

Heart Rate Variability as a Non-invasive Objective Parameter for Predicting the Occurrence of Chemotherapy-induced Peripheral Neuropathy in Patients With Gastrointestinal Cancer

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Abstract. *Background/Aim:* Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common chemotoxicities. However, no effective clinical CIPN screening methods have been reported. This study aimed to investigate whether changes in heart rate variability (HRV) could predict the development of CIPN for early symptom control in chemotherapy-prescribed patients with gastrointestinal (GI) cancer. *Patients and Methods:* Fifty-five GI cancer outpatients undergoing palliative chemotherapy including taxanes and/or platinum compounds were enrolled. CIPN was diagnosed using National Cancer Institute Common Toxicity Criteria for Adverse Event (NCI-CTCAE). HRV measures were derived from electrocardiogram signals. *Results:* Twelve weeks after starting chemotherapy, 39 (70.9%) patients who complained of NCI-CTCAE grade 1-3 sensory changes were diagnosed with CIPN. Standard deviation of normal-to-normal R-R intervals (SDNN), high frequency (HF), low frequency (LF), and LF/HF ratio changed significantly during 3 assessment periods. Percentage changes in SDNN and HF were related to the occurrence of CIPN symptoms. A decision tree model indicated that patients with a rapid percentage change decrease in SDNN and HF were CIPN-positive. *Conclusion:* Using SDNN and HF, our decision tree predicted CIPN occurrence. The changes in HRV may occur earlier than sensory CIPN symptoms.

Gastrointestinal (GI) cancers such as liver cancer, stomach cancer, and colon cancer are the third, fifth, and sixth most common cancers in the world, respectively, accounting for approximately one million deaths each year (1, 2). Chemotherapeutic agents such as cisplatin, oxaliplatin, paclitaxel, and docetaxel have emerged as the cornerstones of systemic treatment for patients with GI cancer, in both adjuvant and metastatic settings. With the development of chemotherapeutic agents, the survival of GI cancer patients has increased, and the long-term sequelae of these chemotherapeutic agents has also increased. In GI cancer patients, chemotherapy-induced peripheral neuropathy (CIPN) has been reported to be the most prominent side effect, despite the good tolerability profile of chemotherapeutic agents (3, 4). CIPN may delay the chemotherapeutic schedule and reduce the optimal dose of these agents resulting in a negative effect of cancer treatment. However, no effective clinical CIPN screening methods have been reported yet. Objective, simple, non-invasive parameters are needed for the early detection of CIPN for preventing severe side-effects.

Heart rate variability (HRV) indicates that the autonomic nervous system (ANS) is responding to changes in the body or external environment (5). HRV measurements provide a non-invasive method for evaluating factors affecting the ANS (6), and it has been widely used for studying the ANS for the prognosis of acute myocardial infarction, arrhythmias, cardiac syncope, orthostatic hypotension, sleep apnoea, and urinary incontinence (7-12). However, there have been no studies determining the relationship between CIPN and HRV in cancer patients who have been prescribed chemotherapy. We hypothesized that a change in HRV, reflecting the autonomic symptoms of CIPN, may be apparent prior to the occurrence of sensory symptoms. Patients were periodically monitored for CIPN symptoms and HRV before and after chemotherapy for hypothesis testing.

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Thus, this study aimed to investigate HRV and peripheral neuropathy symptoms in GI cancer patients who have been prescribed chemotherapy and to determine whether the changes in HRV could predict the development of CIPN for early symptom control.

Patients and Methods

Study design and patients. This prospective cohort study was conducted in GI cancer patients who visited GI oncology outpatients' clinic for palliative chemotherapy at our institution (Pusan National University Hospital, South Korea) from May 2018 to February 2019. All patients who received taxanes and/or platinum compounds were considered eligible for participation in the study. The inclusion criteria comprised patients 1) aged >18 years; 2) with histologically confirmed GI cancer; 3) with an Eastern Cooperative Oncology Group performance of ≤1; 4) prescribed chemotherapy involving paclitaxel, docetaxel, nab-paclitaxel, and platinum, such as cisplatin, carboplatin, or oxaliplatin; and 5) without cognitive impairment who understood the study aims and who provided written informed consent to participate. The exclusion criteria comprised patients 1) with psychiatric symptoms, such as delusions, hallucinations, or a past history of these symptoms; 2) with a history of neurotoxic chemotherapy involving oxaliplatin, cisplatin, taxanes, or vinca alkaloids; 3) with other autonomic neuropathies, such as diabetes-related neuropathy, central neuropathy owing to brain disease, neuropathy owing to spinal disease, alcohol-related neuropathy, thyroid disease, Parkinson's disease, and vitamin B12 deficiency; 4) receiving CIPN-related medication; 5) with a family history of genetic/familial neuropathy; 6) who had been hospitalized with an acute medical history within the past 4 weeks; 7) with a history of second- or third-degree atrioventricular heart block, ischemic heart disease, or myocardial infarction within the past 6 months; 8) with heart stents or metal implants (pacemakers, automatic defibrillators, aneurysm clips, vena cava clips, and skull plates); and 9) without skin conditions, such as open wounds, which would prevent the proper application of electrodes.

All participants gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the institutional review board of Pusan National University Hospital (No. 1803-014-065) and was registered in the Clinical Research Information Service (No. KCT0005353).

Evaluation of HRV and acquisition of demographic data. HRV measures were derived from electrocardiogram (ECG) signals, using a QECG-3 monitoring system (Laxtha Inc., Daejeon, Korea). After participants had rested for 10 min in a quiet environment, ECG electrodes were attached to both the wrists and ankles, and the ECG was recorded for 10 min with patients placed in a comfortable seated position. To control for unintended influence on HRV, patients were required to refrain from smoking, consuming alcohol or caffeine, or undertaking exercise for an hour prior to the HRV measurement. ECG data were transferred into a computerized data collection system for interfacing with the data analysis software (TeleScan Ver.2.8; Laxtha Inc., Daejeon, Republic of Korea). In a continuous ECG record, QRS complex was detected, and NN intervals or instantaneous heart rate was determined. SDNN reflects the parasympathetic component of autonomic function, with higher

values indicating greater vagal activity and less sympathetic activity in the sinus node (13, 14). In addition, digitized ECG signals were used for identifying R-wave peaks, and beat-to-beat heart rate intervals were calculated (*i.e.*, R-R intervals). The R-R intervals were subjected to power spectral analysis that yielded HRV measures in two main frequency bands, namely a HF band (0.15–0.4 Hz) indicating vagal tone, and a LF band (0.04–0.15 Hz), largely indicating sympathetic activity. However, power in the LF is also considered to include some vagal influences (13, 15). Therefore, the ratio of LF and HF components, namely the LF/HF ratio, typically represents an index of sympathetic-to-parasympathetic balance, with higher values indicating greater sympathetic dominance (15). Patients were examined for HRV according to symptoms at baseline, 6 weeks, and 12 weeks after the start of chemotherapy.

Patient demographics and clinical data were collected prospectively, including age, sex, body mass index, comorbidity, alcohol intake, smoking habit, type of cancer, and prescribed chemotherapy.

Evaluation of CIPN. Neuropathic pain or other neuropathic symptoms present for more than one month and tingling or pain rating of ≥4/10 (identified using a single numeric analog questionnaire) during the previous week were set as the determining criteria. CIPN was defined as a clinical syndrome characterized as a dose-related, persistent (at least two subsequent cycles without a symptom-free interval) sensory deficit, comprising symmetrical distal numbness, painful or non-painful paraesthesia, and dysesthesia, and diagnosed using the NCI-CTCAE version 4.03 by an oncologist (16, 17). Patients were evaluated for CIPN symptoms according to the clinical syndrome and NCI-CTCAE guidelines at baseline, 6 weeks, and 12 weeks after the start of chemotherapy.

Statistical analyses. Data were presented as frequencies with percentages for categorical variables and mean±standard deviation (SD) for continuous variables. Differences in the patients' characteristics were compared across the subgroups using the chi-squared or Fisher's exact tests for categorical variables, and the independent t-test or Mann-Whitney *U*-test for continuous variables as appropriate. The Shapiro-Wilk test was performed for confirming a normal distribution of the data.

The two-way repeated measures analysis of variance was used for comparing repeated measured numeric variables in groups and within each group, and the Bonferroni procedure was applied in the post hoc analyses. The univariate and multivariate analyses using logistic regression were performed for identifying prognostic factors independently related to CIPN. The ROC curve was used for assessing the sensitivity and specificity of HRV for predicting CIPN. For data visualization, line graphs were also displayed. A recursive partitioning analysis was then performed for stratifying patients into risk groups.

All statistical analyses were performed using SPSS 24.0 and R 3.6.2 software, and a *p*-value of <0.05 was considered statistically significant.

Results

Patient characteristics. In total, 55 patients were enrolled in this prospective study [men, n=42 (76.4%); mean age=63.2 years]. Twenty patients (36.4%) were diagnosed with cholangiocarcinoma; 11, pancreatic cancer; 4, gallbladder

Table I. Study patients' baseline characteristics.

Variable	Overall	At 12 weeks			<i>p</i> -Value
		CIPN (-)	CIPN (+)*		
All patients (%)	55 (100.0)	16 (29.1)	39 (70.9)		
Gender					
Male	42 (76.4)	13 (81.3)	29 (74.4)	0.734 ¹	
Female	13 (23.6)	3 (18.8)	10 (25.6)		
Age (yrs)	63.24±10.40	63.31±8.12	63.21±11.30	0.663 ³	
BMI	21.74±2.77	21.84±2.65	21.70±2.85	0.861 ⁴	
<18.5	7 (12.7)	3 (18.8)	4 (10.3)	0.493 ¹	
18.5-22.9	30 (54.5)	7 (43.8)	23 (59.0)		
≥23.0	18 (32.7)	6 (37.5)	12 (30.8)		
Smoking status (yes)	23 (41.8)	3 (18.8)	20 (51.3)	0.026²	
Alcohol (yes)	2 (3.6)	0 (0.0)	2 (5.1)	1.000 ¹	
DM	15 (27.3)	5 (31.3)	10 (25.6)	0.744 ¹	
HT	22 (40.0)	6 (37.5)	16 (41.0)	0.808 ²	
CVD	4 (7.3)	2 (12.5)	2 (5.1)	0.571 ¹	
Dx					
Cholangiocarcinoma	20 (36.4)	5 (31.3)	15 (38.5)	0.956 ¹	
Gallbladder cancer	4 (7.3)	1 (6.3)	3 (7.7)		
Pancreatic cancer	11 (20.0)	3 (18.8)	8 (20.5)		
Stomach cancer	7 (12.7)	2 (12.5)	5 (12.8)		
Colon cancer	13 (23.6)	5 (31.3)	8 (20.5)		
Chemo Tx					
Nab-paclitaxel	13 (23.6)	3 (18.8)	10 (25.6)	0.696 ¹	
Cisplatin	23 (41.8)	6 (37.5)	17 (43.6)		
Oxaliplatin	19 (34.5)	7 (43.8)	12 (30.8)		

Values are presented either in frequency with percentages in parentheses or mean±standard deviation. CIPN: Chemotherapy-induced peripheral neuropathy; BMI: body mass index; DM: diabetes mellitus; HT: hypertension; CVD: cardiovascular disease. *clinically obvious CIPN. ¹*p*-values were derived using the Fisher's exact test. ²*p*-values were derived using the chi-square test. ³*p*-values were derived using the Mann-Whitney's *U*-test. ⁴*p*-values were derived using the independent *t*-test. The Shapiro-Wilk test was employed for testing normality.

cancer; 7, gastric cancer; and 13, colon cancer. The most used chemotherapeutic agents were cisplatin (41.8%), oxaliplatin (34.5%), and nab-paclitaxel (23.6%). At 12 weeks after starting chemotherapy, 39 (70.9%) patients were diagnosed with CIPN using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) grades 1-3 sensory changes. CIPN-positive patients had a higher rate of smoking (20/39, 51.3%) than CIPN-negative patients (18.8%, *p*=0.026). There were no significant differences in the incidence of diabetes mellitus (DM), hypertension (HT), and cardiovascular disease (CVD) between CIPN-positive and CIPN-negative patients (Table I).

Comparison of HRV between CIPN-positive and CIPN-negative patients at each assessment time point. The standard deviation of normal-to-normal interval (SDNN), high frequency (HF), low frequency (LF), and LF/HF ratio

significantly changed during the three assessment periods (*p*<0.001, *p*<0.001, *p*=0.010, and *p*=0.009, respectively), and the interaction between the groups and time points was also statistically significant for SDNN, HF, LF, and LF/HF (*p*<0.001, *p*<0.001, *p*=0.007, and *p*=0.012, respectively). The post hoc analysis revealed that the significant decrease in SDNN, HF, and LF was attributed to a significant decrease in the CIPN-positive patient group, whereas the significant increase in LF/HF ratio was attributed to a significant increase in the CIPN-positive patient group. In the CIPN-positive patient group during each time point, SDNN continuously narrowed, HF and LF continuously decreased, and LF/HF continuously increased. There were no significant changes in SDNN, HF, LF, and LF/HF in the CIPN-negative patient group. At 12 weeks, SDNN, HF, LF, and LF/HF differed significantly between CIPN-positive and CIPN-negative patients (*p*<0.001, *p*<0.001, *p*=0.015, and *p*=0.032, respectively). Percentage change (%Δ)SDNN, %ΔHF, and %ΔLF at 6 weeks after the start of chemotherapy were found to differ significantly between CIPN-positive and CIPN-negative patients, whereas %ΔLF/HF was marginally significant (*p*=0.082, Table II).

Receiver operating characteristic curves of %ΔHRV at 6 weeks for predicting CIPN. Multivariable prediction probability was calculated using the multivariate logistic regression with 4 HRV variables as covariates. The receiver operating characteristic (ROC) curve analysis indicated that HRV measurements, used for diagnosing CIPN, had a sensitivity of 74.4% (29/39) and a specificity of 93.8% (15/16), with a significantly high area under the curve (AUC) of 0.888 (Figure 1).

The effect of independent variables on CIPN using multivariate logistic regression analysis. The effect of independent variables on CIPN was analysed using multivariate logistic regression analysis, and statistically significant variables were selected using a forward selection method, with a significance level of 0.05. %ΔSDNN [odds ratio (OR)=0.926, 95% confidence interval (CI)=0.870-0.985, *p*=0.015] and %ΔHF (OR=0.931, 95%CI=0.877-0.988, *p*=0.019) were found to be related to CIPN (Table III).

The recursive partitioning models for CIPN. The results of the recursive partitioning models for CIPN are shown in Figure 2. The decision tree used was based on the 4 main variables associated with CIPN, namely, %ΔSDNN, %ΔHF, %ΔLF, and %ΔLF/HF ordered according to their relative importance in the model. The terminal nodes categorized the study samples into 3 prognostic groups according to the probability of CIPN. There was a statistically significant difference in %CIPN between the risk groups at 12 weeks (Fisher's exact test, *p*<0.001).

Table II. Comparison of HRV between CIPN-positive and CIPN-negative patients with GI cancer at each assessment time points.

Variable	At 12 weeks		<i>p</i> -Value	Analysis for repeated measures	
	CIPN (-) (n=16)	CIPN (+)* (n=39)		Source	<i>p</i> -Value
SDNN					
Baseline	33.93±14.01 ^a	34.05±13.95 ^a	0.978 ²	Group	0.062
6 weeks	33.39±14.15 ^a	26.48±9.89 ^b	0.044 ²	Time	<0.001**
12 weeks	35.33±17.22 ^a	22.30±9.60 ^c	<0.001 ²	Group x Time	<0.001**
HF					
Baseline	221.16±145.30 ^a	222.34±176.55 ^a	0.739 ¹	Group	0.140
6 weeks	210.72±141.83 ^a	170.52±174.40 ^b	0.115 ¹	Time	<0.001**
12 weeks	235.45±209.50 ^a	74.73±100.81 ^c	<0.001 ¹	Group x Time	<0.001**
LF					
Baseline	243.83±194.53 ^a	245.43±214.68 ^a	0.882 ¹	Group	0.335
6 weeks	247.16±226.87 ^a	201.06±197.12 ^b	0.326 ¹	Time	0.010**
12 weeks	247.30±323.14 ^a	120.03±146.69 ^c	0.015 ¹	Group x Time	0.007**
LF/HF					
Baseline	1.32±0.82 ^a	1.37±0.59 ^a	0.313 ¹	Group	0.107
6 weeks	1.34±1.05 ^a	1.76±1.10 ^b	0.088 ¹	Time	0.009**
12 weeks	1.35±1.58 ^a	2.76±2.46 ^c	0.032 ¹	Group x Time	0.012**
Variable at 6 weeks					
ΔSDNN	-0.54±3.08	-7.57±7.51	<0.001 ¹		
ΔHF	-10.44±18.28	-51.82±61.20	<0.001 ¹		
ΔLF	3.33±58.71	-44.37±57.40	<0.001 ¹		
ΔLF/HF	0.02±0.30	0.39±0.68	0.092 ¹		
%ΔSDNN	-1.69±8.55	-18.81±18.08	<0.001 ²		
%ΔHF	-5.02±8.08	-32.47±28.44	<0.001 ²		
%ΔLF	-3.42±12.16	-23.07±19.67	<0.001 ¹		
%ΔLF/HF	-0.34±14.18	22.72±40.96	0.082 ¹		

Values are presented as mean±standard deviation; Bonferroni's post hoc test was used for multiple comparisons between the groups at three time points. The mean values with different scripts are different from each other within each group (*p*<0.05). HRV: Heart rate variability; CIPN: chemotherapy-induced peripheral neuropathy; GI: gastrointestinal; SDNN: standard deviation of normal-to-normal; HF: high frequency; LF: low frequency; %Δ: percentage change. ¹*p*-values were derived from the Mann–Whitney *U*-test. ²*p*-values were derived from the independent *t*-test. The Shapiro–Wilk test was employed for testing normality. ΔHRV at 6 weeks from baseline was calculated by the value at 6 weeks – value at baseline. %ΔHRV at 6 weeks from baseline was calculated by ((value at 6 weeks – value at baseline)/value at baseline)×100. *clinically obvious CIPN. ***p*-values were derived from the analysis of variance with repeated measures; Greenhouse–Geisser correction was used when sphericity was not assumed.

Discussion

In our study, 70.9% of patients were diagnosed with CIPN. A percentage change in SDNN and HF at 6 weeks after starting chemotherapy was shown to be an independent factor for predicting the occurrence of CIPN at 12 weeks. The decision tree model revealed that patients who showed a rapid percentage change decrease in SDNN and HF were all CIPN-positive.

The incidence of CIPN has been reported to range widely from 19% to 85% because the questionnaires for diagnosing CIPN have been very subjective (3, 18, 19). CIPN was diagnosed using various types of questionnaires, including clinician-rated tools such as the total neuropathy score (20, 21) and NCI-CTCAE (16, 17) and patient-reported outcomes

such as the Functional Assessment of Cancer Therapy-Gynecologic Oncology Group/Neurotoxicity questionnaire (22, 23) and patient neurotoxicity questionnaire (24, 25). However, the diagnostic tools need to be more objective for ensuring early CIPN detection. Clinicians were not able to detect CIPN when patients complained of mild symptoms, such as tingling, numbness, burning, and stinging. Patients complaining about severe stabbing, shooting, or stinging pain or other serious side-effects could result in dose reduction and treatment interruption, which ultimately may affect the overall survival of cancer patients. Therefore, efficient clinical screening for CIPN is a critical component of optimal patient management (26, 27). Objective parameters are needed for detecting early stages of CIPN and for preventing severe side-effects.

Table III. Results of the logistic regression analysis.

Variable	Univariate model			Multivariate model ¹			Multivariate model ²		
	OR	95%CI	p-Value	OR	95%CI	p-Value	OR	95%CI	p-Value
Age (yrs)	0.999	0.944-1.057	0.972	0.965	0.864-1.077	0.523			
BMI	0.981	0.794-1.212	0.857	0.984	0.707-1.370	0.926			
DM (yes)	0.759	0.211-2.724	0.672	0.930	0.093-9.287	0.951			
Smoking status (yes)	4.561	1.121-18.565	0.034	73.466	3.276-1647.543	0.007			
%ΔSDNN	0.926	0.877-0.977	0.005				0.926	0.870-0.985	0.015
%ΔHF	0.941	0.902-0.982	0.005				0.931	0.877-0.988	0.019
%ΔLF	0.906	0.844-0.973	0.007						
%ΔLF/HF	1.028	1.000-1.056	0.051						
Multivariable predicting probability (%)	1.063	1.030-1.097	<0.001	1.098	1.043-1.155	<0.001			

BMI: Body mass index; DM: diabetes mellitus; SDNN: standard deviation of normal-to-normal; HF: high frequency; LF: low frequency; %Δ: percentage change. ¹All demographic variables and multivariable predicting probability derived from four %ΔHRV variables were considered in the multivariate logistic regression analysis. ²Forward selection method with significant level of entry of 0.05 was used for variable selection in the multivariate logistic regression analysis.

Damage to the nervous system could be detected through early changes in the ANS, even though the precise pathology of CIPN remains unclear (28). In studies concerning the association between autonomic parasympathetic function and the perception of pain owing to CIPN, a correlation was reported between autonomic dysfunction and perceived levels of experimental pain (29-31). Studies on HRV concerning the diagnosis and evaluation of CIPN remain limited. A study of HRV in breast cancer patients receiving paclitaxel suggested impairment of autonomic modulation of the heart rate after chemotherapy. However, there was no correlation between HRV and chemotherapy side-effects (32). A study of pain and HRV in peripheral neuropathy showed a decrease in HF and an increase in the LF/HF ratio when peripheral neuropathic pain increased (29). This finding was associated with increased pain sensitivity as parasympathetic nerve activity decreased. In another study concerning the effects of oxaliplatin in colorectal cancer (33), the authors compared ANS function between 36 colorectal cancer patients and 22 healthy volunteers, which included adrenergic cardiovascular function (orthostatic hypotension), parasympathetic heart innervation (ratio 30/15), and sympathetic skin response; CIPN was related to adrenergic cardiovascular reaction and parasympathetic heart innervation. Therefore, the early detection of autonomic nerve dysfunction may predict the occurrence of CIPN.

Clinically, HRV can be used for monitoring ANS regulation of the body. HRV analyses have been classified into time and frequency domains (34). Time-domain HRV provides the information on the ability of the ANS to control the body, whereas frequency-domain HRV, as a power spectral analysis, is used for the quantitative assessment of ANS function (5, 13, 15). Thus, the HF and SDNN represent

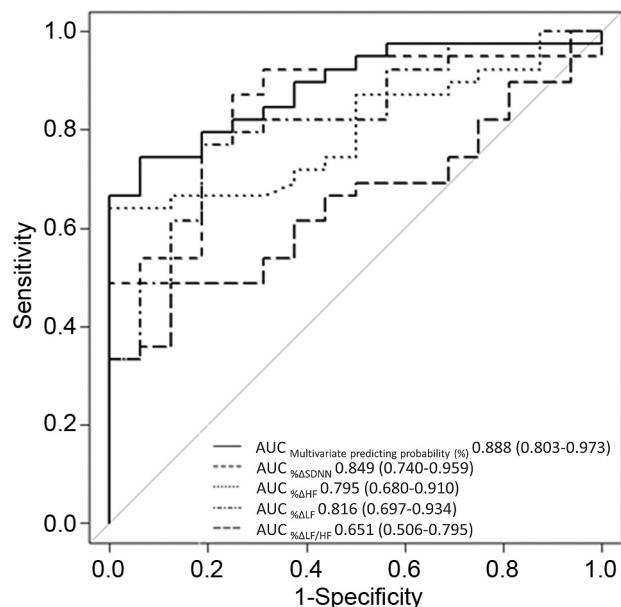


Figure 1. Receiver operating characteristic (ROC) curves of %ΔHRV at six weeks for predicting CIPN. HRV: Heart rate variability; CIPN: chemotherapy-induced peripheral neuropathy; SDNN: standard deviation of normal-to-normal; HF: high frequency; LF: low frequency; %Δ: percentage change.

a state of excitement of the parasympathetic system and the LF and LF/HF ratio represent a state of inhibition of the parasympathetic system or a state of excitement of the sympathetic system (13-15, 34). In our study, patients in the CIPN-positive group showed an increase in the LF/HF ratio and a decrease in the LF, HF, and SDNN parameters. These changes of HRV were presented at 6 weeks after starting

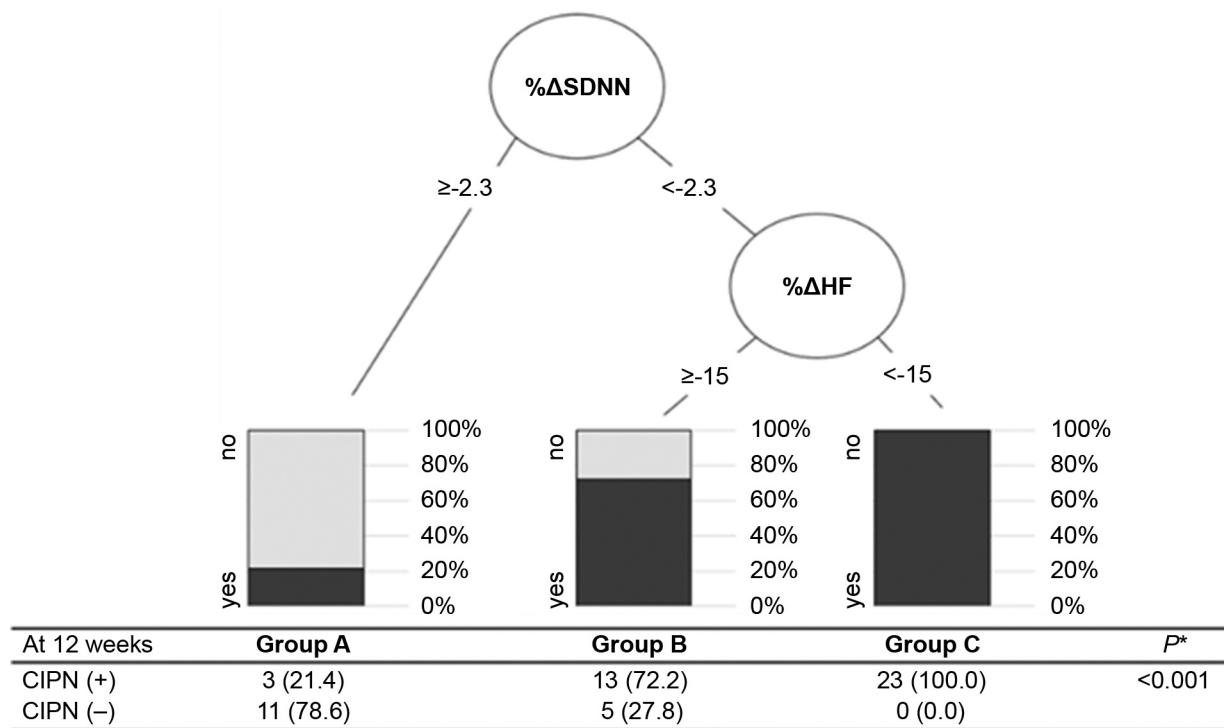


Figure 2. Recursive partitioning tree of $\% \Delta \text{HRV}$ for CIPN. HRV: Heart rate variability; CIPN: chemotherapy-induced peripheral neuropathy; SDNN: standard deviation of normal-to-normal; $\% \Delta$: percentage change; HF: high frequency (* p -value was derived using the Fisher's exact test).

chemotherapy and preceded the sensory symptoms of CIPN.

CIPN-positive patients showed a significant decrease in SDNN and HF, which indicated a decrease in the parasympathetic activity. A percentage change in SDNN and HF at 6 weeks after starting chemotherapy was a significant predictor of the occurrence of CIPN at 12 weeks. Cancer patients undergoing chemotherapy frequently experience circulatory symptoms, such as an unstable heart rate and unstable blood pressure, which may be owing to ANS dysfunction and syncope; these circulatory symptoms occur prior to the appearance of sensory pain symptoms. Parasympathetic dysfunction of SDNN and HF may appear earlier than the clinical symptoms of CIPN, such as pain. One study reported differences concerning HRV between patients with advanced-stage breast cancer and those with benign breast cancer (35). The patients with advanced-stage breast cancer showed lower SDNN values; however, there were no differences in the frequency-domain parameters between these patients.

Several studies have reported the risk factors for predicting the occurrence of CIPN. In 57 breast cancer patients, age, body mass index, and body surface area were found to be significantly associated with the development of CIPN after receiving paclitaxel (36). In 88 patients with advanced or recurrent colorectal cancer, nutritional disorder

was found to be significantly associated with the development of CIPN after receiving oxaliplatin (37).

In 255 patients from 3 cancer centres in Hong Kong, Singapore, and the United Kingdom, older age, platinum-based chemotherapy, history of neuropathy, symptom burden, number of chemotherapy cycles received, and alcohol intake were reported to be independent risk factors for the development of CIPN (38). The meta-analysis of four studies (701 patients) reported baseline neuropathy, smoking history, decreased creatinine clearance, and specific sensory changes during chemotherapy as clinical risk factors for the development of CIPN (39). In our study, smoking and HRV variables were significantly associated with the development of CIPN.

Our study has some limitations. First, despite the efforts to accurately diagnose patients' CIPN symptoms with clinician-rated tools, such as the NCI-CTCAE, there was a lack of other comparative objective parameters for neurological assessment as a reference. To ensure the reliability of neurological evaluation, future studies are needed for comparing HRV and other objective indicators. Second, the relatively small number of patients did not allow us to investigate the influence of different exposures of various chemotherapeutic agents on HRV because it was difficult to obtain data from patients with terminal cancer

undergoing chemotherapy. Further research in the form of a well-designed, large-sample study is necessary for investigating the effects of various chemotherapy agents on HRV. Third, as there were no long-term follow-up data, the relationship between CIPN recovery and HRV could not be determined. Long-term observational studies are needed after the end of chemotherapy for confirming the relationship between CIPN and HRV.

Conclusion

In summary, the decision tree model using SDNN and HF was found to predict the development of CIPN. Thus, HRV could be used for detecting early changes of CIPN. A further study is needed with more comparative objective parameters for evaluating autonomic changes in GI cancer patients with CIPN.

Conflicts of Interest

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

Authors' Contributions

A. Jang contributed to the conception and design of the research; A. Jang and Y. M. Seol contributed to the acquisition, analysis, and interpretation of the data. A. Jang drafted the manuscript; Y. M. Seol critically revised the manuscript. A. Jang and Y. M. Seol agree to be fully accountable for ensuring the integrity and accuracy of the work. All the Authors read and approved the final manuscript.

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