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ORIGINAL ARTICLE

Multicenter, cross-sectional observational study of the impact of neuropathic pain on quality of life in cancer patients

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Abstract

Purpose Neuropathic cancer pain (NCP) is a common and potentially debilitating symptom in cancer patients. We investigated the prevalence of NCP, as well as its management and association with QOL.

Methods Cancer patients with pain ≥1 on the visual analogue scale (VAS) were surveyed with the Douleur Neuropathique (DN4) questionnaire, the Brief Pain Inventory-Short Form (BPI-SF), and the EuroQOL five dimensions (EQ-5D) questionnaire. The associations between NCP and pain severity

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or NCP and QOL, while controlling for variables relevant to QOL, were then analyzed.

Results A total of 2003 patients were enrolled in this survey; the prevalence of NCP was 36.0% (n = 722, 95% CI, 32.5–39.5). We found that NCP in cancer patients was closely correlated to a higher pain severity (BPI-SF; 4.96 ± 1.94 versus 4.24 ± 2.02, $p < 0.001$), and in patients with NCP, pain more severely interfered with daily living, as compared to those without NCP (BPI-SF; 4.86 ± 2.71 versus 4.41 ± 2.87, $p < 0.001$). Patients with NCP also had worse QOL than those without NCP, as measured by EQ-5D index score (0.47 ± 0.30 vs. 0.51 ± 0.30, p = 0.005), and this was confirmed using multivariate analysis ($p < 0.001$), even after controlling for other variables such as age, sex, disease stage, cancer duration, radiotherapy, chemotherapy, and comorbidities. Importantly, adjuvant analgesics were used in less than half of patients with NCP (n = 358, 46.4%).

Conclusions We found that NCP in cancer patients was significantly associated with a worsened QOL, and current management is inadequate. Therefore, future research aimed at developing improved strategies for management of NCP is required.

Keywords Neuropathic pain · Quality of life · Neoplasm · Pain management

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Introduction

Pain has been recognized as a key symptom in various types of cancer, and it is the most common symptom leading to a cancer diagnosis (in about 30% of patients) [1]. Although recent guidelines have emphasized the treatment of pain in cancer patients, it remains undertreated [2, 3]. It has also been found that cancer patients with pain have significantly lower levels of performance status and higher levels of anger, fatigue, depression, confusion, and lethargy, as compared to those cancer patients who did not experience pain, even after accounting for disease stage [4].

Neuropathic pain may adversely affect quality of life (QOL) in cancer patients and could also increase care difficulty [5, 6]. Previous studies have investigated the impact of NCP on QOL [6–9]. But these mostly focused on chemotherapy-induced peripheral neuropathy (CIPN) alone in specific disease conditions. NCP is particularly important to diagnose because distinct treatment strategies are required that differ from those needed for nociceptive pain [10–12]. Critically, the features associated with NCP, including, but not limited to CIPN, especially among cancer patients, are poorly understood. To obtain a comprehensive insightful overview of NCP in cancer patients, it will be necessary to investigate the characteristics of a large group of general cancer patients with NCP, including those in all stages of disease, regardless of the treatments they have received.

This study was performed on behalf of Korean Cancer Study Group Neuropathic Cancer Pain Survey and was designed to assess the current status of NCP in cancer patients. We aimed to accomplish three main objectives: (i) determine the prevalence and associated characteristics of NCP in patients with cancer pain, (ii) identify the current patterns of management for NCP, and (iii) assess the association of NCP with QOL. We found that NCP was associated with a lower QOL in cancer patients, even after controlling for other potentially confounding variables, and it also remains undertreated, highlighting the need for improved pain management strategies.

Methods

Study design

This observational study is non-interventional, multicenter, and cross-sectional. The study was performed between February 2013 and March 2014 in the oncology clinic of 28 general hospitals, representing the general cancer patient population in the Republic of Korea. The first step of the study procedure was to interview and screen individual patients by medical personnel. Informed consent was then obtained from all eligible patients. Patients who signed the consent were next

asked to complete a survey questionnaire about pain and QOL. Physicians evaluated the patients to determine the presence of neuropathic pain, and both demographic and clinical information was retrieved from the medical records. Lastly, the questionnaires and case report forms were collected, and the study data were analyzed. Central institutional review board (IRB) of Korean Cancer Study Group (KCSG) approved this study (study ID: KCSG PC13-02). After central approval, institutional approval was obtained again by every institution of the participating investigators.

Patients

A total of 2003 patients were enrolled in the survey. Inclusion criteria were patients who (1) were aged 20 years or older, (2) were diagnosed with cancer, (3) had pain with a visual analogue scale (VAS) measurement of one or higher, and (4) could understand and sign the informed consent. Patients were excluded if they had pain that is unrelated to cancer as per a physician's discretion.

Data collection and measurement

Clinical information potentially related to pain or neuropathic pain, including past medical histories, were collected from patient medical records. Current pain control status was evaluated by reviewing all drugs administered during the preceding 6 weeks. The presence of neuropathic pain was determined using the DN4 questionnaire where a total score of 4 or higher was defined as NCP in this study. The questionnaire consists of 10 items, 7 items related to pain quality which are based on an interview with the patient, and 3 items which are based on the clinical examination. A score of 1 is given to each positive item and a score of 0 to each negative item. The total score is calculated as the sum of all 10 items, and the cutoff value for the diagnosis of neuropathic pain is a total score of 4 out of 10 [13]. Pain characteristics were further evaluated using the Brief Pain Inventory-Short Form (BPI-SF) [14], Korean version [15]. BPI-SF is a self-administered questionnaire used to evaluate pain on its severity and its impact on the patient's daily functioning. Items in the pain severity evaluate the pain "at its worst," "at its least," and "on average" over the previous 24 h, as well as pain at the time of completing the questionnaire. On the other hand, the pain interference scale asks the patient to rate how their pain interferes with their enjoyment of life, general activity, walking ability, mood, sleep, normal work, and relationships with other people. Patients respond on a 0 to 10 numerical scale where higher scores indicate higher level of pain and interference [14, 15]. Health-related QOL was measured using the Korean version of the EuroQOL five dimensions (EQ-5D) and the EQ-5D visual analogue scale (VAS) [16–18]. The EQ-5D index score consisted of five metrics, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with three grades of severity for each item. The EQ-5D index score ranges from 0 to 1, with larger values indicating a better QOL. The EQ-5D VAS is simple thermometer-like bar scale, in which a patient can draw a line between 0 (worst) and 100 (best) indicating his or her overall condition, which is a gross self-assessment of general health status of the day that the survey is administered.

Statistical analyses

We estimated a target sample size based on the assumption that the prevalence of neuropathic pain is 30% [19]. With a significance level of 0.05 and an estimated error rate of 2%, the required number of patients to be enrolled was calculated to be about 2000:

$$n = p(1-p)\left(\frac{za/2}{d}\right)^2, \quad p = 0.3, \quad Za/2 = 1.96 \ \textit{when} \ a = 0.05, \quad d = 0.02.$$

For the data analysis, descriptive statistics were performed to determine the demographic and clinical characteristics of patients (Table 1). A Student's t test was performed to compare the mean differences in pain level and QOL between the NCP and non-NCP groups (Tables 2 and 4). Univariate regression analyses were performed to explore the factors associated with QOL (EQ5D) (Table 3). Using the determinants that were significantly (p value < 0.05) associated with EQ5D in this univariate analysis, we performed multiple regression analysis. To determine if there were any interactions between two independent variables, we performed multiple regression analysis including sex (p value 0.338), other statistically significant (p value < 0.05) variables, and potential interaction terms. Among all multiple regression models, we selected the model with the smallest Akaike information criterion value. All statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Corporation, NY, USA).

Results

Patient characteristics

Demographic and clinical characteristics of all patients are presented in Table 1. The majority of patients had advanced-stage cancer (71.3%) and had or were receiving chemotherapy (87.5%). Among comorbidities, the prevalence of diabetes (15.4%) appeared to be the highest among our study population. Other comorbidities relevant to neuropathic pain were rare. For management of pain, opioid analgesics were most

Table 1 Characteristics of study participants

Patient data	Total n = 2003 n (%)
Gender	
Male	1089 (54.4)
Female	914 (45.6)
Age, median (range)	61.0 (21–94)
Time from diagnosis of cancer (months), median (range)	13.0 (1–336)
Stage	
1	46 (2.3)
2	103 (5.1)
3	250 (12.5)
4	1428 (71.3)
Unknown	176 (8.8)
Comorbidities and history[a, b]	
Diabetes	309 (15.4)
Liver cirrhosis	44 (2.2)
Traumatic injury	43 (2.1)
Herpes zoster	41 (2.0)
Management of pain[a]	
Opioid analgesics	1313 (65.6)
Non-opioid analgesics	748 (37.3)
Anticonvulsants	464 (23.2)
Antidepressants	134 (6.7)
Corticosteroids	91 (4.5)
Benzodiazepines	68 (3.4)
Others	48 (2.4)
None as analgesic	257 (12.8)
Experienced treatment[a]	
Chemotherapy	1753 (87.5)
Surgery	799 (39.9)
Radiation	602 (30.1)
None	220 (11.0)
Chemotherapeutic agents[a, c]	
Alkylating agents	1209 (60.4)
Taxanes	485 (24.2)
Vinca alkaloids	150 (7.5)
Others	1500 (74.9)
Primary and metastatic sites of cancer[a]	
Gastrointestinal tract	982 (49.0)
Respiratory system	490 (24.5)
Skins, bones, connective tissue	288 (14.4)
Lymphatic-hematopoietic system	272 (13.6)
Genitourinary system	269 (13.4)
Breast	221 (11.0)
Head and neck region	188 (9.4)
Others/multiple primary	70 (3.5)
Unknown	6 (0.3)

[a] Permitted overlap

[b] Comorbidities with incidence of less than 2% were not presented in this table

[c] N = 1751 (missing N = 2, those who did not select type of chemotherapeutic agents were excluded). Others include antimetabolites, topoisomerase inhibitors, cytotoxic antibiotics, etc.

commonly used among all patients (65.6%), followed by non-opioid analgesics (37.3%) and anticonvulsants (23.2%).

Prevalence and management of neuropathic pain

NCP was present in 722 out of the 2003 patients surveyed, and thus the prevalence of NCP was found to be 36.0% (95% CI, 32.5–39.5). Among the patients diagnosed with NCP (N = 722), in most cases, it was associated with chemotherapy; 668 patients (92.5%) had received or were receiving chemotherapy, while 54 patients (7.5%) had never received chemotherapy. The prevalence of NCP was significantly higher among patients who had received or were receiving chemotherapy (n = 1753) compared to its prevalence of those who have never received chemotherapy (n = 250) (38.1 versus 21.6%, $p < 0.001$, Supplementary Appendix Table 1). Patients with moderate to severe pain (VAS ≥ 4, n = 497) had a higher prevalence of NCP than those with mild pain

($n = 225$) (42.4 vs. 27.1%) (Fig. 1). However, fewer than half of the patients with both moderate to severe pain and NCP were being treated with adjuvant analgesics targeting the NCP ($n = 358$, 49.6%) (Fig. 1), although these were more frequently prescribed in this group than to those without NCP (23.0%) ($p < 0.001$ by χ^2 test, details in Supplementary Appendix Fig. 1).

Prevalence and management of cancer pain

More than half of the patients ($n = 1173$, 58.6%) had moderate to severe pain (VAS ≥ 4), implying that cancer pain was not being adequately managed. Contrary to NCP, the portion of severe pain was significantly higher among patients who have never received chemotherapy ($n = 250$) compared to those had received or were receiving chemotherapy ($n = 1753$) ($p = 0.010$, Supplementary Appendix Table 1). Pharmacologic management for the pain was presented at Table 1. Even though all patients participating in this study were those who reported some degree of cancer pain, still 12.8% ($n = 257$) of the total patients were not prescribed any analgesic. When comparing pain treatment patterns in patients with or without NCP, we found that anticonvulsants, antidepressants, and benzodiazepines were more commonly used in patients with NCP then patients without NCP, whereas opioids, non-opioids, and corticosteroids were more commonly used in patients without NCP.

NCP association with pain severity and QOL

The pain severity score from the BPI-SF was measured in all patients; however, the pain interference score could not be measured in two patients. All patients answered the EQ-5D VAS, but six did not complete the EQ-5D index score questionnaire. Table 2 shows the differences in the mean pain and QOL scores in those with or without NCP. Patients with NCP had higher pain severity scores ($p < 0.001$) and higher pain interference scores ($p < 0.001$) in their daily living, than those without NCP. The QOL, as measured by the EQ-5D index score, was significantly worse in patients with NCP, than in those without NCP ($p = 0.005$). When analyzed by subscales of the EQ-5D, patients with NCP had a greater number of extreme problems than those without NCP in both the pain/discomfort and the anxiety/depression domain ($p < 0.001$ and $p = 0.007$, respectively). Proportion distributions by each level of mobility, self-care, and usual activities domains were not significantly different between patients with and without NCP (Supplementary Appendix Table 2).

Factors associated with QOL

We analyzed demographic and clinical factors potentially affecting the EQ-5D index score and found that younger age ($p < 0.001$), shorter duration of cancer ($p = 0.015$), absence of comorbidities ($p < 0.001$), and absence of neuropathic pain ($p = 0.005$) were associated with better QOL scores in our univariate analysis. Conversely, patients with stage IV cancers ($p < 0.001$), those who never received chemotherapy ($p < 0.001$), or those who underwent radiotherapy ($p < 0.001$) had worse QOL status (Table 3). Even after a multivariate analysis, a diagnosis of NCP was among the factors that significantly affected QOL ($p < 0.001$); EQ-5D index score was 0.442 in patients with NCP and 0.497 in patients without NCP ($p < 0.001$), after adjusting for other variables.

The effect of adjuvant analgesics targeting NCP on pain and QOL

We investigated the mean pain and QOL score differences in patients receiving adjuvant analgesics targeting NCP and in those who did not. We found that patients with NCP who were managed with adjuvant analgesics had less interference with their daily living ($p = 0.041$) and had a better QOL (by EQ-5D VAS score) ($p = 0.043$) (Table 4). If we again examine the details of the EQ-5D index score, a smaller proportion of patients having extreme problems were observed in the group receiving adjuvant analgesics, as compared to the group that were not receiving adjuvant analgesics in the mobility, self-care, and usual activities domains ($p = 0.028$, 0.031, and 0.005, respectively, linear-by-linear association). Proportion distributions in the pain/discomfort and anxiety/depression

Table 2 Pain and QOL scores in patients with and without NCP

Mean ± SD	Total ($n = 2003$)	NCP ($n = 722$)	Non-NCP ($n = 1281$)	p[a]
Pain VAS at screening	4.37 ± 2.27	4.90 ± 2.27	4.08 ± 2.01	<0.001
Pain Severity from BPI-SF	4.50 ± 2.02	4.96 ± 1.94	4.24 ± 2.02	<0.001
Pain Interference score from BPI-SF	4.57 ± 2.82	4.86 ± 2.71	4.41 ± 2.87	<0.001
EQ-5D index score	0.49 ± 0.30	0.47 ± 0.30	0.51 ± 0.30	0.005
EQ-5D VAS	57.42 ± 30.48	56.53 ± 21.42	57.92 ± 34.55	0.327

SD standard deviation, *NCP* neuropathic cancer pain, *VAS* visual analogue scale

[a] p value by Student's t test

Table 3 Univariate and multivariate analyses of factors associated with QOL (EQ-5D index score)

	Univariate analysis		Multivariate analysis	
	B^a	p^a	B^b	p^b
Sex, male (female)[c]	0.013	0.338	0.026	0.067
Age, ≥60 (<60)	−0.065	<0.001	−0.055	0.000
Duration of cancer, ≥13 months (<13 months)	−0.033	0.015	−0.024	0.102
Stage, IV (stages I–III)	−0.110	<0.001	−0.102	0.000
Chemotherapy, done (never done)	0.116	<0.001	0.069	0.000
Radiotherapy, done (never done)	−0.048	0.001	−0.050	0.001
Surgery, done (never done)	0.020	0.137		
Comorbidities, present (none)	−0.085	<0.001	−0.072	0.000
Diagnosis of NCP, DN4 ≥ 4 (DN4 < 4)	−0.039	0.005	−0.053	0.000
NCP-targeted therapy, present (none)	−0.012	0.421		

[a] By regression analysis

[b] By multiple regression analysis, $R^2 = 0.065$

[c] Reference variables are in parenthesis

domains were not significantly different between the two groups (Supplementary Appendix Table 3).

Discussion

In this study, we clearly found that patients with NCP have a worse QOL than those without NCP. This difference is statistically significant, even after controlling for other variables affecting QOL. In addition to NCP, older age, advanced cancer stage, never having received chemotherapy, have received radiotherapy, and presence of comorbidities were associated with low QOL scores. This is particularly meaningful, as we included patients who never received chemotherapy in our survey.

To the best of our knowledge, this is the first study that clearly demonstrates the relationship between NCP and QOL in a population of cancer patients encompassing a broad array of conditions. Apart from studies on CIPN, those that directly assessed QOL differences in various cancer patients with or without NCP are rare. As we expected, we observed that regardless of receiving chemotherapy or not, diagnosis of NCP was a significant factor that lowered patients QOL. Our study population consisted mainly of incurable advanced-stage cancer patients, as well as patients undergoing treatment and cancer survivors. By doing this, we tried to obtain a global perspective of the general features of neuropathic pain in cancer patients and clarify its association with QOL.

One recently published study showed that neuropathic symptoms, such as numbness and tingling, are associated with poor QOL [6]. However, this study focused on CIPN in

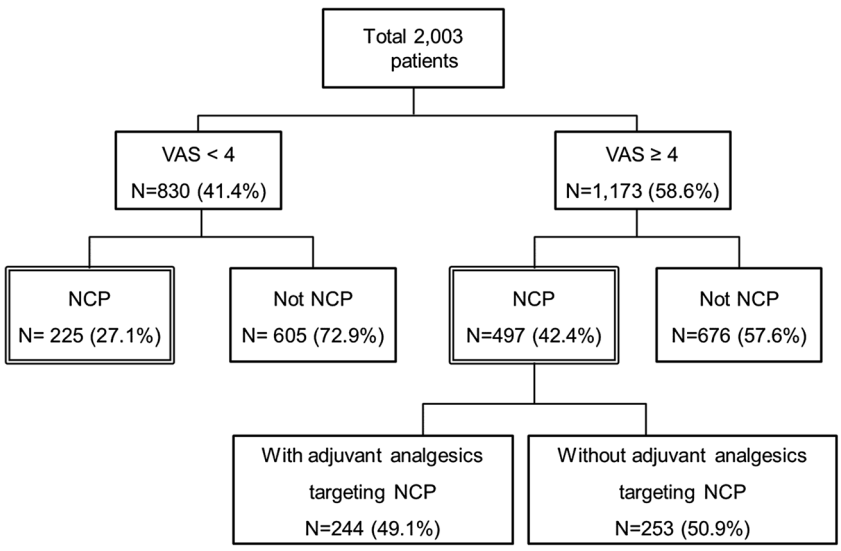

Fig. 1 Prevalence of NCP according to pain intensity. NCP was more prevalent in patients with moderate to severe pain than in those with mild cancer pain (comparison between double-lined boxes; $p < 0.001$ by χ^2 test). Among patients having pain with a severity of VAS ≥4, less than half were treated with adjuvant analgesics targeting NCP (*lower boxes*). Treatment with adjuvant analgesics targeting NCP was defined as the administration of antidepressants, anticonvulsants, corticosteroids, benzodiazepines, and with or without opioid or non-opioid analgesics

Table 4 Comparison of pain and QOL scales in patients diagnosed with NCP, with and without adjuvant analgesics targeting NCP

Mean ± SD	Total (n = 772)		p[a]
	With adjuvant analgesics targeting NCP (n = 358)	Without adjuvant analgesics targeting NCP (n = 364)	
Pain VAS at screening	4.82 ± 2.25	4.98 ± 2.29	0.372
Pain Severity from BPI-SF	4.88 ± 1.95	5.04 ± 1.93	0.262
Pain Interference score from BPI-SF	4.66 ± 2.63	5.07 ± 2.78	0.041
EQ-5D index score	0.49 ± 0.28	0.45 ± 0.31	0.090
EQ-5D VAS	58.15 ± 19.77	54.93 ± 22.84	0.043

SD standard deviation, *NCP* neuropathic cancer pain

[a] p value by Student's t test

patients receiving chemotherapy. There are many additional studies that have examined the relationship between CIPN and QOL, and the negative association between the two is well-established. According to a recent systematic review [20], out of 11 studies that assessed the relationship between CIPN and QOL, eight showed a correlation between CIPN and worsened QOL [8, 21–26]. The remaining three studies did not find an association between CIPN and QOL. Among those eight studies that reported an association between CIPN and a lower QOL, one recent large-scale study showed that out of 1643 colorectal cancer survivors, those who reported to have a greater number of neuropathy symptoms (upper 10%) had a statistically significantly worse QOL, as compared to those with fewer neuropathy symptoms (lower 90%) [8]. Other studies demonstrated the association of CIPN and worse QOL in patients with colorectal cancer [7], lung cancer [21], lymphoma [24], ovarian cancer [26], and various solid tumors [23].

In this study, neuropathic cancer pain was diagnosed in 722 patients, out of 2003 patients surveyed, and the estimated prevalence was 36%. This was similar to result from recent systematic review reporting that the prevalence of pain with neuropathic component was 39.1% (95% CI, 28.9%–49.5%) [27]. More recently, a European survey estimated an occurrence rate of 32.6% (95% CI, 29.62–35.58) for cancer-related neuropathic pain among cancer patients having chronic pain [28].

The etiology of NCP has not been fully defined. Although according to a systematic review [27], only 20.3% of cases were attributed to cancer treatment, a recently published study suggests that a larger portion of neuropathic pain originates from anticancer treatment (68.9% tumor-related, 42.9% treatment-related) [29]. In our present study, most patients with NCP had received, or had been receiving chemotherapy (87.5%), implying that a larger portion of NCP may be caused by anticancer treatments than previously known.

Although it is recommended that anticonvulsants or antidepressants are used in combination with opioid analgesics for management of NCP [30–32], we found that adjuvant analgesics, such as anticonvulsants, antidepressants, corticosteroids, benzodiazepines, or phenothiazines, were rarely used for the purpose of pain control in our study population. Less than half of patients with NCP were prescribed adjuvant analgesics, along with opioids or non-opioid analgesics. This proportion is not increased, even in patients experiencing moderate-to-severe pain and NCP, and this suggests that physicians should pay increased attention to pain in their cancer patients.

Our study has several limitations. First, in spite of the clear association between NCP and worsened QOL, we could not confirm a causal relationship between NCP and QOL, due to our cross-sectional study design. Additionally, although there was a statistical significance between NCP and non-NCP patients, the QOL difference was relatively small. Second, the population included in this study was heterogeneous; we enrolled patients who were receiving anticancer treatments, those who were under palliative care after finishing chemotherapy, and those who never underwent chemotherapy. This is what distinguishes our study from the other studies, which mostly focuses on CIPN in patients receiving a specific chemotherapy regimen. Such heterogeneity may attenuate or potentiate the association between NCP and QOL. By virtue of this heterogeneity however, this study can provide a general overview of the neuropathic pain in the cancer patients until more evidence on NCP etiology is available. Third, due to our cross-sectional study design, patients having a DN4 score <4 included both of patients who had never had NCP and those who may have experienced NCP but its symptoms were improved after management. From our study results, it is impossible to distinguish the two. Fourth, cutoff for poorly controlled pain was NRS score of 4, which was arbitrarily decided by the investigators instead of reflecting patients' personalized pain goal. And because we included patients who were not receiving any analgesics, the population without analgesics may have affected the overall outcome, such as the relationship between NCP and QOL.

In summary, this study provides a clinically meaningful overview of neuropathic pain in patients with cancer pain. We found that there was a clear association between NCP and both increased pain severity and worsened QOL. These results suggest the need for prospective study aimed at clarifying the causality between neuropathic pain and worsened QOL. Furthermore, in general, pain was not adequately managed in our study population, and NCP-targeting drugs are not widely used. Therefore, new management strategies with improved efficacy are required, as current pharmacological management is not sufficient to alleviate neuropathic pain, and efforts to elucidate the detrimental effect of neuropathic pain will be meaningless, in the absence of effective methods to improve it.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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