R interval (RRI) values were obtained upon starting, completing, and 3-5 weeks after radiotherapy. Results: Between July 2020 and July 2021, 11 patients were enrolled. The median average NRS score was 5 (range=2-10). HADS-assessed median anxiety and depression scores were 8 (range=1-13 and 2-21). For patients with an NRS score ≥4, NRS score was significantly associated with low-frequency/high-frequency (LF/HF) component ratio (p=0.03). Heart rate during physical activity was significantly higher than resting heart rate; however, mean resting LF/HF was significantly higher than LF/HF during physical activity. During rest, excluding patients with a HADS depression score ≥7 in an NRS score 1-3, there was a trend for a positive correlation between the NRS score and the mean LF/HF (p=0.07). Conclusion: HRV measurements can objectively evaluate pain due to bone metastasis. However, we must consider that the effects of mental status, such as depression, on LF/HF also affect HRV in patients with cancer with mild pain.*

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Key Words: Heart rate variability, pain, numerical rating scale, bone metastasis, radiotherapy.

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In the United States, prescription drugs, including painkillers, have become the major category of abused substances, with the potential to overtake illicit drugs (1). In particular, prescription opioids are more common as gateway drugs than marijuana (2, 3) and represent a social problem caused by the overestimation of pain. Severe pain is associated with a poor quality of life (4), and pain and psychiatric disorders have a high probability of coexistence (5). In contrast, underestimation of pain exacerbates patient distress. Therefore, the accurate estimation and management of pain are important.

In clinical practice, subjective evaluation methods of pain, such as the numerical rating scale (NRS) (6), visual analogue scale (VAS) (7), and face scale (8), are commonly used, and an objective evaluation method has not been established. Proper objective assessment of pain should be minimally invasive and immediate. Previous studies have reported that functional magnetic resonance imaging (9) and biomarkers, such as interferon-γ, interleukin-10, and tumour necrosis factor (10) are useful for objective assessment of pain. However, these techniques cannot evaluate pain immediately or noninvasively. Pain activates the sympathetic nerves during transmission from peripheral nerves to the dorsal horn of the spinal cord and limbic system. Therefore, it may be possible to objectively evaluate pain by measuring sympathetic nervous system activity. Heart rate variability (HRV) analysis is an immediate and non-invasive technique because it measures autonomic nervous system activity (11) according to fluctuations in heartbeat intervals (R-R intervals; RRI), which reflect autonomic control. In previous studies reporting the usefulness of HRV for pain assessment, pain after minor spinal surgery was related to increased sympathetic nervous system activity (12), and chronic low back pain and chemotherapy-induced peripheral neuropathy were related to decreased parasympathetic nervous system activity (13, 14). However, few studies have examined the usefulness of HRV in cancer pain management.

In this study, we aimed to evaluate the efficacy of HRV as an objective assessment of pain caused by bone metastasis, which is the leading cause of cancer-associated pain.

Patients and Methods

Patients. From July 2020 to July 2021, we prospectively recruited patients treated with radiotherapy for painful bone metastasis that met the following criteria: i) pathological diagnosis of cancer; ii) no bone metastasis causing severe pain other than the radiation field; iii) expected prognosis of ≥3 months; iv) self-evaluation of pain, anxiety, and depression; and v) received sufficient explanation for participating in this study and who provided voluntary written consent. This study excluded patients whose RRI could not be accurately evaluated due to arrhythmia or pacemaker, those with psychiatric comorbidities, such as depression and anxiety disorder, those with apparently impaired cognitive function, and those with bone fracture and strong nerve infiltration caused by bone metastasis.

This study was approved by the ethics committee of the Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, according to institutional policy (IRB No. 2623). Written informed consent was obtained from all patients.

Assessment of pain. Pain assessment was based on self-reported pain using the NRS, which comprised an 11-point scale from 0 to 10 (0 being ‘no pain’ and 10 being ‘worst pain you can imagine’ (6). Each patient selected a number that best described their average, maximum, and minimum pain of the day.

Assessment of anxiety and depression. Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS) (15, 16), which is a 14-item self-report measure. In this scale seven items measure depression and the other seven measure anxiety. Each item is rated on a 4-point scale from 0 to 3; a higher score indicates more frequent symptoms. The total score for each subscale ranged from 0 to 21. In either subscale, a score of 0-7 was ‘normal’, 8-10 was ‘suggestive presence’, and ≥11 was ‘probable presence’.

Measurement of autonomic activity. Autonomic activity was evaluated based on HRV, which was measured using a wearable device (Union Tool Co., Tokyo, Japan; Figure 1A) and an analysis software (WIN Frontier Co., Ltd., Tokyo, Japan; Figure 1B). RRI was obtained using a wearable device with electrode pads attached to the patient’s left anterior chest (Figure 1C). The small wearable heart rate sensor can measure RRI, body surface temperature, and triaxial acceleration. The sensor’s sampling frequencies for heart rate interval, body surface temperature, and triaxial acceleration are 1,000, 1, and 31.25 Hz, respectively. A wearable device (Figure 1A) can measure fluctuations in RRI and use HRV to calculate indices of sympathetic and parasympathetic nervous system activities.

Generally, a fluctuation in heartbeat occurs in a living body; when this fluctuation is frequency-analysed, a peak is seen at a certain frequency. In humans, a high-frequency (HF) component (0.15-0.40 Hz), reflecting variation in the respiratory cycle, and low-frequency (LF) component (0.05-0.15 Hz), reflecting fluctuations in blood pressure, reflect autonomic activity. The software performed a frequency analysis with an RRI of 300 s, which is the international standard. HF indicates parasympathetic nervous system activity and LF/HF indicates sympathetic nervous system activity. The total power (TP) is the sum of the HF and LF and serves as a benchmark of total variability.

Measurement of physical activity. Body movement levels were determined based on acceleration sensors embedded in the wearable device, using the supplied software. Because the composite value of triaxial acceleration is correlated with body activity indicators and energy consumption (17), triaxial acceleration was analysed to distinguish between physical activity and rest.

Radiotherapy. External beam radiotherapy (EBRT) was delivered using a three-dimensional conformal technique with a linear accelerator (ONCHOR Impression Plus; Siemens Medical, Erlangen, Germany) using 6- or 10-MV photon beams or stereotactic body radiotherapy (SBRT) with a linear accelerator (Vero4DRT; Hitachi Healthcare, Tokyo, Japan, and BrainLab AG, Feldkirchen, Germany) using a 6-MV photon beam. Three-dimensional planning was performed in all patients using computed tomography (Aquilion LB/16; Canon Medical, Tochigi, Japan). EBRT was performed once a day and five times a week. For patients treated with three-dimensional conformal radiotherapy, a dose of 20.0-30.0 Gy in 5-10 fractions for 5-14 days was administered. For patients treated with SBRT, a dose of 24.0 Gy in two fractions for 2 days was delivered to the spinal metastasis and 35.0 Gy in five fractions for 5-7 days to bone metastases other than the spine.

Assessment schedule of NRS, HADS, and HRV. For patients receiving radiotherapy with five or more fractions, NRS, HADS, and RRI were obtained three times, at the start of radiotherapy, completion of radiotherapy, and 3-5 weeks after completion of radiotherapy. For patients receiving radiotherapy with less than five fractions, NRS, HADS, and RRI were obtained twice, at the start of radiotherapy and 3-5 weeks after completion of radiotherapy. Figure 2 shows an example of the assessment schedule for patients who received 30 Gy in 10 fractions. Heart rate intervals were obtained over approximately 24 h, and the NRS and HADS were assessed based on pain, anxiety, and depression during heart rate measurement.

Statistical analysis. A power analysis was not conducted because the preliminary data obtained in this study could be used for planning a definite study.

For univariate analysis, the relationship between HRV index (HF, LF/HF, and total power) and NRS score and between HRV index and HADS score was evaluated using single regression analysis. A correlation coefficient of ≥0.7 was considered significant. For multivariate analysis, multiple regression analysis was conducted to examine the impact of LF/HF, HF, TP, and heart rate on the NRS and HADS scores. Differences between the mean value of LF/HF and heart rate during physical activity and rest were evaluated using

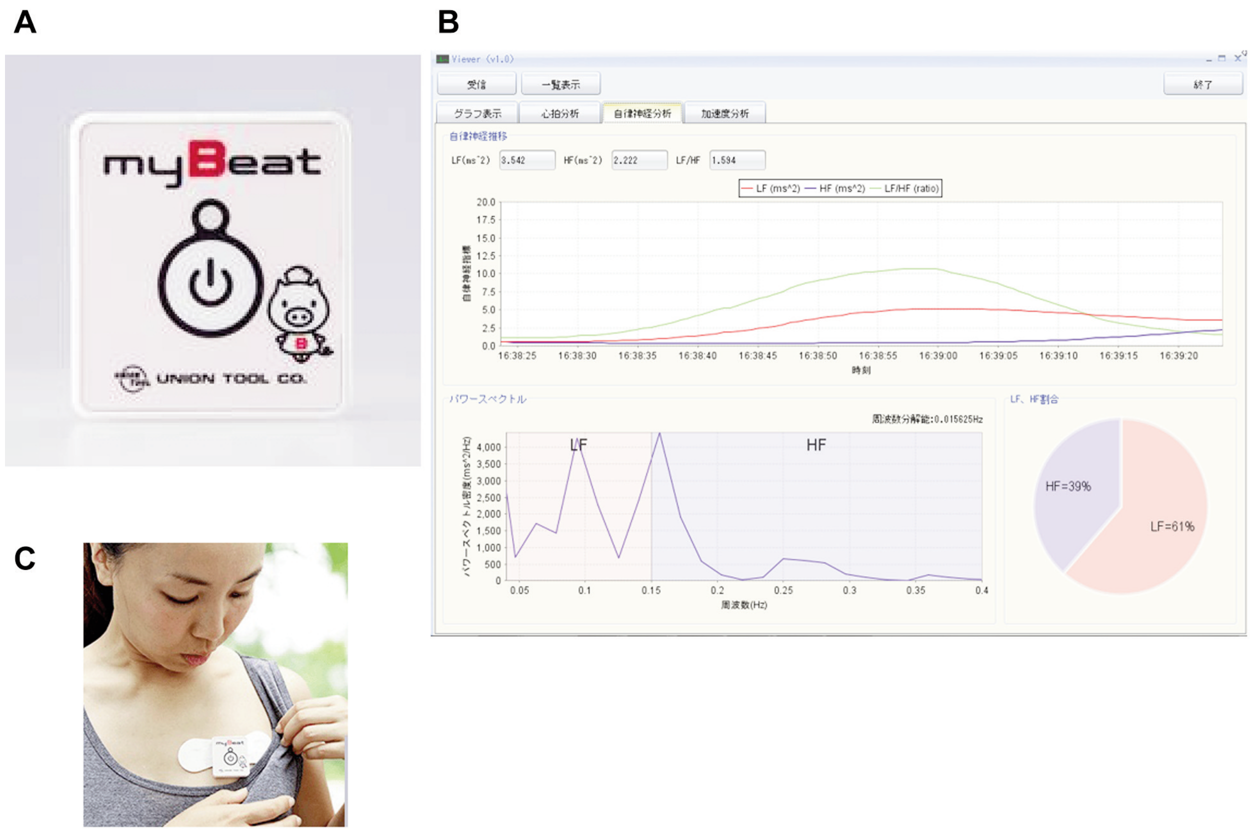

Figure 1. *Wearable device and analysis software for heart rate variability analysis. Heart rate intervals (R-R intervals) were acquired using wearable device (A, WIN Frontier Co. Ltd, Tokyo, Japan), and heart rate variability was analysed using an analysis software (B, Union Tool Co., Tokyo, Japan). A wearable device with electrode pads attached to the patient's left anterior chest (C).*

Student's *t*-test. A significant difference was considered when the *p*-value was ≤0.05. All statistical analyses were performed using SPSS Base System (version 27.0; SPSS, Chicago, IL, USA).

Results

Eleven patients were enrolled in this study. Patient and treatment characteristics are shown in Table I. The median age of the patients was 65 years (range=50-83 years). Eight patients were men and three were women. Six of the 11 patients received radiotherapy for pelvic bone metastasis, four for spinal metastasis, and two for metastasis in other regions, such as the rib and scapula. One patient underwent irradiation for pelvic and spinal metastases simultaneously. Seven of the 11 patients were treated with SBRT.

In four of the 11 patients, who received a dose of 20.0-24.0 Gy in 1-2 fractions, NRS, HADS, and heart rate intervals were obtained at the start of radiotherapy and 3-5 weeks after the completion of radiotherapy. Of the patients, one could not be assessed at completion of radiotherapy because of patient refusal, another could not visit our hospital 3-5 weeks after the completion of radiotherapy because of deterioration of his general condition, and another could not be assessed using the HADS 3-5 weeks after the completion of radiotherapy. Therefore, 27 samples for NRS and heart rate intervals and 26 samples for HADS were analysed.

The median average, maximum, and minimum NRS scores were 5 (range=2-10), 6 (range=2-10), and 3 (range=0-8), respectively. In the HADS assessment, the median anxiety and depression scores were 8 (range=1-13) and 8 (range=2-21), respectively. The mean HF, LF/HF, and TP over approximately 24 h were 0.52 ms^2 (standard deviation, SD=1.66 ms^2), 2.45 (SD=1.20), and 0.94 ms^2 (SD=2.41 ms^2), respectively.

There was no significant relationship between mean LF/HF and anxiety score, mean HF over approximately 24 h and anxiety score, and mean HF and depression score (r<0.001, *p*=0.99; r=0.047, *p*=0.829; and r=0.050, *p*=0.815, respectively). However, mean LF/HF over approximately 24 h tended to be slightly associated with depression score in the HADS (r=0.32, *p*=0.13). For all samples, the NRS score had no significant relationship with the mean LF/HF

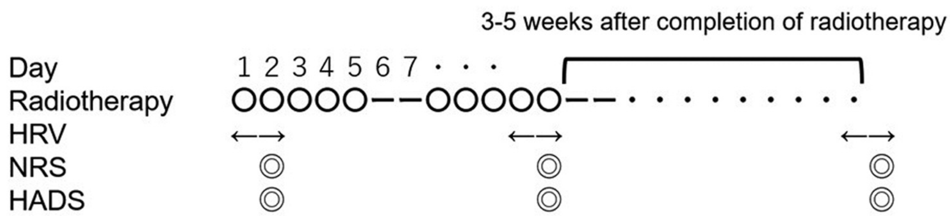

Figure 2. *Assessment schedule of NRS, HADS, and HRV for patients administered a dose of 30 Gy in 10 fractions. NRS, HADS, and heart rate intervals were obtained three times, at the start of radiotherapy, completion of radiotherapy, and 3-5 weeks after completion of radiotherapy. NRS: Numerical rating scale; HADS: Hospital Anxiety and Depression Scale; HRV: heart rate variability.*

Table I. *Patient and treatment characteristics.*

Patient no.	Age	Sex	Primary site	Technique	Irradiation site	Dose
1	77	Female	Thyroid	SBRT	Spine	24 Gy/2 fr
2	83	Male	Kidney	SBRT	Pelvic bone	35 Gy/5 fr
3	52	Female	Uterine	3DCRT	Rib	20 Gy/5 fr
4	56	Male	Rectum	SBRT	Pelvic bone	35 Gy/5 fr
5	70	Male	Lung	SBRT	Scapula	35 Gy/5 fr
6	65	Male	Colon	SBRT	Spine	20 Gy/1 fr
7	50	Male	Kidney	SBRT	Pelvic bone	24 Gy/2 fr
8	59	Male	Prostate	3DCRT	Pelvic bone	20 Gy/5 fr
9	74	Male	Kidney	SBRT	Spine	24 Gy/2 fr
10	51	Female	Breast	3DCRT	Pelvic bone	30 Gy/10 fr
11	77	Male	Prostate	3DCRT	Spine, pelvic bone	20 Gy/5 fr

SBRT: Stereotactic radiotherapy; 3DCRT: three-dimensional radiotherapy; fr: fraction.

(Figure 3A) and HF (Figure 3B) (r=0.094, p=0.66 and r=0.071, p=0.74, respectively). For samples with NRS ≥4, NRS score was significantly associated with LF/HF (Figure 3C, r=0.58, p=0.03), but not with HF (Figure 3D, r=0.37, p=0.197).

Figure 4 shows the heart rate and mean LF/HF ratio during physical activity and rest for all patients. Although the heart rate during physical activity was slightly higher than that at rest (p=0.073), the mean LF/HF ratio at rest was significantly higher than that during physical activity (p=0.024). At rest, mean LF/HF was not associated with NRS score for all samples (Figure 5A) or those with NRS ≥4 (Figure 5B) (r=0.11, p=0.61 and r=0.21, p=0.49, respectively). Excluding those with a HADS depression score ≥7 in an NRS score 1-3, there was a trend for a positive correlation between the NRS score and the mean LF/HF (Figure 5C, r=0.51, p=0.07).

Discussion

HRV analysis is an immediate and non-invasive technique because it measures autonomic nervous activity according to fluctuations in RRI. The aim of this study was to evaluate the efficacy of HRV in objectively assessing pain caused by bone metastasis. Masel *et al*. reported that LF/HF positively correlates with NRS score, which measures cancer pain in palliative care patients (13). For patients with acute pain after minor surgery, both LF/HF and LF positively correlate with NRS, and LF values of >298 m^2 and LF/HF >3.1 indicate NRS >3 (12). Gockel *et al*. reported that TP negatively correlates with moderate perceived disability, as measured by the Oswestry disability index for patients with chronic low back pain (18). Previous studies have shown a positive correlation between pain and sympathetic nervous system activity and a negative correlation between pain and parasympathetic nervous system activity (12, 13, 18). In this study, the NRS score was not significantly related to sympathetic or parasympathetic nervous system activities. However, in patients with an NRS ≥4, the NRS score positively correlated with sympathetic nervous system activity. In recent studies, RRI has been obtained for a short duration (10-30 min) at rest (12, 19) or for a long duration (24 h) (13). However, HRV measured over 24 h was not evaluated separately in relation to pain during physical activity or rest (13). Generally, in patients with bone metastasis, pain is enhanced by patient weight during

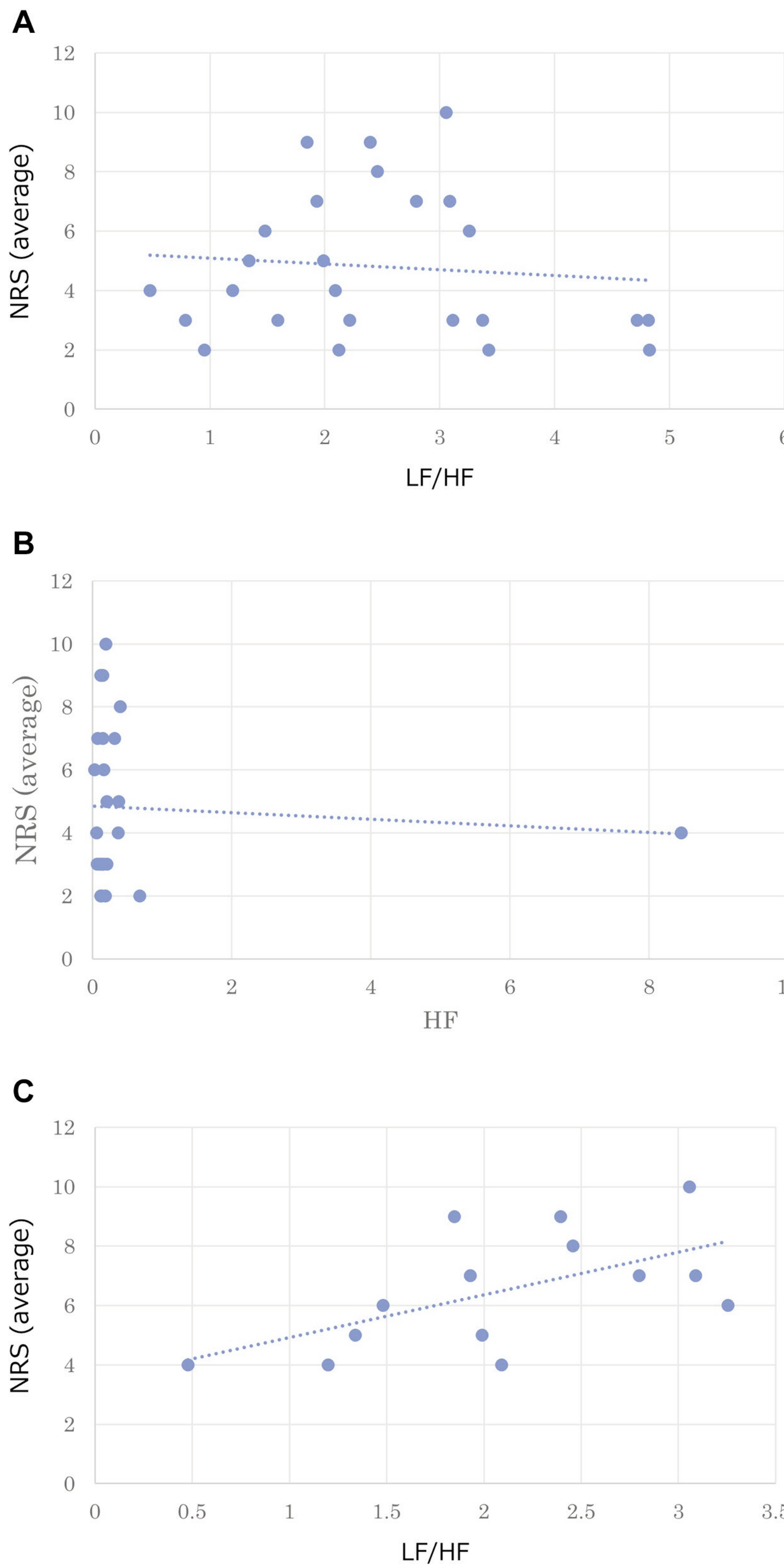

Figure 3. *Relationship between sympathetic nervous system activity and numerical rating scale (NRS) score. Relationship between mean low-frequency/high-frequency (LF/HF) and NRS score (A), mean HF and NRS score (B), mean LF/HF and NRS ≥4 (C), and mean HF and NRS ≥4 (D).*

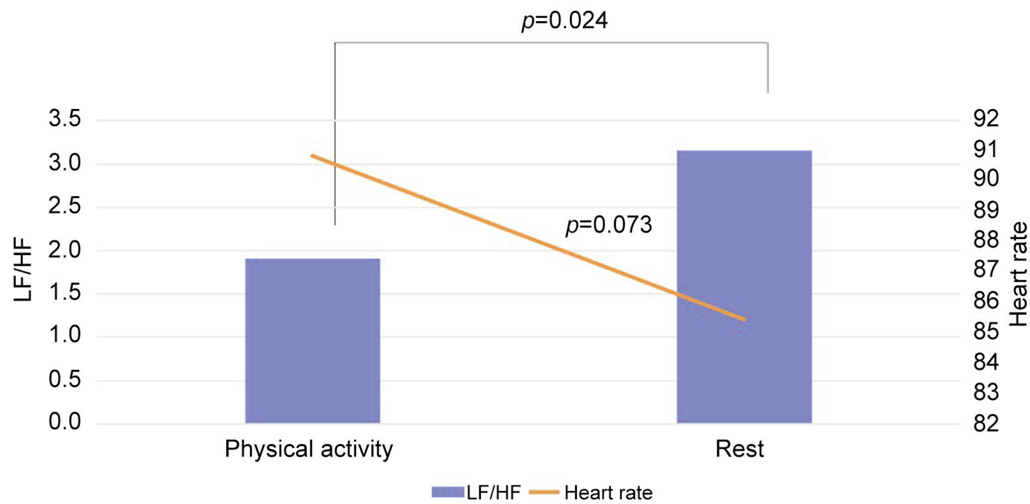

Figure 4. *Heart rate and mean low-frequency/high-frequency (LF/HF) component at rest and during physical activity.*

physical activity because bone metastasis induces micropathological fractures. Nonetheless, in clinical practice, patients with cancer complain of more severe pain at rest than during physical activity. Few reports have investigated whether HRV measurement should be performed during physical activity or at rest. In this study, the heart rate at rest was slightly lower than that during physical activity, but the sympathetic nervous system activity was significantly enhanced at rest. Therefore, the best time to obtain the heart rate intervals was considered to be at rest. However, in this study, there was no relationship between LF/HF at rest and NRS score for all samples and samples with NRS ≥4 (p=0.61 and 0.49, respectively).

Several previous reports have shown that depression and anxiety disorders are associated with autonomic activity estimated using HRV (19-21). Lower HF correlates with depressive symptoms and anxiety disorder (19, 21), and higher LF/HF correlates with major depressive disorder (20). In this study, mean LF/HF over approximately 24 h tended to be slightly associated with depression score in the HADS (p=0.13). It may be a concern that mental conditions, such as depression affect LF/HF. Except for samples with a depression score of ≥7 in the HADS and NRS 1-3, NRS and sympathetic activity tended to correlate (p=0.07). Therefore, when assessing cancer pain using HRV, the mental condition of patients with mild pain should be considered. However, HRV may be useful in detecting patients with moderate to severe pain or depression who are in need of medical intervention.

This study has some limitations. First, the impact of our findings is limited by the small sample size. Second, the daily NRS scores may have been influenced by the regular administration of painkillers to patients. This was not controlled for in our study and could have affected our findings. However, we are currently conducting a multicentre prospective study to evaluate the usefulness of HRV for objective pain assessment, including information on the type of painkiller, time taken for painkiller action, and specific time of increased pain.

In conclusion, HRV has the potential to objectively evaluate cancer pain caused by bone metastases. However, in patients with cancer with mild pain, we must consider that mental status, such as depression, affects LF/HF.

Conflicts of Interest

All Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

KNM, MK, WM, KO, and HI conceptualized the study, developed the methodology, and conducted the formal analysis and investigation. KNM, TS, KI, and SH prepared the initial draft of the manuscript. HI reviewed and edited the manuscript. KNM validated and supervised the project and administrated the project administration.

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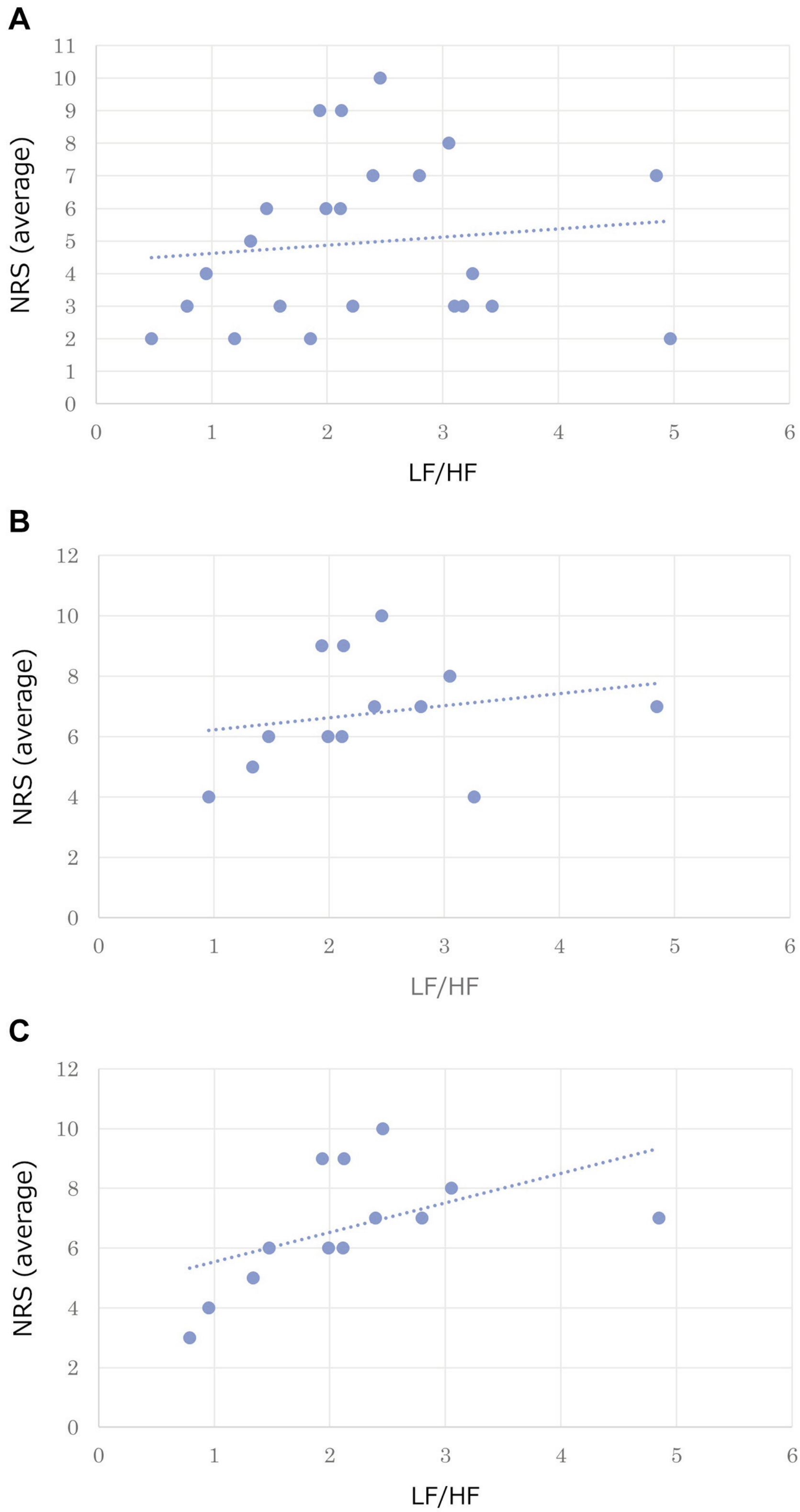

Figure 5. *Relationship between mean low-frequency/high-frequency (LF/HF) component at rest and numerical rating scale (NRS) score. Relationship between mean LF/HF at rest and NRS score (A), mean LF/HF at rest and NRS ≥4 (B), and mean LF/HF at rest and NRS score excluding samples with depression score ≥7 in NRS score 1-3 (C).*

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