



# The influence of chemotherapy-induced neurotoxicity on psychological distress and sleep disturbance in cancer patients

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## ABSTRACT

### Purpose

In the present study, we aimed to investigate the effects of chemotherapy-induced peripheral neurotoxicity (CIPN) on psychological distress and sleep quality in cancer patients.

### Methods

A total of 706 cancer patients were interviewed for the study. In the 4th week of treatment, patient CIPN was measured using the Patient Neurotoxicity Questionnaire (PNQ). The sleep quality and psychological distress of patients were measured using the Pittsburgh Sleep Quality Index (PSQI), the Distress Thermometer (DT), and the Hospital Anxiety and Depression Scale (HADS). Multiple logistic regression was applied to determine the independent effects of CIPN on psychological distress and sleep disturbance in the patients.

### Results

These correlation coefficients were obtained: 0.387 ( $p < 0.0001$ ) between the PNQ total score and the DT score, 0.386 ( $p < 0.0001$ ) between the PNQ total score and the HADS Depression score, 0.379 ( $p < 0.0001$ ) between the PNQ total score and the HADS Anxiety score, and 0.399 ( $p < 0.0001$ ) between the PNQ total score and the PSQI global score. The prevalence rates of distress, depression, anxiety, and poor sleep quality in the five PNQ grades were statistically significantly different ( $p < 0.0001$ ). After controlling for age, sex, education level, social supports, fatigue, disease stage, and tumour site, the PNQ grades were found to be associated with depression ( $p < 0.0001$ ), anxiety ( $p < 0.0001$ ), and poor sleep quality ( $p < 0.0001$ ).

### Conclusions

Chemotherapy-induced peripheral neurotoxicity negatively affects psychological distress and sleep

quality in cancer patients treated with chemotherapy. High PNQ grades were significantly associated with poor psychological status and sleep quality. Our results emphasize the importance of assessing peripheral neuropathies during chemotherapy and of adjusting treatment plans based on assessment results.

### KEY WORDS

Neuropathy, chemotherapy, anxiety, depression, sleep quality

## 1. INTRODUCTION

Antitumour chemotherapy drugs play an important role in comprehensive treatment for malignant tumours, but drug-induced side effects often plague cancer patients and clinicians<sup>1</sup>. Peripheral neuropathy is a common side effect that develops in cancer patients during chemotherapy<sup>2</sup>. Chemotherapy-induced peripheral neurotoxicity (CIPN) is defined as damage to the peripheral nervous system experienced by patients receiving neurotoxic chemotherapy<sup>3</sup>. This complication is often characterized by pain, numbness, and tingling in the hands and feet<sup>4</sup>. Existing studies report that the prevalence of neurotoxicity is about 85%–95% for oxaliplatin, 45%–98% for cisplatin, and 57%–98% for vincristine<sup>5–7</sup>. Of the patients experiencing neurotoxicity, 20% had severe symptoms; 51%, moderate symptoms and; 29%, mild symptoms<sup>8</sup>.

When a patient develops CIPN, a doctor can prescribe chemotherapy dose reduction, a change in the chemotherapy regimen, or early cessation of chemotherapy<sup>9</sup>. Symptoms of CIPN such as neuropathic pain, numbness, tingling, and function loss greatly affect the physiologic and psychologic status of patients and reduce their quality of life (QOL)<sup>10–13</sup>. Chemotherapy-induced peripheral neurotoxicity is associated with pain, sensory discomfort, disrupted sleep, and fatigue<sup>14</sup>. Furthermore, symptoms associated with CIPN can affect the psychological, social, and spiritual well-being of a patient<sup>15</sup>. Treatment-related neuropathy can present a constant reminder of having

cancer and contribute to anxiety and depression<sup>16</sup>. The inability to walk or stand for long periods of time leaves patients with CIPN unable to participate in many activities, leading to feelings of social isolation and psychological distress<sup>14</sup>. Chemotherapy-induced peripheral neurotoxicity has been associated with changes in physical function. Specific reductions in QOL scores because of CIPN symptoms have been estimated to range from 15% to 20%<sup>17</sup>. Patients who were treated for breast cancer with paclitaxel or docetaxel were found to have problems with their balance and to require more time to perform a short walking task<sup>18</sup>. Other studies found that patients with painful CIPN had more difficulty with fine motor tasks using their hands<sup>19</sup>. Patients might also notice difficulty with writing or with typing on a keyboard.

Several researchers have evaluated the influence of neurotoxicity on QOL in cancer patients<sup>3,10–13</sup>, but studies about the specific effects of neurotoxicity on psychological distress and sleep quality in cancer patients are limited.

Psychological distress in patients with cancer can affect their survival and rehabilitation. Psychological distress has been linked to decreased social functioning, increased physical and cognitive impairment<sup>20–22</sup>, and nonadherence to treatments and health-promoting behaviors<sup>23,24</sup>. Patients with psychological distress have a high probability of tumour recurrence<sup>25,26</sup>, low survival rates<sup>27,28</sup>, and poor performance status and QOL<sup>29,30</sup>. Several factors, including the side effects of treatment, poor support systems, and pain<sup>31</sup>, can promote depression in cancer patients. Severity of pain from CIPN is associated with depression<sup>32</sup>, and CIPN-induced limitations can potentially increase levels of stress and anxiety in cancer patients<sup>20</sup>. Individuals with CIPN might be unable to perform tasks independently and are at higher risk for developing depression<sup>32</sup>.

Sleep disturbances are common among patients undergoing chemotherapy<sup>33</sup>. Sleep deprivation might cause immunosuppression<sup>34</sup>, reduced functioning, greater pain, low energy, and mental health problems<sup>35</sup>. Factors influencing sleep disturbance include anxiety and difficulties in coping with disease, fatigue, and chemotherapy<sup>36</sup>. Chemotherapy-induced peripheral neurotoxicity might be one of the factors influencing sleep disturbance. Previous studies reported that higher degrees of sleep disturbance are associated with more severe CIPN<sup>16</sup>.

In the present study, we performed a cross-sectional survey to establish the relationships of CIPN with sleep quality and psychological distress.

## 2. METHODS

### 2.1 Participants

The study subjects were newly diagnosed cancer patients admitted to four provincial-level hospitals

in Fuzhou, China, between January 2012 and June 2013. Eligible patients were undergoing chemotherapy, had no history of mental or psychological disease, had no nervous system diseases or diabetes before developing cancer, were aged 18 to 70 years, and understood their cancer diagnosis. Patients with tumour metastasis to the brain or with diabetes, bone and joint disease, foot disease, and skin disease were excluded. Patients with a history of sleep disorders before their cancer diagnosis were also excluded.

All participants provided written informed consent, and the study was approved by the relevant institutional review boards for human research of Fujian Medical University.

### 2.2 Measures

The Patient Neurotoxicity Questionnaire (PNQ) was used to quantify the symptoms and the severity of CIPN<sup>9</sup>. The PNQ is a self-administered questionnaire comprising two items:

- Do you have numbness, pain, or tingling in your hands or feet?
- Do you have weakness in your arms or legs?

These two items are rated 1–5 on the following scale: 1 = No, 2 = Mild, 3 = Moderate, 4 = Moderate-to-Severe, and 5 = Severe. The CIPN of each patient was assessed by summing the scores for the two items, with the final score being called the PNQ total score. The PNQ total score ranges from 2 to 10, with a high total score indicating severe CIPN symptoms. A PNQ total score of 2 was defined as grade A; 3–4, as grade B; 5–6, as grade C; 7–8, as grade D; and 9–10, as grade E<sup>37</sup>. The validity of the PNQ has been confirmed in many studies<sup>37,38</sup>.

The Distress Thermometer (DT), recommended by the U.S. National Comprehensive Cancer Network<sup>39</sup>, was used to measure self-reported levels of participant distress. The DT is a visual analog scale that participants use to rate their level of distress over the preceding 7 days; scores range from 0 (none) to 10 (extreme). A high DT score indicates severe distress. Some studies have determined that a cut-off score of 4 or greater indicates distress<sup>40,41</sup>. The validity of the Chinese version of the DT was confirmed in a previous study<sup>42</sup>.

The Hospital Anxiety and Depression Scale (HADS)<sup>43</sup> is a 14-item questionnaire (7 items on the Anxiety subscale and 7 on the Depression subscale) used to evaluate anxiety and depression in patients. Scores for each item range from 0 to 3, and patients score the items based on their current situation. Scores for both the Anxiety and Depression subscales range from 0 to 21, with 0–7 indicating asymptomatic status, 8–10 indicating suspicious symptoms, and 11–21 indicating certainly existing symptoms<sup>43</sup>. The Chinese version of the HADS was

confirmed to be suitable for Chinese patients<sup>44</sup>. In the present study, patients were considered to have depression when their score on the Depression subscale exceeded 11. Likewise, patients were considered to have anxiety when their score on the Anxiety subscale exceeded 11.

The Pittsburgh Sleep Quality Index (PSQI) was used to assess the quality of sleep of the study patients<sup>45</sup>. The PSQI is a valid and reliable tool that measures sleep quality and quantity. It consists of 19 self-rated questions divided into seven component scores or subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. A global score ranging from 0 to 21 can be obtained from the sum of the seven components, and higher scores denote poorer sleep quality. The original authors of this index identified a cut-off global score of more than 5 to distinguish poor sleepers (>5) from good sleepers ( $\leq 5$ )<sup>45</sup>.

The Multidimensional Fatigue Inventory (MFI-20)<sup>46</sup> was used to measure fatigue in the participants. The MFI-20 comprises 20 items covering general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. Each item is self-scored from 1 (true) to 4 (not true) based on the patient's current situation. The MFI-20 total score ranges from 20 to 80 and indicates an individual's degree of fatigue; a high total score indicates serious fatigue. A previous study by our group confirmed that the Chinese-version MFI-20 is a reliable and valid instrument for assessing fatigue and can effectively measure the physical and mental fatigue of cancer patients in China<sup>47</sup>.

### 2.3 Procedure

Data on each patient were collected by trained graduate students from Fujian Medical University. Before the first treatment cycle, the age, sex, marital status, education level, social supports, and disease-related features of each patient were obtained. At week 4 of treatment, patient CIPN was measured. Patients were asked to complete the DT, HADS, and PSQI questionnaires after the 4th week of treatment.

### 2.4 Statistical Analysis

Chi-square and Pearson correlation tests were used to determine potential associations between grade of CIPN and psychological distress, and between grade of CIPN and sleep quality. Multiple logistic regression was applied to determine the independent effects of CIPN on psychological distress and sleep quality after controlling for sociodemographic characteristics and disease-related factors. The significance level was set at 0.05.

## 3. RESULTS

Of the 874 cancer patients eligible for the study, 54 did not consent to participate, and 114 did not complete the questionnaires during the study period. The remaining 706 who were enrolled included 449 men (63.60%; mean age:  $53.85 \pm 13.84$  years) and 257 women (36.40%; mean age:  $51.00 \pm 12.20$ ). The mean age of the cohort overall was  $52.81 \pm 13.33$  years, and 289 patients (40.93%) had fewer than 6 years of education. The tumour sites in this group were lung ( $n = 143$ , 20.25%), breast ( $n = 45$ , 6.37%), esophagus ( $n = 40$ , 5.66%), stomach ( $n = 160$ , 22.66%), liver ( $n = 93$ , 13.17%), colorectum ( $n = 107$ , 15.15%), cervix ( $n = 76$ , 10.76%), and others ( $n = 42$ , 5.95%). The proportion of patients with disease stages I, II, III, and IV was, respectively, 11.04%, 24.29%, 36.58%, and 28.09%. The major chemotherapy drugs received by these patients included cisplatin, carboplatin, oxaliplatin, and paclitaxel.

### 3.1 Prevalence of Neurotoxicity

The proportion of patients with PNQ of grades A, B, C, D, and E was, respectively, 30.31%, 42.78%, 16.29%, 6.66%, and 3.97%. Of the overall group, 516 patients (73.09%) reported a PNQ total score of 4 or less (mild or no neurotoxicity), 115 (16.29%) reported a PNQ total score of 5 or 6 (moderate neurotoxicity), and 75 (10.62%) reported a PNQ total score of 7 or greater (severe neurotoxicity). The prevalence of moderate or severe neurotoxicity was 26.91% (95% confidence interval: 23.64% to 30.18%).

### 3.2 Neurotoxicity and Psychological Distress

The correlation coefficient between the PNQ total score and the DT score was 0.387 ( $p < 0.0001$ ); between the PNQ total score and the HADS Depression score was 0.386 ( $p < 0.0001$ ); and between the PNQ total score and the HADS Anxiety score was 0.379 ( $p < 0.0001$ ). Table 1 shows the prevalence rates of psychological distress, depression, and anxiety by PNQ grade. The chi-square tests results in Table 1 suggest that differences in the prevalence rates of distress, depression, and anxiety between the PNQ grades are statistically significant (for distress:  $\chi^2 = 55.75$ ,  $p < 0.0001$ ; for depression:  $\chi^2 = 44.3$ ,  $p < 0.0001$ ; and for anxiety:  $\chi^2 = 37.66$ ,  $p < 0.0001$ ).

Multivariate logistic regression was used to examine the independent effects of PNQ grade on the anxiety and depression status of the patients after controlling for age, sex, education level, social supports, sleep quality (0, good; 1, poor), fatigue, disease stage, and tumour site. At a significance level of  $\alpha = 0.05$ , PNQ grade was associated with both depression and anxiety (Table II), which suggests that CIPN is an independent risk factor for both depression and anxiety. The odds ratios for depression were 1.35

for grade B symptoms, 1.83 for grade C symptoms, 2.47 for grade D symptoms, and 3.35 for grade E symptoms. The odds ratios for anxiety were 1.45 for grade B symptoms, 2.10 for grade C symptoms, 3.05 for grade D symptoms, and 4.43 for grade E symptoms. Grade A PNQ was used as the reference.

TABLE I Prevalence rates of psychological distress, depression, and anxiety by Patient Neurotoxicity Questionnaire (PNQ) grade

Variable	Pts (n)	Prevalence rate (%)		
		Distress	Depression	Anxiety
PNQ grade				
A	214	36.45	55.14	64.95
B	302	47.68	68.21	77.48
C	115	64.35	79.13	88.69
D	47	72.34	87.23	100.00
E	28	92.86	100.00	100.00
Chi-square statistic <sup>a</sup>		55.75	44.30	37.66
<i>p</i> Value <sup>b</sup>		<0.0001	<0.0001	<0.0001

<sup>a</sup> Compares prevalence rates for the five PNQ grades.

<sup>b</sup> Corresponding to the chi-square statistic.

Pts = patients.

### 3.3 Neurotoxicity and Sleep Quality

The correlation coefficient between the PNQ total score and the PSQI global score was 0.399 ( $p < 0.0001$ ). The prevalence rates of poor sleep quality were 51.86%, 68.54%, 83.48%, 89.36%, and 96.43% for, respectively, PNQ grades A, B, C, D, and E. Comparison of the prevalence rates of poor sleep quality by PNQ grade indicated that poor sleep quality was associated with severe CIPN symptoms ( $\chi^2 = 58.90$ ,  $p < 0.0001$ ).

Multivariate logistic regression was used to examine the independent effect of PNQ grade on sleep quality after controlling for age, sex, education level, social supports, anxiety (0, no; 1, yes), depression (0, no; 1, yes), disease stage, and tumour site. At a significance level of  $\alpha = 0.05$ , PNQ grade was associated with poor sleep quality ( $\beta = 0.649$ , standard error = 0.110,  $p < 0.0001$ ), which suggests that CIPN is an independent risk factor for poor sleep quality. The odds ratios for poor sleep quality were 1.91 for grade B symptoms, 3.66 for grade C symptoms, 7.01 for grade D symptoms, and 13.41 for grade E symptoms. Again, grade A PNQ was used as the reference.

### 4. DISCUSSION AND CONCLUSIONS

Our findings suggest that CIPN has a negative effect on psychological distress and sleep quality in cancer

TABLE II Multivariate logistic regression analysis for depression and anxiety

Variable		$\beta$	Standard error	Wald statistic	df	<i>p</i> Value
Independent	Covariate					
Depression	Age	0.024	0.007	13.509	1	<0.001
	Sex	-0.200	0.177	1.281	1	0.258
	Education level	-0.201	0.094	4.548	1	0.033
	PNQ grade	0.302	0.111	7.444	1	0.006
	Fatigue	0.105	0.013	61.20	1	<0.001
	Sleep quality	1.070	0.200	28.605	1	<0.001
	Social support	-0.084	0.044	3.719	1	0.054
	Disease stage	0.140	0.119	1.385	1	0.239
	Tumour site			16.838	9	0.051
Anxiety	Age	0.006	0.008	0.591	1	0.442
	Sex	0.136	0.229	0.351	1	0.553
	Education level	-0.080	0.096	0.687	1	0.407
	PNQ grade	0.372	0.127	8.533	1	0.003
	Fatigue	0.050	0.012	17.063	1	<0.001
	Sleep quality	0.815	0.205	15.755	1	<0.001
	Social support	-0.032	0.044	0.527	1	0.468
	Disease stage	0.315	0.626	0.252	1	0.615
	Tumour site			19.906	9	0.019

PNQ = Patient Neurotoxicity Questionnaire.

patients treated with chemotherapy. In particular, PNQ grades D and E were associated with a high risk of poor psychological status and sleep quality. Our findings emphasize the importance of assessing peripheral neuropathies during chemotherapy and of adjusting treatment plans based on the assessment results. Assessment results also provide important information that can help clinicians to modify treatment programs appropriately.

Peripheral neuropathies are common side effects of chemotherapy drugs. Several studies have indicated that up to 90% of all chemotherapy patients might experience CIPN<sup>5-7,9,48</sup>. Chemotherapy-induced peripheral neuropathy might not develop until after the completion of chemotherapy and can last for years beyond completion of cancer treatment<sup>16</sup>.

Considering the increasing emphasis given to the QOL of cancer patients<sup>4</sup>, the association between CIPN and QOL has been explored by several researchers. By producing unpleasant symptoms, limiting functional performance, and causing distress, CIPN negatively influences the QOL of cancer patients<sup>49</sup>. Nonetheless, little literature is available on the associations between neuropathy, psychological distress, and sleep quality.

Anxiety, depression, and sleep disorders are important factors affecting the QOL of cancer patients<sup>25,26,35,50</sup>. Treatment side effects can exacerbate patient anxiety or depression<sup>50</sup> and affect sleep quality<sup>51</sup>. In a cross-sectional study of patients with colorectal cancer<sup>16</sup>, researchers reported that depressive symptoms ( $r = 0.38, p = 0.0001$ ) and higher degrees of sleep disturbance ( $r = 0.35, p = 0.0004$ ) are significantly associated with peripheral neuropathy of greater severity. Their findings are consistent with those in the present study. Pain, which is one of the main factors affecting depression and sleep disturbance in cancer patients<sup>50,52</sup>, might partly explain the relationships of CIPN with psychological distress and sleep disturbance. Chemotherapy-induced peripheral neuropathy can cause neuropathic pain<sup>49</sup>, and patients with pain in their hands or feet are at higher risk for developing depression, anxiety, and sleep disturbances. In addition, CIPN-induced limitations such as numbness, tingling, swelling, and muscle weakness limit the ability of patients to perform tasks independently. Those limitations might induce depression and anxiety<sup>20,32</sup> and negatively affect sleep quality.

The most extensively recognized physician-based approach for assessing CIPN is the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events*<sup>9</sup>. However, that approach requires cooperation on the part of the patient and skill on the part of the physician to obtain essential diagnostic information. Other available patient-based questionnaires include the Functional Assessment of Cancer Therapy (FACT)—Taxane and the FACT—Gynecologic Oncology Group—Neurotoxicity<sup>53,54</sup>. However, although those instruments are more discerning, they

also include questions that are not specific to CIPN assessment. The PNQ is a simple, self-administered instrument. Its specific questions are designed to obtain, directly from the patient, clinically relevant and quantifiable CIPN diagnostic information about the incidence and severity of subjective CIPN symptoms<sup>55</sup>. Moreover, the PNQ is designed to clearly delineate between no interference and interference with defined activities of daily living. Hence, it is a useful instrument, with high acceptance by physicians<sup>37</sup>. Several researchers have reported that PNQ sensory and motor scores are correlated with the FACT and the FACT—Gynecologic Oncology Group—Neurotoxicity questionnaires ( $r = 0.66$  and  $0.51$  respectively)<sup>38</sup>. Overall, the PNQ can be completed with high compliance to assess CIPN<sup>56</sup>.

The limitations of our study must be mentioned. First, it relied on self-reported data and did not include objective measures of nerve function such as neurologic exams or nerve conduction studies. However, numerous studies have demonstrated the reliability and validity of self-reporting tools for evaluating the severity of neuropathic symptoms in patients receiving chemotherapy<sup>37,38,55,56</sup>, and self-reported neuropathy has been included as an outcome measure in numerous studies<sup>3,37,38</sup>. A second limitation of the study is the cross-sectional nature of the data. Assessments for CIPN, psychological status, and sleep quality were performed only after the 4th week of cancer treatment. Causal relationships between the CIPN and psychological status and sleep quality can therefore not be determined. To yield better assessment results, future research on this topic must use a longitudinal method: that is, patient data must be collected before and at several times during treatment. A third limitation of the study is the lack of an assessment of diseases and treatment-induced side effects other than CIPN pain-related symptoms and physical function (for example, gastrointestinal distress). Such adverse symptoms might have an important effect on psychological status and sleep quality in patients; the effects of CIPN on depression, anxiety, and sleep quality might therefore be overestimated in the present study. Future research should add an assessment of patient FACT scores to identify the effect of CIPN on psychological status and sleep quality.

## 5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare. This study has no financial relationship with any sponsoring organization. The corresponding author has full control of all primary data.

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