



Multidimensional Comparison of Cancer-Related Fatigue and Chronic Fatigue Syndrome: The Role of Psychophysiological Markers

Hye Youn Park¹, Hong Jun Jeon², Young Rong Bang³, and In-Young Yoon^{1,4} ✉

¹Department of Psychiatry, Seoul National University Bundang Hospital, Seongnam, Republic of Korea

²Department of Psychiatry, Konkuk University Medical Center, Seoul, Republic of Korea

³Department of Psychiatry, Dong-A University Hospital, Busan, Republic of Korea

⁴Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea

Objective The present study compared cancer-related fatigue (CRF) and chronic fatigue syndrome (CFS) using multidimensional measurements with the aim of better understanding characteristics and exploring markers of two similar fatigue syndromes.

Methods Twenty-five patients with CRF and twenty patients with CFS completed questionnaires, including the Fatigue Severity Scale (FSS), Hospital Anxiety Depression Scale (HADS), Perceived Stress Scale (PSS), and Pittsburgh Sleep Quality Index (PSQI). Additionally, levels of high sensitivity C-reactive protein (hs-CRP), heart rate variability (HRV), and electroencephalography (EEG) were obtained. Neurocognitive functioning was also evaluated.

Results Both groups showed comparable levels of psychological variables, including fatigue. Compared to CFS subjects, CRF patients had significantly higher hs-CRP levels and a reduced HRV-index. The within-group analyses revealed that the FSS score of the CRF group was significantly related to scores on the HADS-anxiety, HADS-depression, and PSQI scales. In the CFS group, FSS scores were significantly associated with scores on the PSS and the absolute delta, theta, and alpha powers in frontal EEG.

Conclusion Findings indicate that different pathophysiological mechanisms underlie CFS and CRF. Inflammatory marker and HRV may be potential biomarkers for distinguishing two fatigue syndromes and frontal EEG parameters may be quantitative biomarkers for CFS.

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Key Words Fatigue, Cancer, Biomarkers, Electrocardiography, Electroencephalography.

INTRODUCTION

There is a high prevalence of cancer-related fatigue (CRF), which is prolonged fatigue after treatment for cancer, in this population.¹ However, the pathophysiological mechanisms underlying CRF are not yet clearly understood. Most criteria for CRF consist of core characteristics that include complaints of fatigue that result in functional impairments accompanied by cognitive and sleep disturbances.^{2,3} These components

overlap with the diagnostic criteria for chronic fatigue syndrome (CFS),⁴ which is characterized by intense persisting fatigue that limits function. Thus, it has been proposed that similar mechanisms, including inflammation and perpetual deconditioning, underlie these two fatigue syndromes.⁵ Still, the pathophysiology of CFS remains elusive, immune and neuroendocrine dysfunction and psychiatric disorders may be related to this disorder.⁶ Additionally, central nervous system (CNS) abnormalities appear to be involved in the pathophysiology of CFS however, the results have been inconclusive.⁴

Despite the similarities of these two fatigue syndromes, few studies have specifically compared them. Servaes et al.⁵ reported that CFS patient exhibit a more severe degree of fatigue and pain than patients with CRF. Previous study reported the associations between cognitive function and the CRF⁷ and CFS.⁸ However there has been very little comparative examination of cognitive dysfunctions between two syn-

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✉ Correspondence: In-Young Yoon, MD, PhD

Department of Psychiatry, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Republic of Korea

Tel: +82-31-787-7433, Fax: +82-31-787-4058, E-mail: iyoony@snu.ac.kr

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dromes using objective cognitive tests. Recently, Light et al.⁹ identified differential gene expressions related to immune and energy pathways between patients with CRF and CFS but no comparative studies have employed psychophysiological measures such as electroencephalography (EEG) or heart rate variability (HRV), which represent reproducible parameters that can complement psychosomatic performance measures. Resting-state quantitative EEG (qEEG) measures serve as an indicator of brain function and offer a noninvasive assessment of mental aspects of fatigue which is associated with cognitive fatigue.¹⁰ While, HRV is an objective measure of autonomic nervous system (ANS) regulation that reflects stress.¹¹ Recent studies have reported lower values for HRV parameters in cancer patients and comparable values in CFS patients compared to healthy controls; these studies concluded that these changes are specifically related to fatigue.¹²⁻¹⁴ Previous research using qEEG measures have found unstable EEG-vigilance in CRF patients¹⁵ and altered delta and beta activities in CFS^{16,17} patients compared to healthy controls.

These two distinct illnesses may be result from using different strategies to adapt to somatic conditions with different etiologies. A biomarker is defined as an indicator of a biologically derived pathogenic process, and the identification of distinct biomarkers for these two fatigue syndromes may improve our understanding of the biology of fatigue. Furthermore, biomarkers may aid in the differential diagnosis and proper management of patients with chronic, uniform fatigue, especially in oncology settings. The present comparative study examined the shared and specific factors associated with CRF and CFS. For this comparison, multifactorial assessments of chronic fatigue were performed. Additionally, this exploratory study aimed to identify potential objective biomarkers for each fatigue syndrome.

METHODS

Subjects

Subjects were recruited from Seoul National University Bundang Hospital (SNUBH) between November 2013 and September 2015. A total of 68 subjects were screened and 48 provided consent to participate. Of those who provided consent, 45 (25 cancer patients and 20 controls) were eligible and enrolled in this study.

The CRF group consisted of patients with non-metastatic cancer who were experiencing significant fatigue after primary treatment for cancer. All participants were recruited from outpatients of cancer center in the SNUBH. The diagnostic criteria for CRF used in the present study were introduced by previous studies¹⁸ as follows: 1) the presence of fatigue for at least 2 weeks and at least 5 fatigue-related symptoms,

2) the significant impact on work or self-care, 3) the fatigue symptoms are caused by cancer or cancer therapy, 4) the fatigue symptoms are not primarily caused by co-morbid psychiatric disorder. Exclusion criteria were 1) history of a major psychiatric disorder, 2) history of a cardiovascular disorder or event, 2) ongoing treatment with chemotherapy or radiotherapy, and 3) suicidal risk. The subjects in the CFS group were enrolled from outpatients attending fatigue clinic or psychiatric clinic in the SNUBH based on the Oxford criteria for CFS¹⁹ as follows: 1) the presence of fatigue as a main symptom, 2) the significant disability, 3) the absence of a medical or psychiatric disease plausible for fatigue. Subjects with a cardiovascular disorder or event and concurrent medication that may impact on the results were excluded.

The diagnostic interviews of both the CRF and CFS subjects were conducted by three psychiatrists who applied the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and used the Structured Clinical Interview for DSM-IV (SCID)²⁰ to exclude major psychiatric diagnoses.

All subjects included in this study were diagnosed with moderate to severe fatigue, which was diagnosed based on a cut-off score ≥ 4 on the Brief Fatigue Inventory (BFI).²¹ Informed consent was obtained from all subjects after the study information was offered and the study protocol was approved by the Institutional Review Board of SNUBH (No. B-1308/213-003).

Psychological measurements

The BFI includes nine items that are scored on 10-point Likert scales. The Cronbach's α was 0.88 in the present sample.

The Fatigue Severity Scale (FSS) was developed to assess fatigue in patients with chronic diseases.²² The Cronbach's α was 0.92.

The Korean version of the Hospital Anxiety and Depression Scale (K-HADS) was used to evaluate emotional stress in the study subjects.²³ The Cronbach's α in this study was 0.84.

The Perceived Stress Scale (PSS) evaluates one's level of perceived stress.²⁴ The Cronbach's α was 0.77.

Subjective quality and quantity of sleep were assessed with the Pittsburgh Sleep Quality Index (PSQI).²⁵ The Cronbach's α was 0.81.

The Functional Assessment of Cancer Therapy General (FACTG) was used to evaluate quality of life (QoL) in the patients with cancer (CRF group).²⁶ This scale is comprised of the following four domains: physical well-being, social/family well-being, emotional well-being, and functional well-being. The internal consistency was $\alpha=0.79$ in the present study.

Laboratory test for systemic inflammation

Blood samples were drawn to determine serum levels of

high sensitivity C-reactive protein (hs-CRP); all samples were measured with a high-sensitive particle-enhanced immunoturbidimetric assay.

Physiological measurements

For the HRV analyses, high-resolution (1,000 Hz) electrocardiograms (ECGs) were collected over 8 min using the Synamps 2 amplifier (Compumedics; Melbourne, Australia). The ECG was recorded from two electrodes attached to both supraclavicular areas. All analyses were performed using HRV analysis software (Telescan version 2.0, Laxtha, Daejeon, Korea). The following parameters were extracted for the time domain: mean heart period (HP), standard deviation of the NN (SDNN), proportion of NN50 (PNN50), root mean square of the differences in successive NNs (RMSSD), and HRV index. Parametric auto-regression was processed on the power spectral domain analysis and the power levels of the low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.4 Hz) components in the absolute and normalized units (divided by LF+HF) were determined.

To examine EEG characteristics related to mental fatigue, EEG data were acquired immediately after completing 1 hour of neurocognitive testing. The EEG signals were recorded from the scalp with a 64-channel EEG acquisition system over 15 min while the subjects were sitting with their eyes closed. Electrodes were placed according to the extended international 10–20 system. The EEG signals were amplified and digitalized with a 64-channel Neuroscan Synamps (Compumedics USA) with a sampling rate of 1 kHz. A frequency analysis was performed in the frequency domain to investigate fatigue-related CNS signal differences and a Fast Fourier Transform (FTT) was applied to selected 120-s segments without eye blinks or other artifacts. The absolute values of EEG power were extracted for five bands (delta: 1.0–4.0 Hz, theta: 4.0–8.0 Hz, alpha: 8.0–12.0 Hz, beta: 12.0–25.0 Hz, and high beta: 25.0–30.0 Hz) and the absolute power of each electrode was averaged into five grouped cerebral regions: frontal, central, parietal, temporal, and occipital. The power values from the electrodes on both hemispheres were averaged because the hemispheric asymmetry analyses were not significant.

Neurocognitive tests

Three neurocognitive tests were administered to assess attention, executive function, verbal learning, and working memory in relation to CRF and CFS²⁷: the Trail Making Test (TMT), Continuous Performance Test (CPT), and Auditory Verbal Learning Test (AVLT). All tests were performed using the Computerized Neurocognitive Function Test (CNT4.0, Maxmedica Inc., Seoul, Korea).²⁸

Statistical analysis

The demographic and clinical characteristics and categorical variables were analyzed with either Pearson's chi-squared (χ^2) tests or Fisher's exact tests, while t-tests or Mann-Whitney U tests were used to analyze the continuous variables. Absolute power and mean power were log-transformed to normalize the data distributions. Comparisons of absolute power between the groups were performed with a two-way analysis of covariance (ANCOVA) adjusted for covariates was performed to compare the HRV and EEG variables. Within-group analyses were conducted to evaluate the correlations between fatigue severity and the psychophysiological variables in each group. Two-tailed Pearson's correlation or Spearman's rho correlation coefficients (nonparametric test on hs-CRP) were used according to the results of normality tests using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Additionally, univariate linear regression analyses were performed and these analyses were not adjusted for multiple testing thus p-value <0.05 was considered to indicate statistical significance. All analyses were conducted using IBM SPSS Statistics ver. 20 (IBM Corp., Armonk, NY, USA).

To date, no studies have compared the EEG data of CRF and CFS subjects and, thus, the present study determined the effect size and calculated the appropriate sample size from a previous pilot study that investigated the EEG characteristics of CRF patients.¹⁵ The required total sample size was ≥ 38 to obtain a power of 0.8 and an alpha value of 0.05 with two-tailed significance.

RESULTS

Between-group analyses

The demographic and clinical characteristics of both groups are presented in Table 1. There were no differences between the groups in terms of fatigue severity, level of anxiety, depression stress, or sleep disturbances. Compared to the CFS group, the CRF group had a higher level of hs-CRP; this difference remained statistically significant after adjusting for age. The comparisons of the HRV parameters revealed that the CRF group had significantly lower PNN50 (%) and HRV index values than the CFS group. Additionally, in the frequency domain, LF power was significantly lower in the CRF group than the CFS group after adjusting for age. A recent study produced Korean norms for HRV parameters, and we included these normative data as reference values for controls (Table 2).²⁹

In the neurocognitive tests, the mean time to complete the TMT-B was longer in the CRF group than in the CFS group but there was no difference between the groups after adjustment with covariates (age and educational level) and Bonferroni correction for multiple comparisons. Spectral analyses of

absolute EEG powers and two-way ANCOVA tests were performed for each cortical region but there was no significant difference (Table 3).

Within-group analyses

The partial correlation analysis and univariate linear regression analysis examined the relationships between fatigue severity (FSS score) and the psychophysiological variables,

Table 1. Demographic and clinical characteristics of the subjects

Variables	CRF group (N=25)	CFS group (N=20)	t-value	p-value
Age (years)*	55.52±9.39	50.05±9.25	1.953	0.057
Sex (male/female)†	9/16	7/13	0.005	0.944
Educational level†			4.346	0.226
Elementary school	0 (0)	1 (5)		
Middle school	3 (12)	0 (0)		
High school	12 (48)	8 (40)		
≥University	10 (40)	11 (55)		
Type of cancer†				
Breast	10 (40)			
Gastrointestinal	6 (24)			
Lung	5 (20)			
Thyroid	4 (16)			
Time since the treatment finished†				
<2 years	12 (48)			
≥2 years	13 (52)			

*data given as mean±standard deviation, †data given as number (%). CRF: cancer-related fatigue, CFS: chronic fatigue syndrome

Table 2. Psychophysiological variables and inflammatory marker

Variables	CRF group (N=25)	CFS group (N=20)	t-value/z score	p-value
Self-questionnaires				
BFI	6.26±1.41	6.87±1.57	-1.37	0.179
FSS	6.66±1.21	6.89±1.36	-0.60	0.551
HADS-anxiety	8.64±3.24	10.50±4.41	-1.63	0.110
HADS-depression	10.08±2.63	11.05±3.38	-1.084	0.285
PSS	20.36±4.91	22.35±5.34	-1.30	0.201
PSQI	10.44±4.05	9.35±3.59	0.94	0.351
Inflammatory marker				
hs-CRP (mg/dL)*	0.35±0.57	0.08±0.14	-2.403	0.016
Heart rate variability				
			(Reference value)	
Mean HP (ms)	938.55±132.8	916.19±111.63	-	0.59
SDNN (ms)	37.10±18.27	46.20±16.65	(41±18)	-1.70
PNN50 (%)	28.61±18.49	39.98±12.97	-	-2.36
RMSSD (ms)	33.11±28.20	35.74±26.68	(24±15)	-0.33
HRV index	10.60±3.71	13.40±4.25	-	-2.31
LF [ln(ms ²)]	4.98±0.96	5.59±0.71	(5.70±1.05)	-2.40
Normalized LF (nu)	48.36±16.23	55.06±16.02	(67.9±18.8)	-1.36
HF [ln(ms ²)]	5.06±0.89	5.37±0.89	(5.27±1.14)	-1.14
Normalized HF (nu)	51.64±16.23	44.94±16.02	(32.1±18.8)	1.36

Data given as mean±standard deviation. *Mann-Whitney U test. Reference values are based on the normative HRV parameters in Koreans.²⁹ CRF: cancer-related fatigue, CFS: chronic fatigue syndrome, BFI: Brief Fatigue Inventory, FSS: Fatigue Severity Score, HADS: Hospital Anxiety and Depression Scale, PSS: Perceived Stress Scale, PSQI: Pittsburgh Sleep Quality Index, hs-CRP: high sensitivity C-reactive protein, HP: heart period, SDNN: standard deviation of normal beat to beat intervals, PNN: proportion of NN50, RMSSD: root mean square successive difference, LF: low frequency power, HF: high frequency power

including the psychological questionnaires, hs-CRP levels, HRV parameters, and qEEG data after adjusting for age. In the CRF group, the FSS score was significantly related to the psychological variables [HADS-anxiety: $r=0.500$, regression coefficient (b)= 0.187 , $p=0.011$; HADS-depression: $r=0.451$, $b=0.208$, $p=0.024$; and PSQI: $r=0.530$, $b=0.154$, $p=0.008$] (Figure 1). The psychological variables related to the QoL dimensions (FACTG subscale) were also assessed and revealed

that the FSS score was negatively correlated with the physical well-being subscale ($r=-0.544$, $b=-3.189$, $p<0.001$) after controlling for the other psychological variables.

In the CFS group, the FSS score was correlated with the PSS score ($r=0.547$, $b=0.162$, $p=0.013$), RMSSD ($r=-0.509$, $b=-0.032$, $p=0.026$), LF power ($r=0.484$, $b=0.047$, $p=0.036$), and HF power ($r=-0.508$, $b=-0.051$, $p=0.026$). The FSS score was also correlated with the absolute delta ($r=0.487$, $b=3.982$,

Table 3. Comparisons of neurocognitive performances and absolute electroencephalography (EEG) powers in frontal region

Variables	CRF group (N=25)	CFS group (N=20)	t-value	p-value
Neurocognitive tests				
ACPT-omission (N)	7.13±8.64	4.90±4.69	1.03	0.308
ACPT-comission (N)	4.29±6.64	3.00±2.47	0.82	0.416
ACPT-response time (msec)	0.85±0.09	0.83±0.07	0.61	0.545
RAVLT-Trial A1 (N)	5.61±1.53	6.15±1.50	-1.18	0.245
RAVLT-Trial A5 (N)	10.65±3.46	12.20±2.24	-1.71	0.094
Delayed free recall (N)	9.57±3.59	10.20±2.69	-6.48	0.521
Delayed cued recall (N)	11.65±4.92	13.65±1.57	-1.84	0.076
TMT-A-time (sec)	35.24±18.90	28.55±8.52	1.47	0.150
TMT-A-error (N)	2.28±3.09	1.90±2.73	0.43	0.668
TMT-B-time (sec)	64.80±30.41	48.05±16.65	2.35	0.024
TMT-B-error (N)	2.68±2.75	1.55±1.67	1.61	0.114
Absolute EEG powers (log)				
Frontal delta power	1.21±0.61	1.24±0.18	-0.44	0.661
Frontal theta power	0.98±0.24	1.00±0.30	-0.26	0.795
Frontal alpha power	1.02±0.39	0.96±0.46	0.51	0.611
Frontal beta power	1.00±0.28	0.98±0.25	0.31	0.755
Frontal high beta power	0.32±0.28	0.29±0.26	0.44	0.665

Data given as mean±standard deviation. CRF: cancer-related fatigue, CFS: chronic fatigue syndrome, ACTP: Auditory Continuous Performance Test, RAVLT: Rey Auditory Verbal Learning Test, TMT: Trail Making Test

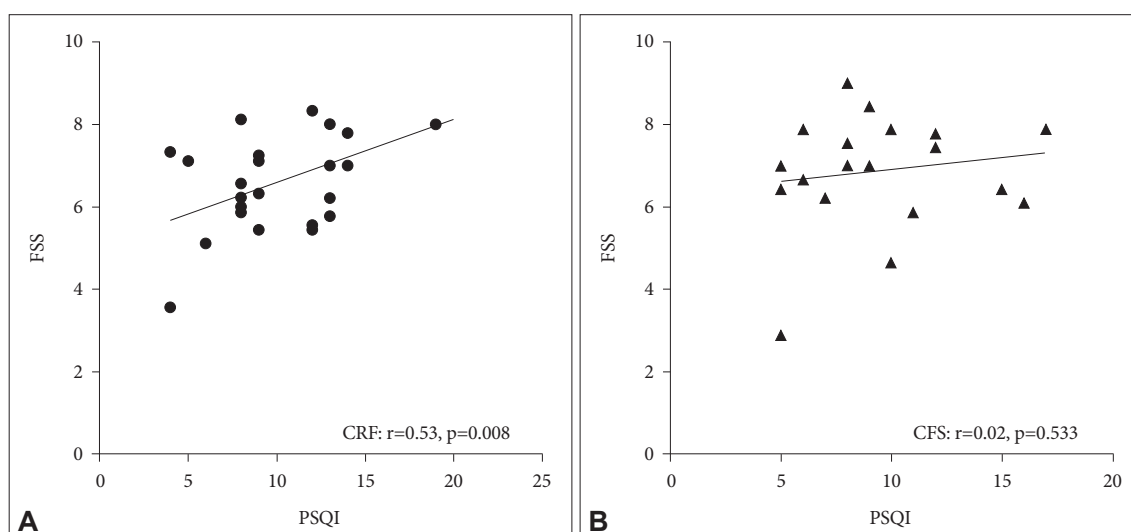


Figure 1. Plot of correlations between PSQI scores and FSS scores in the CRF (A) and CFS (B) groups. Lines show linear regression within each group. FSS: Fatigue Severity Score, PSQI: Pittsburgh Sleep Quality Index, CRF: cancer-related fatigue, CFS: chronic fatigue syndrome.

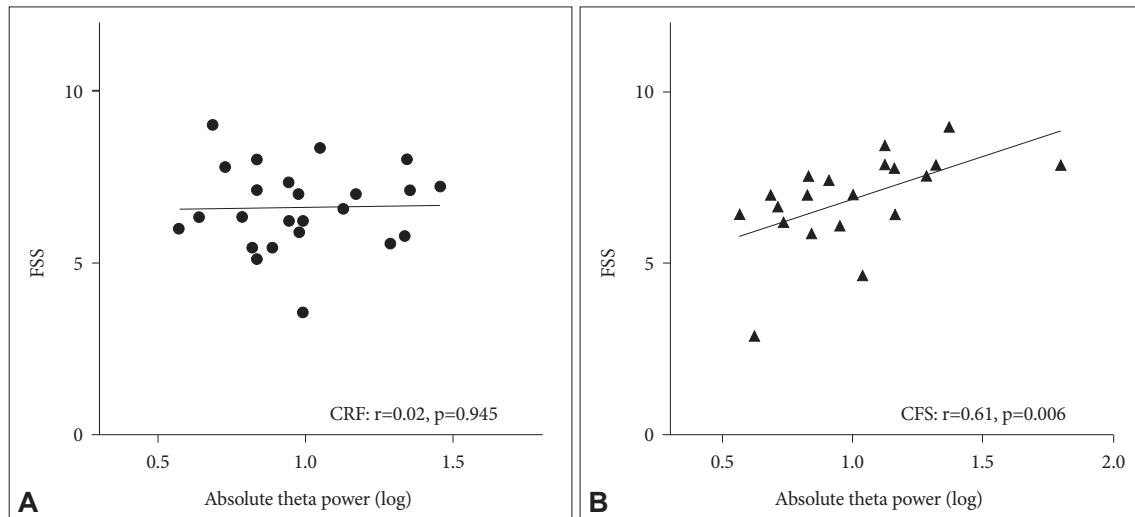


Figure 2. Plot of correlations between FSS scores and absolute theta EEG power in the frontal region in the CRF (A) and CFS (B) groups. Lines show linear regression within each group. FSS: Fatigue Severity Score, EEG: electroencephalogram, CRF: cancer-related fatigue, CFS: chronic fatigue syndrome.

$p=0.034$), theta ($r=0.610$, $b=2.849$, $p=0.006$) (Figure 2), and alpha ($r=0.476$, $b=1.407$, $p=0.039$) powers in the frontal region.

DISCUSSION

The present study investigated the similarities and differences of CRF and CFS. In terms of the biological measurements, the CRF group had higher levels of hs-CRP and reduced values for PNN50, the HRV index, and LF power. The within-group analyses revealed that the severity of CRF was related to anxiety, depression, and sleep disturbances. On the other hand, the severity of CFS was associated with perceived stress, RMSSD, LF, and HF power from among the HRV parameters, and frontal delta, theta, and alpha activities from the qEEG variables.

In a previous qualitative study, Bennett et al.²⁷ found that, except for pain, both CRF and CFS exhibited similar core symptoms of fatigue, cognitive deficits, and mood disturbances. Consistent with previous findings, the present study showed that patients with CRF were similar to patients with CFS in terms of psychological variables. Although we excluded potential subjects if an alternative major psychiatric disorder could explain their severe fatigue, it is readily apparent that depressive symptoms (measured by the HADS) and sleep disturbances (measured by the PSQI) were prevalent, similar to the previous study.²⁷ The HADS used in the present study offers the advantage of reducing potential contamination with a measure of fatigue as it does not include the physical symptoms common to depression and fatigue.³⁰ Some studies have suggested that, as fatigue and depression are independent conditions in cancer patients, depression is a comorbid condition of CRF.³¹ However, according to the litera-

ture, depression and poor sleep are consistently associated with both fatigue syndromes due to common mechanisms, and they are also confirmed predisposing factors for the development of CRF as well as CFS.^{4,30,32} The causality and directionality of these relationships remain uncertain; thus, further longitudinal studies are needed. In terms of inflammation, higher levels of hs-CRP were observed in the CRF group compared to the CFS group. The level of CRP has been consistently identified as a reliable biomarker of CRF but its relationship to CFS was inconclusive in a multiple adjusted analysis.^{33,34} Active inflammatory reactions caused by cancer or anticancer treatments might have influenced this group difference.³⁴ Recent studies have reported lower values for HRV parameters in cancer patients, which are specifically related to fatigue.^{12,13} Tumor-related factors, anticancer treatment, and distress modulate the ANS and alter HRV in patients with cancer.³⁵ On the other hand, CFS patients show a similar pattern of HRV when compared with healthy controls;¹⁴ however, fewer studies have assessed HRV in CFS patients. Our results support previous findings showing that CFS patients presented higher SDNN, RMSSD and HF values than those of the control group, and obtained values intermediate between those of the CRF and control groups with regard to the LF, normalized LF, and normalized HF which implies that fatigue and cancer may be independently related to altered HRV parameters; however, this remains inconclusive due to the limitations of indirect comparisons. In the frequency domain of the HRV parameters, patients with CFS in the present study had relatively higher level of LF power, which represent sympathetic activity and tend to be elevated in individuals with mental stress.³⁶ Thus, higher sympathetic tone in CFS patients may reflect a mental aspect of the CFS. The present findings sug-

gest that hs-CRP and HRV variables may be biomarkers that reflect different mechanisms from other insults between two syndromes. However, the present study is the first to directly compare the hs-CRP, HRV variables of CRF and CFS patients and the present results should be interpreted with caution. Regarding neurocognitive functioning, previous studies using formal cognitive tests with CRF patients found impairments in attention and verbal memory.³⁷ Similar results have been reported in patients with CFS,³⁸ but there have been discrepancies in the prevalence and domains affected. This is the first comparison to measure the symptoms related to both fatigue syndromes using neurocognitive tests, and we observed no significant differences in the neurocognitive functioning of the two groups; this supports previous findings²⁷ showing that cognitive impairments may be related to chronic fatigue rather than to a specific fatigue syndrome. Future studies with larger sample and measures of multiple cognitive domains could clarify these relationships.

Similar to previous studies,^{18,39} the present findings indicate that depression, anxiety, and insomnia are possible quantitative markers predictive of the severity of CRF in cancer patients, even though these factors are not specific to CRF. Additionally, we observed that CRF was associated with the physical well-being of cancer patients after adjusting for other psychological factors. Previous research reporting predictors that discriminated among the different dimensions (e.g., emotional, mental, and physical fatigue) of CRF demonstrated that depression was related to all types of fatigue and that high scores on the PSQI were associated with the severity of physical fatigue.³² These results may imply that the association between CRF and physical well-being was mediated by the quality of sleep. In terms of inflammation, higher levels of CRP are associated with greater fatigue in cancer patients.⁴⁰ However, these associations were not observed in the present sample of CRF, this inconsistency may be due to our small sample size and other CRP-related factors, including body mass index (BMI), types of cancer, and medications, as a recent review pointed that these relationships were no longer significant after adjustment for medications and comorbidities.⁴¹ The EEG measures were not significantly related to fatigue severity in the CRF group in the present study. In a previous study, patients with cancer report persistent levels of physical fatigue while mental fatigue, as measured by EEG power, is prominent only during chemotherapy.¹⁰ These findings suggest that persistent CRF is more likely to be multidimensional fatigue beyond mental fatigue.⁴²

In the CFS group, fatigue severity was associated with perceived stress. The relatedness between mental stress and CFS is mediated by dysfunctional ANS activity during the stress response.³³ The present study observed negative associations

between RMSSD and HF power and the severity of CFS. The RMSSD and HF power components are indices of parasympathetic activity.⁴³ During mental stress, the ANS balance tends to shift toward parasympathetic withdrawal and it is widely accepted that decreased HF power is associated with psychological stress.⁴⁴ A recent review found that patients with CFS exhibit reduced HRV and HF, but these changes were only significantly apparent during sleep.¹⁴ Another study⁴⁵ also reported correlations between the severity of CFS and HRV parameters. Though CFS patients showed relatively higher PNN50 (%) and HRV index than those of CRF group in the present study, findings suggest that HRV measures may be non-invasive, quantitative markers that reflect the severity of CFS. This difference could be explained by the fact that patients with CFS are less likely to have other factors affecting HRV parameters such as medications and medical comorbidities.⁴¹

A variety of studies strongly suggest that CNS dysfunction is involved in CFS.⁴ Recent studies using qEEG measures^{16,17} have found altered delta activity in the fronto-limbic regions in CFS and suggested that delta activity could be a salient feature for differentiating between CFS and control subjects.⁴⁶ While, Trejo et al.⁴⁷ and Wascher et al.⁴⁸ found that increased frontal theta power is associated with increased mental fatigue, because it might be assigned to the recruitment of executive function. In the present study, there were positive associations between the severity of CFS and slow wave (delta and theta) and alpha power activities in the frontal region. Taken together, these results regarding the relationships of slow and alpha waves with CFS severity provide evidence that mental fatigue is one component of a neurobiological mechanism underlying the pathophysiology of CFS.

There are several limitations should be considered. First, the statistical power of the present study may have been compromised by the modest sample size. Second, it was not possible to include healthy controls or cancer patients without chronic fatigue and this may have weakened the ability to distinguish between fatigue-related and cancer-related factors though we administered norm-referenced values. Finally, although age and educational level were adjusted for, it was not possible to control for medications, BMI, or individual activity, which could also affect physiological variables.⁴¹ Nonetheless, this is the first comparative study to assess CRF and CFS using physiological measures such as HRV and EEG parameters.

Two fatigue syndromes could have dissimilar mechanisms, such that inflammatory markers and HRV measures could be possible biomarkers used to differentiate these, especially in cancer patients or survivors. In the context of mental fatigue, frontal EEG parameters may contribute to quantitative biomarkers for CFS. Therefore, the present findings have po-

tential implications that will contribute to a better understanding of two fatigue syndromes, these exploratory examinations of biomarkers that will aid in future researches on fatigue syndromes and their mechanisms.

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