Original Article

Optimizing Clinical Screening for Chemotherapy-Induced Peripheral Neuropathy

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Abstract

Context. Efficient and accurate clinical screening for treatment-related toxicities is a critical component of optimal patient management. A number of alternate screening tools for chemotherapy-induced peripheral neuropathy (CIPN) have been proposed in response to demonstrated limitations with standard clinical screening, although their relative diagnostic value is unclear.

Objectives. The aim of this study is to evaluate the relative construct validity and discriminant properties of available CIPN screening tools.

Methods. Patients treated with known potentially neurotoxic therapies underwent CIPN evaluation at one or multiple timepoints ($N = 316$ patients; age $= 56 \pm 13$ years). At each testing session ($N = 644$ testing sessions), patients were evaluated using screening tools and comprehensive CIPN assessments. Comprehensive assessments were clinician-rated (Total Neuropathy Score, reduced) or patient-reported outcome (PRO; Functional Assessment of Cancer Therapy-Gynecologic Oncology Group/Neurotoxicity questionnaire). Similarly, screening tools were clinician-rated (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) or PRO (Patient Neurotoxicity Questionnaire, PRO-CTCAE).

Results. Analyses revealed moderate-to-high correlations between screening tools and comprehensive assessments ($0.55 \leq rho \leq 0.75$; $P < 0.001$) and similar discriminant properties across screening tools ($P > 0.01$). Screening tool grading corresponding to clinically significant (grade 2/3) vs. low-grade (grade 0/1) CIPN would correspond to greater ratings of CIPN severity by more comprehensive assessments in a predicted 77%−91% of cases (c-statistic = 0.77−0.91; $P < 0.01$).

Conclusions. PRO screening tools provide adequate CIPN screening while avoiding potential biases demonstrated to limit currently used clinician-rated screening tools. Addition of a brief objective test did not add value to PRO screening. Up to 23% of patients would be misidentified through screening, providing quantitative evidence of the limitations of available screening tools. More extensive CIPN evaluations are critical in patients at risk of serious neurotoxicity. J Pain Symptom Manage 2019;58:1023−1032.

Key Words

Neurotoxicity, quality of life, cancer survivorship, chemotherapy

Introduction

Efficient and accurate clinical screening for toxicities is a critical component of treatment and symptom management both during cancer treatment and in survivorship. Neurotoxicity is an unfortunately common side effect of cancer treatment, with over two-thirds of patients developing chemotherapy-induced peripheral neuropathy (CIPN) by the end of

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treatment.[1,2] Up to 40% of patients experience long-lasting neuropathy symptoms into survivorship.[3] CIPN typically presents as numbness and tingling in the hands and feet and is notably associated with balance and locomotor deficits,[4,5] reduced quality of life,[6] and an increased incidence of falls.[4,7]

At present, CIPN is most commonly assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE),[8] although studies have demonstrated that this scale has only moderate reliability[9,10] and limited responsiveness.[11] Accordingly, a substantive body of research has been conducted in the area of CIPN assessment,[10] with multiple clinician-rated (i.e., Total Neuropathy Score)[12] and patient-reported (PRO; i.e., European Organisation for Research and Treatment of Cancer CIPN-20; Functional Assessment of Cancer Therapy-Gynecologic Oncology Group/Neurotoxicity questionnaire [FACT-GOG/Ntx])[13,14] instruments developed and determined to be more sensitive, responsive, and reliable.

In clinic, however, practical and time limitations of consults limit the scope of toxicity screenings. Although brief, the efficacy of these screenings is critical, as results have implications for treatment (dose reductions, early treatment cessation) and survival[15–19] and referrals to supporting departments or allied health services (i.e., neurology, rehabilitation).[2] A recent Delphi survey of clinical CIPN assessments rated instruments with greater than three items poorly with respect to feasibility for routine clinical use,[20] creating a guideline for the practical scope of clinical CIPN screening tools. Within these parameters, several patient-reported tools for clinical screening of CIPN (Patient Neurotoxicity Questionnaire [PNQ];[21] PRO-CTCAE[22]) have been developed and independently validated against larger patient-reported outcome instruments. However, these tools have yet to be validated against a comprehensive CIPN assessment strategy including both clinician-rated and patient-reported measures of CIPN.[23] In addition, the relative merit of available clinical screening tools for CIPN is yet to be evaluated, as well as the potential utility of adding a brief objective assessment to established tools. Accordingly, the aim of this study is to evaluate the relative concurrent validity and discriminant properties of available CIPN screening tools—NCI-CTCAE, PNQ, PRO-CTCAE—a pilot clinical screening tool combining patient-reported and objective items.

Methods

Patients

Patients who attended research clinics for a comprehensive testing session as a part of ongoing studies (IN FOCUS study; www.infocusstudy.org.au) between May 2017 and December 2018 were included in the study. Included patients were either on current treatment or within five years of the completion of treatment with known neurotoxic agents (bortezomib, cisplatin, docetaxel, lenalidomide, oxaliplatin, paclitaxel, nab-paclitaxel, thalidomide, vinblastine, vincristine, vinorelbine).[2] Oncology clinic lists were used to identify potentially eligible patients. Confirmation of suitability for the study was sought from the treating clinician before potential patients were approached by research staff. No specific exclusion criteria were applied to obtain a clinically relevant sample, given that clinical CIPN screening tools would need to be universally applicable in patients receiving neurotoxic treatments. In patients receiving chemotherapy treatment, data were collected before chemotherapy cycle administration. The study was approved by the Human Research Ethics Committees of South Eastern Sydney Local Health District and Sydney Local Health District (Royal Prince Alfred Hospital zone) and was conducted in accordance to the Declaration of Helsinki. All patients gave informed written consent before study participation.

CIPN Assessments

Patient-reported CIPN was assessed using the FACT-GOG/Ntx-11,[14] a validated 11-item questionnaire addressing CIPN symptoms and related functional difficulties. Each item is scored from 0 (not at all) to 4 (very much), with the total number of points subtracted from 44 possible points; a lower FACT-GOG/Ntx score indicates greater CIPN severity.

Clinician-rated CIPN was assessed using the Total Neuropathy Score, reduced version (TNSr),[24] a validated 8-item instrument combining a clinical assessment of sensory symptoms and weakness with pinprick, vibration sensibility, tendon reflex and strength assessments, and sural and tibial nerve conduction studies. Nerve conduction studies were performed in the left sural and tibial nerves according to standard procedures,[25] with the peak amplitude graded according to age-matched reference ranges.[24,26–28] Each item is scored from 0 to 4, resulting in a sum score with 32 possible points; greater scores indicate greater CIPN severity. Clinician-rated assessments were completed by trained researchers experienced in the assessment of CIPN.

Clinical Screening Tools

Clinical screening tools are detailed in Table 1 and were selected to evaluate sensory neuropathy severity and/or its interference with function based on the predominantly sensory pathogenesis and presentation of CIPN.[2,29] Clinical screening tools comprised 1) the peripheral sensory neuropathy item from the NCI-CTCAE

Table 1
Description of Clinical Screening Tools

Tools	Grade 0	Grade 1	Grade 2	Grade 3
NCI-CTCAE	No symptoms	Asymptomatic, loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental activities of daily living	Severe symptoms; limiting self-care activities of daily living
PRO-CTCAE[a]	None	Mild	Moderate	Severe
PNQ[b]	I have no numbness, pain, or tingling in my hands or feet.	I have mild tingling pain or numbness in my hands or feet. This does not interfere with my activities of daily living.	I have moderate tingling pain or numbness in my hands or feet. This does not interfere with my activities of daily living.	I have moderate to severe tingling, pain, or numbness in my hands or feet. This interferes with my activities of daily living.
Pilot tool				
Item 1	*Same as the PNQ question above*			
Item 2	Normal upper limb vibration sense	Reduced vibration sense in fingers	Reduced vibration sense in wrist	Reduced vibration sense in elbow
Item 3	Normal lower limb vibration sense	Reduced vibration sense in toes	Reduced vibration sense in ankle	Reduced vibration sense in knee

NCI-CTCAE = the National Cancer Institute Common Terminology Criteria for Adverse Events; PRO-CTCAE = patient-reported outcome Common Terminology Criteria for Adverse Events; PNQ = Patient Neurotoxicity Questionnaire.
[a]PRO-CTCAE severity graded by patients in response to the prompt "In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?"
[b]PNQ severity graded by patients in response to the prompt "Please indicate the statement that best corresponds to your current symptoms."

v4.03 (clinician-rated),[8] 2) symptom severity item from the "numbness and tingling" section of the PRO-CTCAE (PRO),[22] and 3) sensory item from the PNQ (PRO),[21] as well as 4) a pilot screening tool described in the next paragraph (clinician-rated + PRO). PRO-CTCAE evaluates symptom severity only, while PNQ, NCI-CTCAE, and the pilot tool address both symptom severity and interference with function. All screening tools were completed during the same comprehensive testing session. NCI-CTCAE grades were assigned by trained researchers immediately after each comprehensive testing session. NCI-CTCAE grade 0 was defined as "asymptomatic," with grades ≥1 defining "symptomatic" patients. All grade 4 PRO-CTCAE and PNQ symptoms were combined with grade 3, with grades 0–3 used across scales for analysis.

The pilot screening tool was designed to examine the utility of a combined patient-reported and objective clinical screening tool by combining the sensory item of the PNQ[21] with upper and lower limb vibration assessments from the TNS.[24] These items were selected because the PNQ and TNS (clinical version) were identified as the best available patient-reported and objective/clinical assessments in a Delphi survey of clinical CIPN assessments.[20] Vibration testing was the selected item from the TNS because of its strong correlation with neurophysiologic data in patients with CIPN.[23,30] Vibration testing was conducted using a standard tuning fork and standard clinical methodology[31,32] to maximize prospective clinical utility. A score out of six possible points (Table 1) was created by summing the grade from item 1 (patient-reported) and the highest grade out of items 2 and 3 (vibration). This score was converted to a 0–3 grading scale to correspond to the other screening tools: Grade 0 = 0 points; Grade 1 = 1–2 points; Grade 2 = 3–4 points; Grade 3 = 5–6 points.

Statistical Analysis

Independent samples t-tests were used to compare demographic and symptom variables. Concurrent validity was evaluated by comparing each clinical screening tool to both the TNSr and FACT-GOG/Ntx scores using nonparametric bivariate correlations (Spearman's ρ).[33] Differences in bivariate correlations were analyzed pairwise using Fisher's Z methodology[34] and the Bonferroni-Holm correction for multiple comparisons.[35] The strength of correlations was interpreted as per the study by Hinkle et al. (0–0.3 = negligible; 0.3–0.5 = weak; 0.5–0.7 = moderate; >0.7 = strong).[36]

The discriminant properties of each clinical screening tool were analyzed using one-way analyses of variance (ANOVAs) with a Bonferroni post-hoc test; clinical screening tools were independent variables and CIPN assessments were dependent variables

in these analyses. Significance was set at $\alpha = 0.05$ for ANOVAs and post-hoc tests. Discriminant properties were also further analyzed using c-statistics based on the area under the receiver operating characteristic (ROC) curve. ROC curves were plotted to determine the probability that a higher TNSr (greater clinical symptom burden) or lower FACT-GOG/Ntx score (greater patient-reported symptom burden) predicted a higher screening tool grade. ROC curves were plotted to analyze both adjacent screening tool grades and clinically significant (Grade 2/3)[17,37] vs. no/mild (Grade 0/1) CIPN. ROC curves were not plotted for any clinical assessment grades with less than 30 corresponding TNSr or FACT-GOG/Ntx assessments to ensure sufficient statistical power.[38]

Differences in c-statistics were analyzed pairwise using Fisher's Z methodology as per Hanley and McNeil[39] and the Bonferroni-Holm correction for multiple comparisons.[35] Given that the analyses are focused on the comparison of clinical CIPN screening tools and research assessments within a discrete testing timepoint, all assessments were treated identically and without regard to the number of testing sessions completed by each patient. All analyses were conducted in SPSS Statistics 24.0 (IBM, Armonk, NY).

Results

Patients

Data from 316 patients (107 male, 209 female; mean ± SD age = 56 ± 13 years) and 644 comprehensive testing sessions were included in the analysis. Patients completed all four clinical screening tools at all testing sessions. Three hundred five testing sessions were completed during treatment, with 339 testing sessions completed after treatment. Patients presented CIPN symptoms at a majority (59.9%) of testing sessions. Most testing sessions assessed patients who were currently receiving or had received oxaliplatin- or paclitaxel-based chemotherapy regimens for breast or colorectal cancer. Patient demographics for included testing sessions are located in Table 2.

Concurrent Validity

Analyses revealed moderate correlations ($0.55 \leq rho \leq 0.63$; $P < 0.001$) between all clinical screening tools

Table 2
Patient Demographics

Demographics	Total		On Treatment		After Treatment	
N	644		305		339	
Age (mean ± SD)	56 ± 13		55 ± 13		56 ± 13	
Male:female	207:437		97:208		110:229	
Asymptomatic, *n* (%)	258 (40.1)		128 (42.0)		130 (38.3)	
Symptomatic, *n* (%)	386 (59.9)		177 (58.0)		209 (61.7)	
	Mean ± SD	% missing	Mean ± SD	% missing	Mean ± SD	% missing
FACT-GOG/Ntx score	37 ± 7	1.1%	38 ± 6	1.3%	37 ± 8	0.9%
TNSr	3 ± 3	15.2%	2 ± 2	14.6%	3 ± 4	15.6%
Neurotoxic treatment, *N* (%)						
Cisplatin	45 (7.0)					
Docetaxel	61 (9.5)					
Oxaliplatin	129 (20.0)					
Paclitaxel	186 (28.9)					
Paclitaxel + carboplatin	120 (18.6)					
Vincristine	32 (5.0)					
Other	71 (11.0)					
Cancer type, *N* (%)						
Breast	228 (35.4)					
Colorectal	104 (16.1)					
Endometrial	34 (5.3)					
Lymphoma	37 (5.7)					
Myeloma	37 (5.7)					
Ovarian	59 (9.2)					
Prostate	38 (5.9)					
Other	107 (16.6)					

SD = standard deviation; FACT-GOG/Ntx = Functional Assessment of Cancer Therapy-Gynecologic Oncology Group/Neurotoxicity questionnaire; TNSr = Total Neuropathy Score, reduced version.
Missing TNSr assessments were due to incomplete or absent nerve conduction studies (patient declined electrical stimulation in $n = 70$ tests; technical difficulties obtaining sural and/or tibial nerve amplitude in $n = 28$ tests). Patients with missing and complete TNSr assessments were similarly aged and presented similar patient-reported symptom burden (FACT-GOG/Ntx score) ($P > 0.05$). On-treatment and posttreatment cohorts were similarly aged and presented similar proportions of symptomatic vs. asymptomatic patients and similar clinician-rated (TNSr) and patient-reported (FACT-GOG/Ntx) symptom burden ($P > 0.05$). "Other" neurotoxic treatments included were Nab-paclitaxel, bortezomib, cisplatin, docetaxel, lenalidomide, oxaliplatin, paclitaxel, thalidomide, vinblastine, vincristine, and combinations of neurotoxic therapies. "Other" cancer types included were ampullary, appendix, bile duct, bladder, cervical, gastric, liver, lung, esophageal, oropharyngeal, pancreatic, peritoneal, testicular, tongue, unknown primary, urothelial, uterine.

Table 3
Bivariate Correlations (Spearman's ρ Between the Four Clinical Screening Tools and TNSr and FACT-GOG/Ntx Scores)

	NCI-CTCAE	PNQ	PRO-CTCAE	Pilot Tool
TNSr	0.55	0.58	0.56	0.63
FACT-GOG/Ntx score	0.74	0.75	0.75	0.66[a]

TNSr = Total Neuropathy Score, reduced version; FACT-GOG/Ntx = Functional Assessment of Cancer Therapy-Gynecologic Oncology Group/Neurotoxicity questionnaire; NCI-CTCAE = the National Cancer Institute Common Terminology Criteria for Adverse Events; PNQ = Patient Neurotoxicity Questionnaire; PRO-CTCAE = patient-reported outcome Common Terminology Criteria for Adverse Events.
[a]Significantly different from PRO-CTCAE and PNQ ($P < 0.004$; critical α following Bonferroni-Holm correction = 0.0045).

and clinician-rated CIPN (TNSr) and moderate-to-high correlations ($0.66 \leq rho \leq 0.75$; $P < 0.001$) between clinical screening tools and patient-reported CIPN (FACT-GOG/Ntx; Table 3). Concurrent validity was similar among all four clinical screening tools, except for significantly lower validity of the pilot tool as compared to PNQ and PRO-CTCAE with respect to FACT-GOG/Ntx ($P < 0.004$).

Discrimination Between Adjacent Grades of CIPN Severity

Clinical screening tools were broadly able to discriminate worsening neuropathy, with TNSr and FACT-GOG/Ntx scores significantly different across grades in all clinical screening tools (ANOVA main effects: TNSr—$81.3 < F < 129.3$, $P < 0.001$; FACT-GOG/Ntx—$130.4 < F < 255.5$, $P < 0.001$; Fig. 1). PRO-CTCAE and NCI-CTCAE were significantly better able to discriminate Grade 1 vs. 2 symptoms with respect to patient-reported (FACT-GOG/Ntx) vs. clinician-rated (TNSr) symptom burden ($P < 0.001$; critical $\alpha = 0.008$) (Figs. 2 and 3). NCI-CTCAE was also more discriminant with respect to FACT-GOG/Ntx vs. TNSr between Grade 0 and 1 ($P < 0.006$; critical $\alpha = 0.008$) (Figs. 2 and 3).

Greater clinician-rated (TNSr) or patient-reported symptom burden (FACT-GOG/Ntx) had a 61%−79% or 63%−84% probability, respectively, of corresponding to an adjacently higher clinical screening tool grade (Figs. 2 and 3). There were no significant differences in c-statistics between clinical screening tools with respect to TNSr ($P \geq 0.05$; critical $\alpha = 0.008$). Compared with the pilot tool, the PNQ was more likely to correspond to greater patient-reported symptom burden (FACT-GOG/Ntx score) at Grade 3 vs. Grade 2 ($P < 0.007$; critical $\alpha = 0.008$; Fig. 3).

Ability of Screening Tools to Discriminate Clinically Significant Symptoms

To examine the discriminant properties of the clinical screening tools to identify patients with significant neuropathy, clinically significant neuropathy was

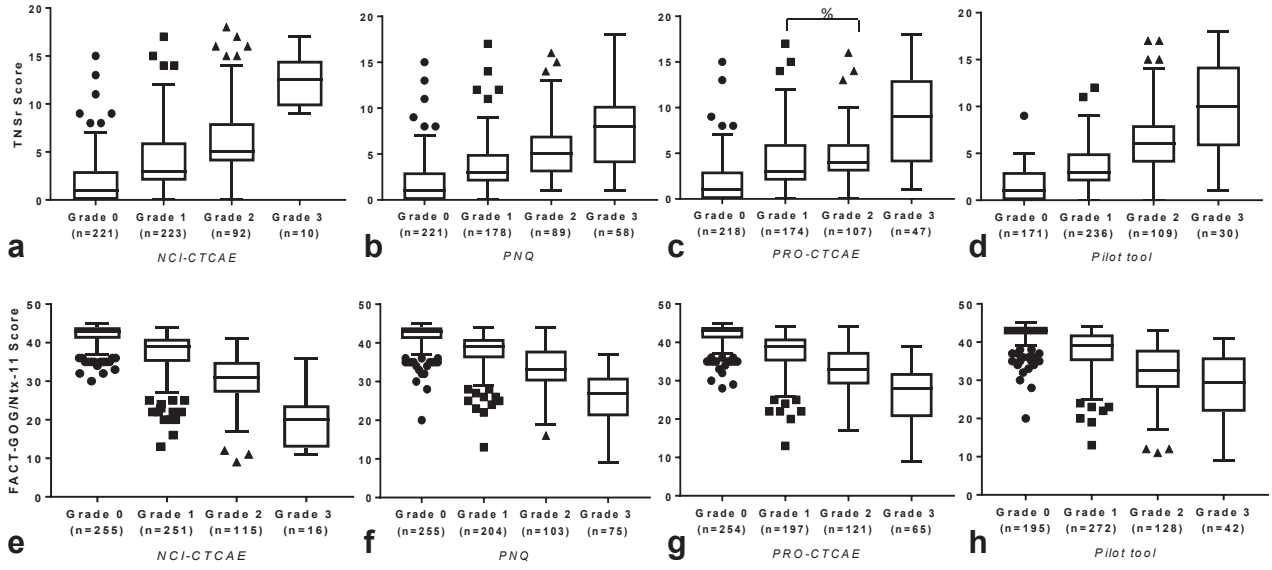

Fig. 1. Distribution of TNSr (a−d) and FACT-GOG/Ntx (e−h) scores for each clinical screening tool grade. Boxes represent the middle 50% of the distribution, bars represent 3/2 the interquartile range, and data points falling outside these bars are plotted independently. TNSr and FACT-GOG/Ntx scores are significantly different between all grades ($P < 0.001$) except where indicated by % ($P = 0.13$). TNSr = Total Neuropathy Score, reduced version; PNQ = Patient Neurotoxicity Questionnaire; PRO-CTCAE = patient-reported outcome Common Terminology Criteria for Adverse Events; NCI-CTCAE = the National Cancer Institute Common Terminology Criteria for Adverse Events; FACT-GOG/Ntx = Functional Assessment of Cancer Therapy-Gynecologic Oncology Group/Neurotoxicity questionnaire.

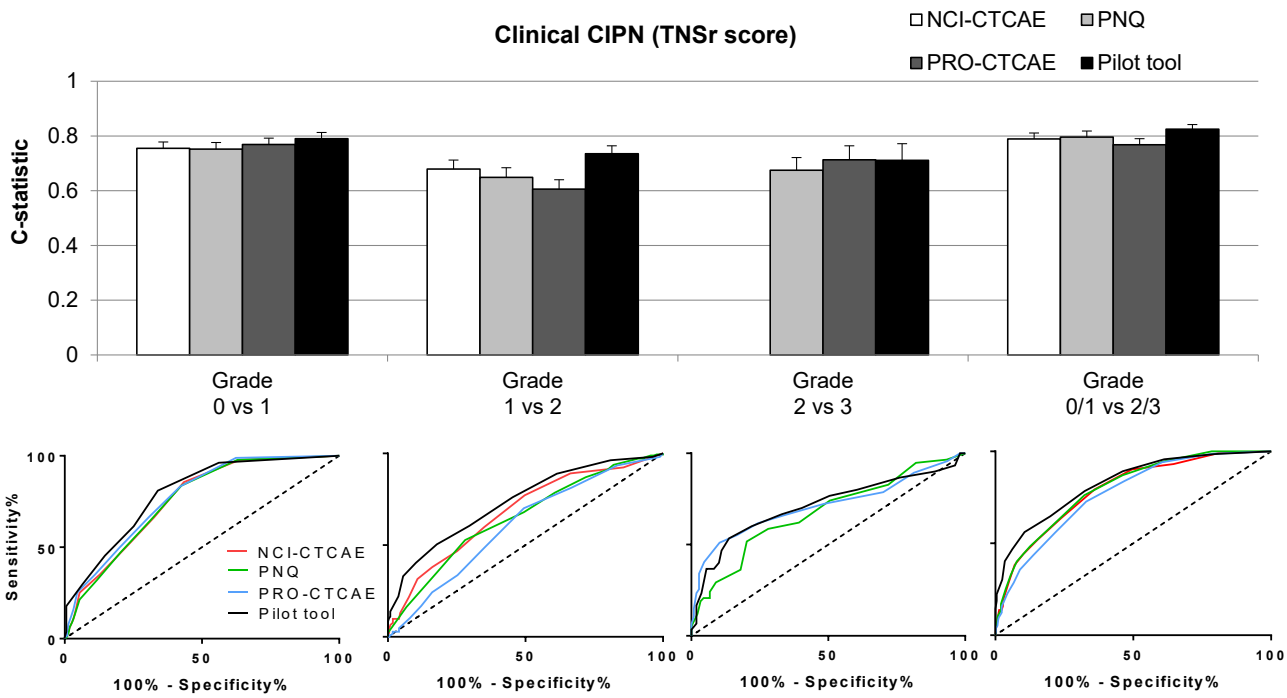

Fig. 2. Discriminant properties of clinical screening tools with respect to clinician-rated CIPN. Bars display c-statistics, representing the area under the respective ROC curves displayed adjacently below. The c-statistic represents the probability that greater clinician-rated symptom burden (higher TNSr) will correspond to a higher screening tool grade for a randomly selected patient. Error bars represent standard error of the c-statistic. NCI-CTCAE Grade 3 symptoms were not analyzed because of low $N = 10$. ROC = receiver operating characteristic; CIPN = chemotherapy-induced peripheral neuropathy; TNSr = Total Neuropathy Score, reduced version; NCI-CTCAE = the National Cancer Institute Common Terminology Criteria for Adverse Events; PNQ = Patient Neurotoxicity Questionnaire; PRO-CTCAE = patient-reported outcome Common Terminology Criteria for Adverse Events.

defined as ≥Grade 2 on all screening tools, and discriminant properties were compared across tools. There were no significant differences between screening tools in TNSr or FACT-GOG/Ntx scores corresponding to clinically significant symptoms ($F < 2.3$; $P \geq 0.08$), suggesting that all tools similarly classified neuropathy severity. All screening tools were able to distinguish between mild/no and clinically significant neuropathy ($P < 0.001$)—clinically significant symptoms had a 77%–83% or 85%–91% probability of corresponding to greater clinician-rated (TNSr) or patient-reported (FACT-GOG/Ntx) symptom burden, respectively (Figs. 2 and 3). NCI-CTCAE, PNQ, and PRO-CTCAE were significantly more discriminant with respect to patient-reported (FACT-GOG/Ntx) vs. clinician-rated (TNSr) symptom burden between Grades 0/1 and 2/3 ($P < 0.001$; critical $\alpha = 0.008$) (Figs. 2 and 3). Compared with the pilot tool, a grade of 2/3 vs. 0/1 on the NCI-CTCAE was more likely to correspond to greater patient-reported symptom burden (FACT-GOG/NTx score) ($P < 0.001$; critical $\alpha = 0.008$) (Fig. 3). No other differences in the discriminant properties of screening tools with respect to clinically significant symptoms were discovered ($P \geq 0.02$; critical $\alpha = 0.008$).

Discussion

The development of efficient and accurate clinical screening tools for treatment toxicities is critical to effective symptom management during cancer treatment and in survivorship. The identification of valid CIPN screening tools is of particular importance because of the high prevalence of CIPN in patients treated with neurotoxic chemotherapies[1] and the impact of screening results on clinical decision-making.[15–18] Although a number of studies have outlined considerations for CIPN endpoints in clinical trials,[40–43] there has been limited focus on the properties of screening tools to triage patients in routine clinical practice.

Results of the present study demonstrate that brief clinician-rated and patient-reported screening tools for CIPN are valid compared with both patient-reported and composite neurological measures of CIPN. Furthermore, brief screening tools also demonstrate discriminant validity in a large sample of patients treated with neurotoxic chemotherapies with varying CIPN severities. These findings suggest that such tools may be useful in clinical practice and may facilitate identification of patients with severe

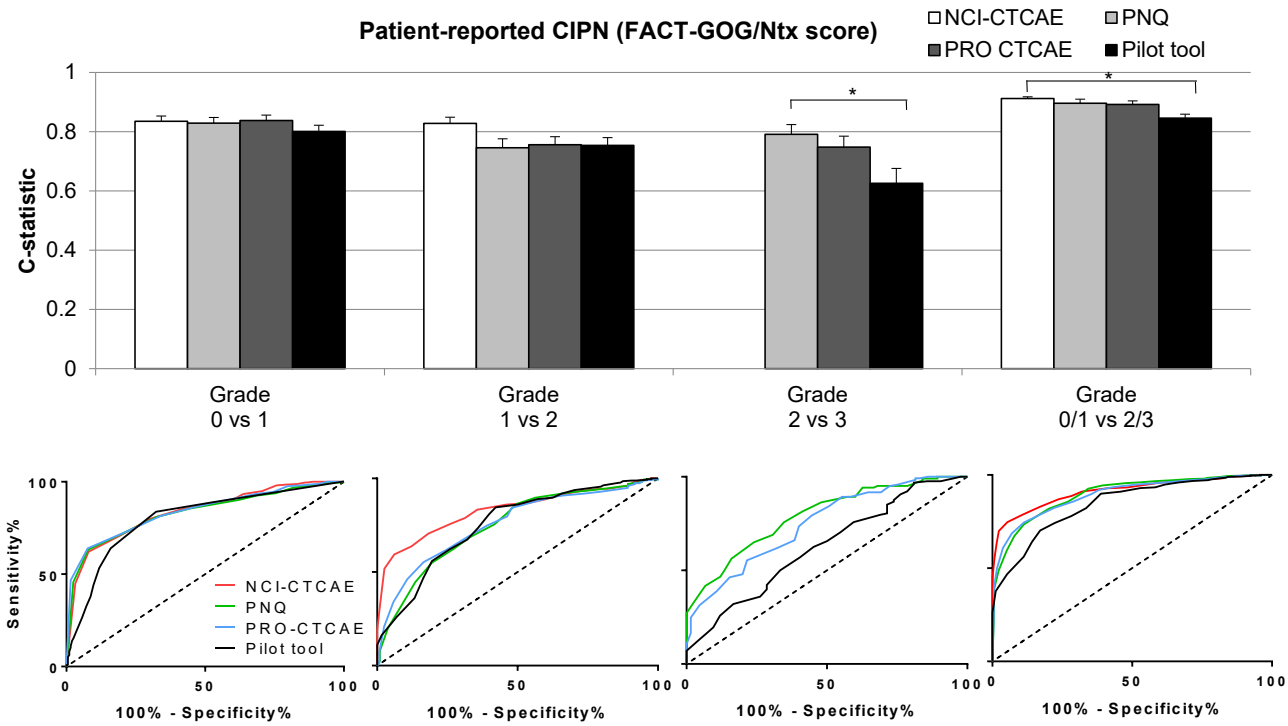

Fig. 3. Discriminant properties of clinical screening tools with respect to patient-reported CIPN. Bars display c-statistics representing the area under the respective ROC curves displayed adjacently below. The c-statistic represents the probability that greater patient-reported symptom burden (higher FACT-GOG/Ntx score) will correspond to a higher screening tool grade for a randomly selected patient. Error bars represent standard error of the c-statistic. *$P < 0.007$ (Critical α following Bonferroni-Holm correction = 0.008). NCI-CTCAE Grade 3 symptoms were not analyzed because of low $N = 16$. ROC = receiver operating characteristic; CIPN = chemotherapy-induced peripheral neuropathy; NCI-CTCAE = the National Cancer Institute Common Terminology Criteria for Adverse Events; PNQ = Patient Neurotoxicity Questionnaire; PRO-CTCAE = patient-reported outcome Common Terminology Criteria for Adverse Events; FACT-GOG/Ntx = Functional Assessment of Cancer Therapy-Gynecologic Oncology Group/Neurotoxicity questionnaire.

neuropathy that warrant further investigation. However, it is important to note that, although clinically significant neuropathy identified by screening tools (Grade ≥2) had a 77%–91% probability of corresponding to greater clinician-rated or patient-reported CIPN symptom burden, conversely up to 23% of patients would be misidentified through screening, providing quantitative evidence of the limitations of available screening tools.

There were no major differences between screening tools—NCI-CTCAE, PNQ, and PRO-CTCAE scales all displayed similar concurrent validity and discriminant properties. However, critically, in this study, NCI-CTCAE grades were assigned by trained specialist CIPN researchers. Compared with patient-reported screening tools, the NCI-CTCAE introduces an additional source of potential bias and inaccuracy given the previously demonstrated impact of training on interrater reliability.[10] Accordingly, single-item patient-reported screening tools (PNQ and PRO-CTCAE) may have broader utility in the clinical setting. NCI-CTCAE, PNQ, and PRO-CTCAE were unsurprisingly generally more discriminant with respect to patient-reported vs. clinical CIPN symptom burden—all three tools are based on evaluations of CIPN symptom severity more comprehensively represented by patient-reported outcome questionnaires.[23] Abnormalities in TNSr items such as pinprick, tendon reflex, vibration, and nerve conduction studies represent increased peripheral nerve dysfunction[12] but may not necessarily be reflected in increased patient-reported symptom burden.[23] Addition of objective vibration perception assessments to a single-item patient-reported screening tool (PNQ) did not add value, with the pilot tool displaying similar or lesser validity and discriminant properties.

Generally, the validity and discriminant properties of the screening tools NCI-CTCAE, PRO-CTCAE, and PNQ were similar to those of prior studies. Concurrent validity of PRO-CTCAE and PNQ compared with longer PROs (FACT-GOG/Ntx or European Organisation for Research and Treatment of Cancer CIPN-20) was consistent with previous research (previous range: $0.45 \leq rho \leq 0.76$;[21,44,45] present study $\rho = 0.74–0.75$). Validity of the NCI-CTCAE compared with clinical neurological assessment (TNSr present

study: ρ = .55) was similar to that of prior studies which also implemented training protocols for NCI-CTCAE grading (previous range: 0.47 ≤ *rho* ≤ 0.74[23,24,46]). Analysis of concurrent validity of the PNQ and PRO-CTCAE with respect to clinician-rated symptom burden (TNSr) has not been previously reported and was found to be similar (ρ = 0.56−0.58). Comparison of the discriminant validity of CIPN screening tools to that of brief objective screening tools for diabetic neuropathy yielded similar to slightly better discrimination for CIPN screening (c-statistics−diabetic neuropathy = 0.70−0.73; present study = 0.77−0.91).[47] A previous study examined the PRO-CTCAE and 0−10 Neuropathy Screening Question in 25 patients with breast cancer, demonstrating that the one-item screening question had a strong concurrent validity compared with the extensively validated EORTRC CIPN-20 questionnaire.[45]

In day-to-day clinical practice, there are significant practical and time limitations of consults which limit the scope of toxicity screenings. To improve feasibility for routine use, CIPN screening tools should contain ≤3 items,[20] creating defined parameters for screening tools to deliver maximum value in the clinic. The screening tools in the present study are brief and feasible, lending potential utility in identifying patients requiring further, more detailed assessment. Referrals to a neurologist for more extensive evaluations of neurophysiologic damage and functional limitations in patients with significant symptoms remain critical to ensure accurate appraisal of CIPN. Given the survival implications of treatment modifications,[15−18] more extensive CIPN evaluations will enable clinicians to make more informed decisions regarding survival benefits vs. neurotoxicity. In survivorship, enhanced CIPN evaluations will enable patients and clinicians to determine the most appropriate treatment strategies from limited pharmacological and rehabilitative options.[48,49] Short feasible tools to triage and enrich the pool of patients going through resource-intensive studies are key to maximizing the benefit of these evaluations.

This study and CIPN screening tools more generally are ultimately, however, limited by the absence of a consensus gold standard CIPN assessment.[2,20] Although assessments of both patient-reported and clinician-rated CIPN symptom burden have been determined to address complementary domains,[23] the relative importance of these domains remains unclear, complicating interpretation of patient-reported and clinician-rated CIPN outcomes. Relatedly, the identification of cutoffs to define clinically significant neuropathy has yet to be achieved. Further research is needed to enhance CIPN assessment strategies toward a consensus gold standard assessment and definition of clinically significant CIPN to strengthen screening and assessment tools for clinical and research applications.

In conclusion, the present study provides evidence for the validity of PROs as screening tools in a large sample with varying severities of CIPN and multiple chemotherapy types. Although we did not demonstrate any major differences in relative validity or discriminant properties between clinical screening tools, the addition of a brief objective assessment to a screening tool was not found to add any additional utility or validity. It is promising that short-form PRO-based tools provide adequate CIPN screening in relation to more comprehensive assessments while avoiding potential operator biases associated with clinical screening tools. The present study suggests that brief patient-reported screening tools may be useful to ensure busy oncology clinicians incorporate the assessment of neurological toxicity in routine oncology practice, while highlighting the importance of identifying patients at risk of serious toxicity for more extensive CIPN assessments to make informed clinical decisions.

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