Predictors of the development of nab-paclitaxel-induced peripheral neuropathy in breast cancer patients: Sub-analysis of a prospective, self-controlled trial

YUKO KANBAYASHI (ykokanba@koto.kpu-m.ac.jp)
Tohoku Ika Yakka Daigaku https://orcid.org/0000-0002-4680-5133

Koichi Sakaguchi
Kyoto Prefectural University of Medicine: Kyoto Furitsu Ika Daigaku

Takeshi Ishikawa
Kyoto Prefectural University of Medicine: Kyoto Furitsu Ika Daigaku

Yoshimi Ouchi
Kyoto Prefectural University of Medicine: Kyoto Furitsu Ika Daigaku

Katsuhiko Nakatsukasa
Kyoto Prefectural University of Medicine: Kyoto Furitsu Ika Daigaku

Yusuke Tabuchi
Kyoto Prefectural University of Medicine: Kyoto Furitsu Ika Daigaku

Fuminao Kanehisa
Kyoto Prefectural University of Medicine: Kyoto Furitsu Ika Daigaku

Ryo Takagi
Hokudai: Hokkaido Daigaku

Isao Yokota
Hokudai: Hokkaido Daigaku

Norito Katoh
Kyoto Prefectural University of Medicine: Kyoto Furitsu Ika Daigaku

Koichi Takayama
Kyoto Prefectural University of Medicine: Kyoto Furitsu Ika Daigaku

Tetsuya Taguchi
Kyoto Prefectural University of Medicine: Kyoto Furitsu Ika Daigaku

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Abstract

Purpose

In a previous study, we showed that cryotherapy and compression therapy have comparable efficacy in preventing nab-paclitaxel-induced peripheral neuropathy. However, even with cryotherapy or compression therapy, there were patients with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade ≧ 2 and/or Patient Neurotoxicity Questionnaire (PNQ) grade ≧ D peripheral neuropathies. Therefore, a sub-analysis was performed to identify predictors of nab-paclitaxel-induced peripheral neuropathy.

Methods

The clinical data in this sub-analysis were the data of 38 breast cancer patients receiving chemotherapy with nanoparticle albumin-bound paclitaxel (nab-PTX) at our outpatient chemotherapy center from August 2017 to March 2019. The number of patients was analyzed assuming that there were data for 76 hands. Variables related to the development of nab-PTX-induced peripheral neuropathy were used for regression analysis. Multivariate ordered logistic regression analysis was performed to identify predictors for the development of nab-PTX-induced peripheral neuropathy.

Results

Significant factors included smoking history [odds ratio (OR) = 4.64, 95% confidence interval (CI) = 1.60–13.5; *P* = 0.0048] with neuropathy evaluated by CTCAE, body mass index (BMI) (OR = 1.13, 95% CI = 1.01–1.26; *P* = 0.039) with neuropathy evaluated by PNQ (sensory), and smoking history (OR = 3.80, 95% CI = 1.40–10.30; *P* = 0.0087) and age (OR = 1.06, 95% CI = 1.01–1.11; *P* = 0.012) with neuropathy evaluated by PNQ (motor).

Conclusions

Smoking history, BMI and age were identified as significant predictors of the development of nab-PTX-induced-peripheral neuropathy.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) can become a major drug-induced adverse reaction that becomes a dose-limiting toxicity of chemotherapy [1–5]. In recent years, the efficacy of cryotherapy using frozen gloves (FGs) and compression therapy using surgical gloves (SGs) to prevent taxane-induced peripheral neuropathy has been reported [6–8]. However, no reports appear to have compared the efficacy of cryotherapy and compression therapy. We therefore planned the present prospective, self-

controlled trial to compare the efficacy of cryotherapy using FGs and compression therapy using SGs to prevent nanoparticle albumin-bound paclitaxel (nab-PTX) -induced peripheral neuropathy [9]. It was found that cryotherapy and compression therapy showed comparable efficacy in preventing CIPN. However, even with cryotherapy or compression therapy, there were patients with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grade ≥ 2 (18.4%) and/or Patient Neurotoxicity Questionnaire (PNQ) grade ≥ D peripheral neuropathies [9]. Therefore, a sub-analysis to identify predictors of nab-PTX-induced peripheral neuropathy was performed.

2. Patients And Methods

2.1. Study design and participants

This was a sub-analysis of a prospective, phase II, self-controlled clinical trial conducted between August 2017 and March 2019 (registered with the University Hospital Medical Information Network in December 2017: UMIN000030536). (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000034856). This trial was approved by the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine, in accordance with the tenets of the Declaration of Helsinki (approval no. ERB-C-906-1) and was registered with the University Hospital Medical Information Network in December 2017 (UMIN000030536). Written, informed consent was obtained from all patients prior to their enrollment. Exclusion criteria were as follows: peripheral sensory/motor neuropathy (CTCAE grade ≥ 2), underlying diseases that could potentially cause peripheral neuropathy (such as diabetes mellitus or postherpetic neuralgia), allergy to the material of FGs (polyurethane and nylon) or the material of SGs (latex), brain metastases, or any other reasons based on the judgment of the primary physician.

Breast cancer patients who received 260 mg/m^2 of nab-PTX as 30-min intravenous infusion every 3 weeks for four cycles were eligible to participate in this trial. Human epidermal growth factor receptor 2 (HER2)-positive patients received trastuzumab after administration of nab-PTX during each cycle. Patients wore an FG on one hand and two SGs of the same size (i.e., one size smaller than the size that best fit their hand) on the other hand during chemotherapy. The hand wearing each glove was randomly assigned, using “dominant hand” as the allocation factor.

2.2. Evaluation of Peripheral Neuropathy

Peripheral neuropathy was evaluated by treating pharmacists and/or nurses using NCI-CTCAE version 4.0 at the following times: pretreatment (baseline); just before each treatment cycle; and six weeks after chemotherapy completion (± 2 weeks). Peripheral neuropathy was also evaluated using the Japanese version of the PNQ, a validated patient-reported questionnaire on neuropathy and activities of daily living that correlates with quality of life [10]. The PNQ comprises two items (sensory and motor neuropathy). The subjective responses to each item are graded from A to E by the patient. Each item of the PNQ was defined as A (no neuropathy), B (mild neuropathy), C (moderate neuropathy that does not interfere with activities of daily living (ADL), D (moderate neuropathy that interferes with ADL), or E (severe neuropathy that interferes with ADL). In this trial, PNQ grades were coded as 1–5, with higher scores indicating more

severe peripheral neuropathy. In this analysis, the values of CTCAE (sensory and motor grades) and PNQ (sensory and motor grades) at the final evaluation were used as the objective variables. As for CTCAE, the same result was obtained for sensory and motor grades, so in the present study, the objective variables that were analyzed were CTCAE, PNQ (sensory), and PNQ (motor).

2.3. Evaluation of Fingertip Temperatures

To investigate mechanisms underlying protection against peripheral neuropathy, the temperature at each fingertip was measured by thermography at the first cycle of nab-PTX. Temperatures at each fingertip on both hands were measured before wearing gloves and 30 min after the end of nab-PTX infusion using a thermographic camera (INFRA-EYE 2000; Fujitsu, Tokyo, Japan).

2.4. Explanatory variables

The following patient data were collected and analyzed to identify the risk factors for CIPN. Variables evaluated included factors that could potentially impact the development of CIPN: demographic data [age, height, weight, and body mass index (BMI)], Eastern Cooperative Oncology Group performance status, smoking history, presence of comorbidity (diabetes mellitus), breast cancer-affected side = dominant hand, breast cancer-affected side = wearing gloves, combination therapy with trastuzumab, surgical glove size, average fingertip temperature after administration, and average difference in fingertip temperature before and after administration. The clinical information before the first dose of nab-PTX was used.

2.5. Statistical Analysis

The analysis was performed assuming that each hand was independent. Since there is a possibility of a correlation between two hands of the same individual, a univariate analysis was performed by adding the patient identification (ID) number to the explanatory variable.

Explanatory variables were examined for multicollinearity (correlation coefficient $|r| \geq 0.7$), since when correlations exist among the variables, this can lead to incorrect results of regression analyses. Explanatory variables were selected based on correlation strength with the level of the CIPN (objective variable) or clinical significance. First, univariate ordered logistic regression analysis between the outcomes and each potential explanatory variable was performed. Subsequently, a multivariate ordered logistic regression model was constructed using the stepwise backward selection procedure with the potential candidate variables. Ordered logistic regression analysis was performed, because the level of CIPN was evaluated by a graded scale, and multiple factors potentially involved as predictors for the development of CIPN had to be evaluated simultaneously.

For all statistical analyses, values of $P < 0.05$ (2-tailed) were considered significant. All analyses were performed using JMP version 14.3.0. (SAS Institute, Cary, NC, USA).

3. Results

Between August 2017 and March 2019, a total of 43 patients with breast cancer were enrolled, of whom 38 were evaluated in this trial [9]. Table 1 presents the clinical characteristics for a total of 76 hands (38 patients), the potential variables related to the development of CIPN, and the results of univariate analysis. Although surgical glove size and average difference in fingertip temperature before and after administration were significant predictors on univariate analysis, they were not used for multivariate analysis due to missing data. Multicollinearity was observed in body weight and BMI. BMI, which was considered the most clinically relevant risk factor for CIPN, was used in the analysis. The backward stepwise selection procedure identified two variables (smoking history, the dominant hand is the breast cancer-affected side) with neuropathy evaluated by CTCAE, two variables (smoking history and BMI) with neuropathy evaluated by PNQ (sensory) and two variables (smoking history and age) with neuropathy evaluated by PNQ (motor).

These variables were then entered into the multivariate ordered logistic regression analysis. Significant factors identified for the development of CIPN included smoking history [odds ratio (OR) = 4.64, 95% confidence interval (CI) = 1.60-13.5; *P* = 0.0048] with neuropathy evaluated by CTCAE, BMI (OR = 1.13, 95% CI = 1.01-1.26; *P* = 0.039) with neuropathy evaluated by PNQ (sensory), and smoking history (OR = 3.80, 95% CI = 1.40-10.30; *P* = 0.0087) and age (OR = 1.06, 95% CI = 1.01-1.11; *P* = 0.012) with neuropathy evaluated by PNQ (motor) (Table 2).

4. Discussion

The multivariate ordered logistic regression analysis performed in the present study showed that the significant predictors for the development of nab-PTX-induced peripheral neuropathy included smoking history with neuropathy evaluated by CTCAE, BMI with neuropathy evaluated by PNQ (sensory), and smoking history and advanced age with neuropathy evaluated by PNQ (motor). “Patients in which the dominant hand was the breast cancer-affected side” tended to develop CIPN evaluated by CTCAE. Surgical glove size and average difference in fingertip temperature before and after administration were also predictors on univariate analysis.

Several studies have reported that smoking was the risk factor for CIPN development [11–14]. The result of the current study is consistent with this previous finding. Thus, clinicians need to know that the incidence and severity of CIPN are higher in patients with a smoking history.

Greenlee et al. in their prospective, observational, cohort study showed that obesity was associated with CIPN in breast cancer patients who received taxane treatment [15]. In this study, BMI was a risk factor for CIPN development. The result of the current study is consistent with this previous finding [15–18]. Clinicians need to pay particular attention to the development of CIPN in obese patients.

Furthermore, the present study also found that advanced age is a risk factor for CIPN [13, 19]. This result is consistent with previous studies. Therefore, clinicians also should be aware that the risk of CIPN increases with age.

In addition, the current study, “wear on the breast cancer-affected side or dominant side hand” was not a risk factor, but patients whose dominant hand was the breast cancer-affected side tended to develop CIPN evaluated by CTCAE, though it was not significant. That is, the risk of developing CIPN was not related to the type of hand (breast cancer-affected side or dominant side) wearing the glove, but CIPN was likely to occur in patients whose dominant side was the breast cancer-affected side. Therefore, clinicians should be aware that, in breast cancer patients, the risk of developing CIPN is higher in patients whose dominant side is the breast cancer-affected side. It was suggested that excessive use of the breast cancer-affected side hand (dominant hand) in daily life may be a risk factor for the development of CIPN. Further verification of this is needed.

Surgical glove size (small) and average difference (large) in fingertip temperature before and after administration were also predictors on univariate analysis. In other words, it was suggested that CIPN could be prevented if the glove pressure is strong, or the cooling temperature is low. This is consistent with the results of previous studies [6–8].

There were several limitations to the current study. First, both hands of the same patient were considered to be independent. Second, since this study was conducted at a single institute, it only analyzed a relatively small number of patients. Therefore, a prospective, multicenter study will be needed to confirm these results.

In conclusion, smoking history, BMI, and advanced age were identified as significant predictors of the development of CIPN in cancer patients treated with nab-PTX. CIPN may develop more easily in patients whose dominant hand is on the breast cancer-affected side. However, these preliminary findings will need to be confirmed in a larger randomized, controlled trial. Nevertheless, these findings may assist in developing chemotherapeutic strategies, including of taxane chemotherapy, with better safety and efficacy, and to improve the quality of life of patients.

Declarations

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Author contributions

Y.K. concept and design, data acquisition, data analysis, data interpretation, manuscript writing; K.S. and T.I. concept and design, data acquisition, data interpretation; Y.O., K.N., Y.T., and F.K. data acquisition, data interpretation; R.T.and I.Y, concept and design, data analysis; N.K. and K.T. concept and design; T.T. concept and design, data acquisition, data interpretation, supervision of the manuscript. All authors read and approved the final manuscript.

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Data availability

Data not available due to ethical restrictions.

Code availability

N/A.

Ethics approval

This trial was approved by the Medical Ethics Review Committee of Kyoto Prefectural University of Medicine, in accordance with the tenets of the Declaration of Helsinki (approval no. ERB-C-906-1) and was registered with the University Hospital Medical Information Network in December 2017 (UMIN000030536).

Informed consent

Written, informed consent was obtained from all patients prior to their enrolment.

Consent for publication

Written, consent for publication was obtained from all patients prior to their enrolment.

Conflict of interest statement

Isao Yokota has received a speaker's fee from Chugai Pharmaceutical Co., Ltd. Norito Katoh has been a speaker and investigator for Taiho Pharmaceutical Co., Ltd. Tetsuya Taguchi received a speaker's fee and research funds from Taiho Pharmaceutical and

Chugai Pharmaceutical Co., Ltd. All other authors declare that they have no conflicts of interest concerning this work.

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Tables

Table 1-1. Clinical characteristics, extracted variables, and results of univariate analyses for CTCAE (n = 76)

CTCAE, the National Cancer Institute Common Terminology Criteria for Adverse Events; CI, confidence interval; BMI, body mass index; PS, Performance Status; SD, standard deviation

*$P < 0.05$

Table 1-2. Clinical characteristics, extracted variables, and results of univariate analyses for PNQ (sensory) (n = 76)

PNQ, the Patient Neurotoxicity Questionnaire; CI, confidence interval; BMI, body mass index; PS, Performance Status; SD, standard deviation

*$P<0.05$

Table 1-3. Clinical characteristics, extracted variables, and results of univariate analyses for PNQ (motor) (n = 76)

PNQ, the Patient Neurotoxicity Questionnaire; CI, confidence interval; BMI, body mass index; PS, Performance Status; SD, standard deviation

*$P<0.05$

Table 2-1 Results of multivariate ordered logistic regression analysis for CTCAE (n = 76)

	Grade 0 (n = 16)	Grade 1 (n = 46)	Grade 2 (n = 10)	Grade 3 (n = 4)	*P* value	Odds ratio (95% CI)
Demographic data						
Age (y), median (range)	59 (45-73)	58 (34-76)	61 (40-66)	66 (62-70)	0.29	1.02 (0.98-1.07)
Height (cm), median (range)	157 (154-159)	156 (148-165)	159 (155-162)	157 (151-163)	0.37	1.05 (0.95-1.15)
Weight (kg), median (range)	47.8 (41.7-67.5)	54 (41.7-79.3)	64.6 (47-67)	44.4 (36.8-52)	0.15	1.04 (0.99-1.09)
BMI (kg/m^2), median (range)	19.5 (17.2-27.3)	22.2 (15.7-30.6)	25.5 (17.9-27.7)	17.9 (16.1-19.7)	0.27	1.07 (0.95-1.20)
PS (0/1)	16/0	44/2	10/0	2/2	0.015*	11.17 (1.59-78.20)
Smoking history, n (%)	2 (12.5)	12 (26.1)	4 (40.0)	4 (100.0)	0.004*	4.79 (1.65-13.92)
The dominant hand is the affected side, n (%)	6 (37.5)	26 (56.5)	8 (80.0)	2 (50.0)	0.085	2.27 (0.89-5.78)
Worn on the affected side, n (%)	8 (50.0)	23 (50.0)	5 (50.0)	2 (50.0)	1.00	1 (0.41-2.44)
Worn on the dominant side, n (%)	9 (56.3)	23 (50.0)	5 (50.0)	2 (50.0)	0.738	0.86 (0.35-2.10)
Combination therapy with trastuzumab, n (%)	6 (37.5)	20 (43.5)	4 (40.0)	2 (50.0)	0.62	1.26 (0.51-3.11)
Treatment						

Neo-adjuvant, n (%)	10 (62.5)	30 (65.2)	6 (60.0)	4 (100.0)	0.51	1.38 (0.54-3.54)
Adjuvant, n (%)	8 (50.0)	10 (21.7)	4 (40.0)	0	0.11	0.44 (0.16-1.20)
Palliative, n (%)	0	4 (8.7)	0	0	0.87	1.19 (0.16-8.78)
Surgical glove size, mean±SD	5.69±0.25	5.85±0.38	6.00±0.33	5.75±0.29	0.017*	5.67 (1.37-23.50)
Average fingertip temperature after administration (°C), median (range)	23.9 (15.3-30.6)	28.5 (12.6-32.6)	29.0 (17-31.1)	28.5 (27.6-29.5)	0.095	1.10 (0.98-1.24)
Average difference in fingertip temperature before and after administration (°C), median (range)	8.1 (1.7-16.3)	3.3 (0.2-18.4)	5.3 (2.1-11.8)	5.1 (4.1-6.0)	0.14	0.91 (0.79-1.03)

Variable	*P* value	Odds ratio	95% CI	
			Lower 95%	Upper 95%
Smoking history	0.0048*	4.64	1.60	13.5
The dominant hand is the affected side	0.081	2.29	0.90	5.79

CI, confidence interval

*$P<0.05$

Table 2-2 Results of multivariate ordered logistic regression analysis for PNQ (sensory) (n = 76)

Variable	*P* value	Odds ratio	95%CI	
			Lower 95%	Upper 95%
Smoking history	0.16	1.99	0.76	5.23
BMI	0.039*	1.13	1.01	1.26

CI, confidence interval; BMI, body mass index

	A (n = 16)	B (n = 46)	C, D or E (n = 10)	*P* value	Odds ratio (95%CI)
Demographic data					
Age (y), median (range)	55 (34-73)	60 (34-76)	63.5 (40-70)	0.084	1.04 (0.99-1.08)
Height (cm), median (range)	157.3 (151-165)	155.9 (148-165)	162 (151.1-165)	0.041*	1.12 (1.01-1.22)
Weight (kg), median (range)	50 (41.7-67.5)	50 (41.7-67)	62.5 (36.8-79.3)	0.0038*	1.07 (1.02-1.13)
BMI (kg/m^2), median (range)	19.8 (17.2-27.3)	20.1 (15.7-30.6)	23.6 (16.1-29.1)	0.047*	1.12 (1.01-1.26)
PS (0/1)	16/1	38/1	18/2	0.45	2.09 (0.31-14.26)
Smoking history, n (%)	5 (29.4)	8 (20.5)	9 (45.0)	0.22	1.82 (0.70-4.71)
The dominant hand is the affected side, n (%)	7 (41.2)	21 (53.8)	14 (70)	0.077	2.22 (0.92-5.39)
Worn on the affected side, n (%)	8 (47.1)	20 (51.3)	10 (50.0)	0.87	1.07 (0.46-2.51)
Worn on the dominant side, n (%)	9 (52.9)	20 (51.3)	10 (50.0)	0.86	0.93 (0.39-2.17)
Combination therapy with trastuzumab, n (%)	7 (41.2)	16 (41.0)	9 (45)	0.62	1.26 (0.51-3.11)
Treatment					

Neo-adjuvant, n (%)	11 (64.7)	23 (59.0)	16 (80.0)	0.30	1.62 (0.65-4.01)
Adjuvant, n (%)	6 (35.3)	13 (33.3)	3 (15.0)	0.11	0.44 (0.16-1.20)
Palliative, n (%)	1 (5.9)	2 (5.1)	1 (5.0)	0.87	1.19 (0.16-8.78)
Surgical glove size, mean±SD	5.71±0.31	5.82±0.39	5.95±0.28	0.025*	4.77 (1.22-18.70)
Average fingertip temperature after administration (°C), median (range)	21.0 (15.3-26.9)	29.0 (12.6-32.6)	31.1 (13.3-31.1)	0.082	1.12 (0.99-1.24)
Average difference in fingertip temperature before and after administration (°C), median (range)	11.5 (3.3-16.3)	3.5 (0.9-18.4)	4.1 (0.2-11.8)	0.018*	0.84 (0.73-0.97)

*P<0.05

Table 2-3 Results of multivariate ordered logistic regression analysis for PNQ (motor) (n = 76)

Variable	P value	Odds ratio	95%CI	
			Lower 95%	Upper 95%
Smoking history	0.0087*	3.80	1.40	10.30
Age	0.012*	1.06	1.01	1.11

CI, confidence interval; SBP, Systolic Blood Pressure; RAS, renin-angiotensin system

*P<0.05

Supplementary Files

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	A (n =41)	B (n =26)	C, D or E (n =9)	*P* value	Odds ratio (95%CI)
Demographic data					
Age (y), median (range)	58 (34-69)	61(40-76)	65 (61-70)	0.013*	1.06 (1.01-1.11)
Height (cm), median (range)	157.3 (148-165)	156.8 (148-165)	158.3 (151.1-162.5)	0.96	1.00 (0.91-1.10)
Weight (kg), median (range)	54 (41.7-67.5)	50.5 (41.7-79.3)	64.6 (36.8-67)	0.48	1.02 (0.97-1.06)
BMI (kg/m^2), median (range)	20.1 (15.7-30.6)	21.4 (17.2-29.1)	24.8 (16.1-27.2)	0.62	1.03 (0.92-1.15)
PS (0/1)	39/2	26/0	7/2	0.24	3.10 (0.47-20.47)
Smoking history, n (%)	7 (17.1)	10 (38.5)	5 (55.6)	0.0093*	3.65 (1.38-9.69)
The dominant hand is the affected side, n (%)	21 (51.2)	17 (65.4)	4 (44.4)	0.65	1.22 (0.51-2.96)
Worn on the affected side, n (%)	20 (48.8)	14 (53.8)	4 (44.4)	0.92	1.04 (0.44-2.49)
Worn on the dominant side, n (%)	21(51.2)	13 (50.0)	5 (55.6)	0.92	1.04 (0.44-2.49)
Combination therapy with trastuzumab, n (%)	17 (41.5)	11 (42.3)	4 (44.4)	0.86	1.08 (0.45-2.61)
Treatment					
Neo-adjuvant, n (%)	28	14	8	0.98	1.01

	(68.3)	(53.8)	(88.9)		(0.41-2.54)
Adjuvant, n (%)	10 (24.4)	11 (42.3)	1 (11.1)	0.63	1.27 (0.49-3.30)
Palliative, n (%)	3 (7.3)	1 (3.8)	0	0.38	0.35 (0.034-3.61)
Surgical glove size, mean±SD	5.82±0.40	5.81±0.29	5.94±0.30	0.47	1.63 (0.43-6.17)
Average fingertip temperature after administration (°C), median (range)	26.1 (12.6-32.6)	29.1 (17.0-31.5)	29.5 (13.3-29.5)	1.00	1.00 (0.89-1.12)
Average difference in fingertip temperature before and after administration (°C), median (range)	5.2 (0.2-18.4)	4.7 (1.5-13.5)	5.8 (0.6-9.3)	0.55	0.96 (0.83-1.10)

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