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Serum sodium ions and chloride ions associated with taxane-induced peripheral neuropathy in Chinese patients with early-stage breast cancer: A nation-wide multicenter study

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ABSTRACT

Background: Taxane-induced peripheral neuropathy (TIPN) is a debilitating adverse effect of cancer treatments with taxanes which may require a reduction or discontinuation chemotherapy and affect clinical and survival outcomes. A number of factors have contributed to the increasing prevalence of TIPN. Nonetheless, limited knowledge exists of potential prechemotherapy blood-based biochemical factors associated with TIPN development.

Methods: We recruited breast cancer patients at seven cancer institutions in China. Participants aged 18 years or older with stage I to III breast cancer who scheduled to undergo primary neoadjuvant and adjuvant chemotherapy with taxanes were eligible. Eligible patients underwent patient-reported neuropathy assessments using the EORTC-CIPN20 questionnaire. Patients completed the questionnaire before commencing treatment and after every cycle. For every patient, we selected the highest TIPN toxicity score for analysis since the first cycle. The posttreatment TIPN severity was compared with blood-based biochemical factors within 30 days before commencing treatment. Independent samples t tests, Mann-Whitney U tests and linear regression were used to identify blood-based and clinical associations with TIPN development.

Results: The study included 873 breast cancer participants who received paclitaxel, docetaxel or nanoparticle albumin-bound (nab)-paclitaxel. In the whole cohort, factors associated with higher TIPN toxicity scores were higher cumulative chemotherapy dose ($\beta = 0.005$; 95% CI, 0.004 to 0.006; $P < .001$), lower sodium ions ($\beta = -0.24$; 95% CI, −0.39 to −0.09; $P = .002$) and higher chloride ions ($\beta = 0.30$; 95% CI, 0.16 to 0.44; $P < .001$).

Conclusions: The findings suggest that breast cancer patients with a higher cumulative chemotherapy dose, lower pretreatment sodium ions, and higher pretreatment chloride ions receiving taxanes should receive closer monitoring to mitigate the development of short-term and long-term TIPN.

1. Introduction

Breast cancer is the most commonly diagnosed malignant tumor and the leading cause of cancer-related deaths in women annually [1]. Taxanes, including paclitaxel, docetaxel and nanoparticle albumin-bound (nab)-paclitaxel, have had an increasing role in treating breast cancer and are now used in most patients receiving neoadjuvant, adjuvant and palliative chemotherapy [2].

Taxane-induced peripheral neuropathy (TIPN) is a common and

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challenging complication arising from taxane treatment [3]. TIPN symptoms include sensory, motor and autonomic effects. TIPN alters sensations in the hands and feet, often designated as a "glove and stocking" distribution. TIPN can also present as motor weakness or cranial nerve damage [4,5], which can alter smell, taste, vision, facial sensation and expression, hearing, balance, speech, swallowing, and muscle tone of the neck [6]. TIPN can occur acutely during chemotherapy. If severe, it can require a reduction of the dose of chemotherapy or even discontinuation prior to completing the planned course [7–9], which may affect clinical and survival outcomes.

To reduce the incidence of TIPN [10,11], identifying who is at higher risk of developing TIPN would be an important step forward. A number of factors have contributed to the increasing prevalence of TIPN [12]. Most of the pharmacogenetic studies have attempted to use genetic signatures based on single nucleotide polymorphisms and genome-wide association studies to predict an individual patient's susceptibility to TIPN. And some genes have been found which are associated with TIPN, such as ABCB1, GSK3B, and RRM1, etc [13,14]. Some studies also demonstrate that clinical and demographic factors are independent predictors of the development of TIPN, such as age, body mass index (BMI), and histopathologic type [15,16]. Potential blood-based associations with TIPN include serum micronutrients vitamin E, vitamin D, prealbumin and hemoglobin [17,18]. Other factors may present a risk for developing TIPN, including the presence of metabolic conditions (i.e., type 2 diabetes [16], obesity [19]) and older age [16]. Although the above factors may be related to TIPN, there are no clinically applicable predictors.

Treatment with chemotherapeutic drugs enhances excitability and reduces thresholds in peripheral nociceptors [20,21]. These electrophysiological changes in neuronal activity are associated with intracellular and extracellular ion concentrations, indicating the involvement of ion channels, including sodium, potassium, chloride and calcium ion channels [22,23].

In clinical practice, blood electrolytes are monitored by detecting blood biochemistry, including sodium ions (Na^+), potassium ions (K^+), chloride ions (Cl^-), calcium ions (Ca^{2+}), magnesium ions (Mg^{2+}) and other analytes. There are some studies regarding ion channels associated with TIPN. Drugs targeting Na^+ channels, such as lidocaine and mexiletine demonstrated transient *anti*-allodynic effects and persistent analgesic effects in patients with TIPN [24,25]. However, there remains a lack of convincing evidence supporting its efficacy. $Ca^{2+}$and Mg^{2+} infusion is assumed to be one of the most promising strategies used for TIPN prevention. In some studies involving colorectal cancer patients, the administration of a Ca^{2+} and Mg^{2+} infusion to reduce oxaliplatin-induced neurotoxicity demonstrated inconsistent conclusions with positive [26–29] or negative results [30,31].

For this study, we enrolled patients with breast cancer treated with three kinds of taxanes, paclitaxel, docetaxel and nab-paclitaxel. We aimed to investigate the association of pretreatment blood-based biochemical factors with patient-reported TIPN severity, evaluated using the EORTC-CIPN20 questionnaire.

Abbreviations

TIPN	taxane-induced peripheral neuropathy
nab-paclitaxel	nanoparticle albumin-bound-paclitaxel
BMI	body mass index
BSA	body surface area
SD	standard deviation
K^+	potassium ions
Na^+	sodium ions
Cl^-	chloride ions
GLU	glucose
TBIL:	total bilirubin
CRE	creatinine;
Ca^{2+}	calcium ions
Mg^{2+}	magnesium ions
CHOL:	cholesterol
TG	triglyceride;
HDL-CHO	high-density lipoprotein cholesterol
LDL-CHO	low-density lipoprotein cholesterol
ALB	albumin
IQR	interquartile ranges
HER2	human epidermal growth factor receptor
NKCC1	Na^+-K^+-2 C l^- cotransporter 1
KCC2	K^+- Cl^- cotransporter 2

2. Materials and methods

2.1. Participants

Participants aged 18 years or older with stage I to III breast cancer who scheduled to undergo primary neoadjuvant and adjuvant chemotherapy with taxanes were eligible from seven hospitals in China between December 2019 and December 2021. Patients were excluded if they had preexisting risk factors for neuropathy, such as diabetes mellitus, thyroid disease, treatment history with other potentially neurotoxic medication, alcohol, or a family history of neuropathy. We also excluded patients who could not give informed consent for any reason. The study was approved by the ethics committee of the National Cancer Center, and written informed consent was obtained from each participant (19/327–2111). For this study, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

2.2. Patient-reported TIPN toxicity scores

The EORTC-CIPN20 was administered to patients before commencing treatment and after every cycle until they completed the whole treatment. For every patient, we selected the highest TIPN toxicity score since the first cycle for analysis. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-TIPN 20-item scale (EORTC-CIPN20) is a patient-reported outcome measure [32], and its validity for TIPN has been demonstrated by several studies [8,33,34]. The EORTC-CIPN20 is a 20-item self-report questionnaire with three subscales containing 9 items for sensory symptoms, 8 for motor symptoms, and 3 for autonomic symptoms. Each item is scored from 1 (not at all) to 4 (very much), combining for a total score ranging from 20 (no symptoms) to 80 (severe symptoms), with higher scores indicating worse symptoms.

2.3. Clinical and blood-based risk factors

Clinical information (i.e., age, BMI [calculated as weight in kilograms divided by height in meters squared], body surface area (BSA) prior to commencing treatment, cumulative chemotherapy dose) was retrieved from medical records. The relative dose intensity was calculated by dividing the total cumulative chemotherapy dose administered by the total dose planned as a percentage. Blood-based results were retrospectively collected from the medical records. The blood test corresponding to the closest date within 30 days before commencing

treatment was selected for analysis. The laboratories in the seven cancer institutions used the same testing instruments and techniques to ensure the uniformity and stability of lab results of patients' baseline blood electrolyte level. We defined blood-based outliers using the mean plus or minus standard deviation (mean ± SD) of the blood biochemistry indexes. The mean and SD were calculated according to the results of patients' blood biochemical test. According to the mean and SD of these blood biochemistry indexes showed in Table 1, the reference ranges included potassium ions (K^+, 3.93–4.59 mmol/L), sodium ions (Na^+, 138.5–142.7 mmol/L), chloride ions (Cl^-, 102.1–106.9 mmol/L), glucose (GLU, 4.49–6.61 mmol/L), total bilirubin (TBIL,≤ 14.7 μmol/L), creatinine (CRE, 45.7–64.7 μmol/L), calcium ions (Ca^{2+}, 2.25–2.45 mmol/L), magnesium ions (Mg^{2+}, 0.80–0.94 mmol/L), cholesterol (CHOL, 4.10–6.16 mmol/L), triglyceride (TG,≤ 2.51 mmol/L), high-density lipoprotein cholesterol (HDL-CHO, 1.07–1.71 mmol/L), low-density lipoprotein cholesterol (LDL-CHO, 2.47–4.09 mmol/L), albumin (ALB, 39.1–46.7 g/L).

2.4. Statistical analysis

All analyses were conducted using SPSS Statistics Software version 24 (IBM). Descriptive data are presented as the means with standard deviations (SDs) or medians with interquartile ranges (IQRs). Independent samples t tests for normally distributed data and Mann-Whitney U tests for nonnormally distributed data were used to compare clinical, blood-based and TIPN outcomes for the whole cohort and every chemotherapy type. Linear regression was used to identify blood-based and clinical (i.e., age, BMI, BSA, cumulative chemotherapy dose) factors associated with TIPN. TIPN toxicity score was the dependent variable in the univariate and multivariable analyses to assess TIPN on a continuous linear scale, which was normally distributed. Continuous variables associated with TIPN ($P < .10$) in the univariate analysis were included in the multivariable model analysis. We used backward linear regression to eliminate factors not contributing to the final model ($P > .10$). Variables with $P < .05$ in the multivariable model were considered significant. Normality and data variance were checked using *P*–P residual

Table 1
Clinical and demographic characteristics of patients who received taxane chemotherapy.

Characteristics	Participants, No. (%)			
	Whole cohort (n = 873)	Paclitaxel (n = 489)	Docetaxel (n = 282)	Nab-paclitaxel (n = 102)
Grade				
1	23 (2.6)	11 (2.2)	11 (3.9)	1 (1.0)
2	406 (46.5)	228 (46.6)	145 (51.4)	33 (32.4)
3	333 (38.1)	190 (38.9)	98 (34.8)	45 (44.1)
Undefined	111 (12.8)	60 (12.3)	28 (9.9)	23 (22.5)
Molecular subtype				
Luminal A	79 (9.0)	40 (8.2)	35 (12.4)	4 (3.9)
Luminal B1 (HER2-negative)	333 (38.1)	201 (41.1)	98 (34.8)	34 (33.3)
Luminal B2 (HER2-positive)	159 (18.2)	70 (14.3)	77 (27.3)	12 (11.8)
HER2-positive	134 (15.4)	64 (13.1)	56 (19.9)	14 (13.7)
Triple-negative	168 (19.3)	114 (23.3)	16 (5.6)	38 (37.3)
Indication of treatment				
Neoadjuvant	157 (18.0)	90 (18.4)	37 (13.1)	30 (29.4)
Adjuvant	716 (82.0)	399 (81.6)	245 (86.9)	72 (70.6)
Age, median (IQR), y	50 (42–58)	50 (42–58)	50 (44–58)	50 (40–58)
Days since treatment, median (IQR)	42 (21–65)	40 (21–62)	46 (23–69)	53 (22–84)
Cumulative chemotherapy dose, median (IQR), mg/m^2	281.6 (163.4–489.1)	332.9 (171.3–508.8)	150.0 (74.1–225.6)	525.2 (249.9–867.4)
Relative dose intensity, median (IQR), %	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)	100.0 (100.0–100.0)
Body surface area, mean (SD), m^2	1.68 (0.13)	1.68 (0.13)	1.68 (0.14)	1.68 (0.13)
Body mass index, mean (SD)[a]	23.9 (3.5)	23.9 (3.4)	23.8 (3.6)	24.4 (3.2)
Blood-based biochemical factor				
Potassium ions, mean (SD), mmol/L	4.26 (0.33)	4.25 (0.34)	4.26 (0.30)	4.32 (0.31)
Sodium ions, mean (SD), mmol/L	140.6 (2.1)	140.7 (2.3)	140.3 (1.9)	140.4 (2.2)
Chloride ions, mean (SD), mmol/L	104.5 (2.4)	104.4 (2.4)	104.5 (2.3)	104.7 (2.2)
Glucose, mean (SD), mmol/L	5.55 (1.06)	5.59 (0.93)	5.34 (0.93)	5.90 (1.80)
Total bilirubin, mean (SD), umol/L	10.2 (4.5)	9.9 (4.7)	10.7 (4.0)	10.7 (4.3)
Creatinine, mean (SD), umol/L	55.2 (9.5)	55.1 (9.2)	55.4 (9.4)	53.9 (9.5)
Calcium ions, mean (SD), mmol/L	2.35 (0.10)	2.35 (0.10)	2.34 (0.11)	2.36 (0.11)
Magnesium ions, mean (SD), mmol/L	0.87 (0.07)	0.87 (0.06)	0.87 (0.06)	0.86 (0.09)
Cholesterol, mean (SD), mmol/L	5.13 (1.03)	5.05 (0.97)	5.22 (1.08)	5.25 (1.07)
Triglyceride, mean (SD), mmol/L	1.56 (0.95)	1.58 (0.99)	1.47 (0.92)	1.64 (0.75)
High-density lipoprotein cholesterol, mean (SD), mmol/L	1.39 (0.32)	1.38 (0.32)	1.43 (0.32)	1.37 (0.30)
Low-density lipoprotein cholesterol, mean (SD), mmol/L	3.28 (0.81)	3.21 (0.78)	3.36 (0.86)	3.37 (0.81)
Albumin, mean (SD), g/L	42.9 (3.8)	43.2 (3.5)	42.5 (3.8)	42.5 (4.8)
Blood parameters outside normal range				
Low potassium ions	123 (14.1)	73 (14.9)	38 (13.5)	12 (11.8)
Low sodium ions	116 (13.3)	57 (11.7)	43 (15.2)	16 (15.7)
High chloride ions	118 (13.5)	63 (12.9)	39 (13.8)	16 (15.7)
High glucose	127 (14.5)	83 (17.0)	21 (7.4)	23 (22.5)
High total bilirubin	66 (7.6)	35 (7.2)	24 (8.5)	7 (6.9)
High creatinine	119 (13.6)	68 (13.9)	43 (15.2)	8 (7.8)
Low calcium ions	112 (12.8)	62 (12.7)	34 (12.1)	16 (15.7)
High magnesium ions	87 (10.0)	54 (11.0)	23 (8.2)	10 (9.8)
High cholesterol	226 (25.9)	120 (24.5)	75 (26.6)	31 (30.4)
High triglyceride	253 (29.0)	141 (28.8)	71 (25.2)	41 (40.2)
Low high-density lipoprotein cholesterol	118 (13.5)	70 (14.3)	38 (13.5)	10 (9.8)
High low-density lipoprotein cholesterol	135 (15.5)	65 (13.3)	49 (17.4)	21 (20.6)
Low albumin	120 (13.7)	52 (10.6)	47 (16.7)	21 (20.6)

Abbreviations: IQR, interquartile range; HER2, human epidermal growth factor receptor.
[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

plots. We defined blood-based outliers using the median ± standard deviation.

3. Results

3.1. Baseline demographic characteristics and clinical history

Patient characteristics are summarized in Table 1. A total of 873 participants were included in the study. Among the 873 participants, the median (IQR) age was 50 (42–58; range, 24–79). The median (IQR) treatment duration was 42 (21–65) days. Overall, 489 (56.0%) patients received paclitaxel, 282 (32.3%) patients received docetaxel, and 102 (11.7%) patients received nab-paclitaxel. A total of 157 (18.0%) patients received neoadjuvant chemotherapy, and 716 (82.0%) patients received adjuvant chemotherapy. Seventy-nine (9.0%) patients were luminal A, 338 (38.1%) patients were luminal B1 (HER2-negative), 159 (18.2%) patients were luminal B2 (HER2-positive), 134 (15.4%) patients were HER2-positive, and 168 (19.3%) patients were triple-negative (Table 1). Patients reveived the following 5 primary regimens: anthracycline and cyclophosphamide plus taxanes with (without) anti-HER2 (AC-T (H); 292 (33.4%) patients); taxanes, carboplatin, with (without) anti-HER2 ((TCb (H); 272 (31.2%) patients); taxanes, cyclophosphamide with (without) anti-HER2 ((TC (H); 216 (24.7%) patients); anthracycline, taxanes with (without) anti-HER2 (AT (H); 57 (6.5%) patients) and other taxane-based regimens (36 patients (4.2%)) (Supplementary Table S1). The chemotherapy regimens were selected by clinicians who were treating the patients and represent commonly used regimens recommended for the (neo)adjuvant treatment of early breast cancer [35–37].

3.2. Patient-reported TIPN toxicity scores

Patient-reported TIPN toxicity scores are presented in Table 2. A total of 779 (89.2%) patients reported neuropathy symptoms. The mean (SD) total score was 24.8 (4.8) for the whole cohort, 24.4 (4.4) for the paclitaxel group, 24.8 (4.9) for the docetaxel group and 27.0 (5.9) for the nab-paclitaxel group (Table 2). As the mean TIPN toxicity score was 24.8 for the whole cohort. And the scores were integral numbers. Therefore, the cutoff value of TIPN score was defined as 25. Differences in clinical characteristics between those with a TIPN toxicity score of <25 and ≥ 25 were analyzed. There were significant differences in cumulative chemotherapy dose between the two groups. However, no differences were found between other clinical characteristics, such as pathological grade, molecular subtype and chemotherapy regimen (Supplementary Table S2).

3.3. Blood-based parameters outside normative ranges

The median (IQR) time between the closest date of blood test before chemotherapy and the date to undergo the first cycle of treatment was 4 (2–8) days. Before commencing chemotherapy, some participants demonstrated blood parameters outside normative ranges, including 123 (14.1%) participants with low K^+, 116 (13.3%) participants with low Na^+, 118 (13.5%) participants with high Cl^-, 112 (12.8%) participants with low Ca^{2+}, and 87 (10.0%) participants with high Mg^{2+} (Table 1). In the whole cohort, compared with patients with Cl^- levels within the reference range, those with high pretreatment Cl^- demonstrated higher TIPN toxicity scores (mean [SD], 25.6 [6.0] vs. 24.6 [4.6]; P = .015) and higher motor toxicity scores (mean [SD], 9.2 [2.2] vs. 8.9 [1.9]; P = .016) (Table 3). Patients with low pretreatment Na^+ demonstrated higher TIPN toxicity scores (mean [SD], 25.3 [5.8] vs. 24.7 [4.6]; P = .013) and higher motor toxicity scores (mean [SD], 9.0 [2.3] vs. 8.9 [1.9]; P = .006) (Table 3). In the paclitaxel-treated group, patients with high pretreatment Cl^- demonstrated higher TIPN toxicity scores (mean [SD], 25.2 [4.3] vs. 24.2 [4.3]; P = .016) and higher motor toxicity scores (mean [SD], 9.0 [1.8] vs. 8.8 [1.8]; P = .020) (Table 3). In the docetaxel-treated group, patients with low pretreatment Na^+ demonstrated higher TIPN toxicity scores (mean [SD], 26.1 [7.3] vs. 24.6 [4.3]; P = .001), higher motor toxicity scores (mean [SD], 9.4 [3.0] vs. 9.0 [1.9]; P < .001) and higher autonomic toxicity scores (mean [SD], 4.1 [1.1] vs. 3.8 [0.8]; P = .031) (Table 3). These findings indicated a higher neuropathy burden among the group with abnormal levels of serum electrolytes.

3.4. Factors associated with TIPN using the toxicity score

As for correlation between univariate blood-based and clinical factors and TIPN, we found TIPN toxicity score was positively correlated with cumulative chemotherapy dose (Fig. 1A) and Cl^- (Fig. 1B), but negatively correlated with Na^+ (Fig. 1C). Moreover, TIPN toxicity score showed no relation to K^+, Ca^{2+} and Mg^{2+} (Fig. 1D–F). A multivariable model found a significant association of baseline blood-based and clinical factors with TIPN ($F_{3,869} = 19.7$; P < .001; $r^2 = 0.08$) (Table 4). Factors associated with higher TIPN toxicity scores were higher cumulative chemotherapy dose (β = 0.005; 95% CI, 0.004 to 0.006; P < .001), lower Na^+ (β = −0.24; 95% CI, −0.39 to −0.09; P = .002) and higher Cl^- (β = 0.30; 95% CI, 0.16 to 0.44; P < .001). Sensory toxicity scores were also associated with these factors (Supplementary Table S3). Moreover, higher motor toxicity scores ($F_{3,869} = 12.6$; P < .001; $r^2 = 0.04$) were associated with a higher cumulative chemotherapy dose (β = 0.001; 95% CI, 0.001 to 0.002; P < .001), higher BMI (β = 0.04; 95% CI, 0.004 to 0.08; P = .031) and higher Cl^- (β = 0.08; 95% CI, 0.03 to 0.14; P = .003) (Supplementary Table S3). Higher autonomic toxicity scores ($F_{3,869} = 11.3$; P < .001; $r^2 = 0.05$) were associated with a higher cumulative chemotherapy dose (β = 0.001; 95% CI, 0 to 0.001; P < .001), higher Cl^- (β = 0.04; 95% CI, 0.01 to 0.06; P = .005) and higher glucose (β = 0.08; 95% CI, 0.03 to 0.14; P = .003) (Supplementary Table S3).

3.5. Factors associated with TIPN by chemotherapy type

To determine if these associations were the same for paclitaxel (489 patients), docetaxel (282 patients) and nab-paclitaxel (102 patients) treated cohorts, subgroup analyses were conducted. In the paclitaxel-treated group, the multivariable model found an association with TIPN ($F_{2,486} = 19.2$; P < .001; $r^2 = 0.07$). Factors associated with higher TIPN toxicity scores were higher cumulative chemotherapy dose (β = 0.005; 95% CI, 0.003 to 0.006; P < .001) and higher Cl^- (β = 0.29; 95% CI, 0.13 to 0.45; P < .001) (Table 4 and Fig. 2).

In the docetaxel-treated group, the multivariable model found an association with TIPN ($F_{3,278} = 8.7$; P < .001; $r^2 = 0.08$). Factors associated with higher TIPN toxicity scores were higher cumulative chemotherapy dose (β = 0.010; 95% CI, 0.004 to 0.016; P = 001), higher BMI (β = 0.19; 95% CI, 0.04 to 0.35; P = .015) and lower Na^+ (β = −0.40; 95% CI, −0.69 to −0.10; P = .008) (Table 4 and Fig. 2).

In the nab-paclitaxel-treated group, the multivariable model found an association with TIPN ($F_{1,100} = 15.7$; P < .001; $r^2 = 0.13$). The only

Table 2
Total, sensory, motor and autonomic toxicity scores in patients who received taxane chemotherapy.

Score	Whole cohort (n = 873)		Paclitaxel (n = 489)		Docetaxel (n = 282)		Nab-paclitaxel (n = 102)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total[a]	24.8	4.8	24.4	4.4	24.8	4.9	27.0	5.9
Sensory[a]	12.0	2.8	11.7	2.5	11.9	2.7	13.8	3.5
Motor[a]	9.0	2.0	8.9	1.8	9.0	2.1	9.3	2.4
Autonomic[a]	3.8	0.9	3.8	0.9	3.9	0.9	3.9	0.9

[a] The EORTC-CIPN20 questionnaire is evaluated on a scale from 20 to 80. Sensory subgroup is evaluated on a scale from 9 to 36. Motor subgroup is evaluated on a scale from 8 to 32. Autonomic subgroup is evaluated on a scale from 3 to 24.

Table 3
Comparisons in TIPN development by pretreatment blood-based impairment status among patients treated with taxane.

Score	Whole cohort			Whole cohort			Paclitaxel			Docetaxel		
	High chloride ions			Low sodium ions			High chloride ions			Low sodium ions		
	Yes (n = 118)	No (n = 755)	*P*-value	Yes (n = 116)	No (n = 757)	*P*-value	Yes (n = 63)	No (n = 426)	*P*-value	Yes (n = 43)	No (n = 239)	*P*-value
Total, mean (SD)[b]	25.6 (6.0)	24.6 (4.6)	.015[a]	25.3 (5.8)	24.7 (4.6)	.013[a]	25.2 (4.3)	24.2 (4.3)	.016[a]	26.1 (7.3)	24.6 (4.3)	.001[a]
Sensory, mean (SD)[b]	12.4 (3.3)	11.9 (2.7)	.29	12.4 (3.3)	11.9 (2.7)	.64	12.4 (3.0)	11.6 (2.4)	.33	12.5 (3.9)	11.8 (2.4)	.06
Motor, mean (SD)[b]	9.2 (2.2)	8.9 (1.9)	.016[a]	9.0 (2.3)	8.9 (1.9)	.006[a]	9.0 (1.8)	8.8 (1.8)	.020[a]	9.4 (3.0)	9.0 (1.9)	<.001[a]
Autonomic, mean (SD)[b]	4.0 (1.0)	3.8 (0.8)	.07	3.9 (1.0)	3.8 (0.9)	.47	3.8 (0.9)	3.8 (0.9)	.024[a]	4.1 (1.1)	3.8 (0.8)	.031[a]

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy.
[a] $P \leq .05$.
[b] The EORTC-CIPN20 questionnaire is evaluated on a scale from 20 to 80. Sensory subgroup is evaluated on a scale from 9 to 36. Motor subgroup is evaluated on a scale from 8 to 32. Autonomic subgroup is evaluated on a scale from 3 to 24.

factor associated with higher TIPN toxicity scores was a higher cumulative chemotherapy dose (β = 0.006; 95% CI, 0.003 to 0.009; P < .001) (Table 4 and Fig. 2).

4. Discussion

Our findings are clinically relevant, encouraging consideration of baseline serum levels of plasma ions when prescribing potentially neurotoxic chemotherapy regimens. Irrespective of causation, TIPN results in substantial short-term and long-term morbidity, consistently rated as a key contributor to adverse outcomes in survivors [34]. Identifying patients at risk of short-term and long-term neurotoxicity is critical to developing personalized treatment approaches. Importantly, the risk factors identified in our analysis are routinely available in clinical practice without additional specialized assessments. Prospective validation of these risk factors to examine the benefit of closer neurological surveillance of those with substantial TIPN risk is an important next step. Future examination of intervention for the validated risk factors (i.e., ion level) may be warranted to investigate the impact on TIPN outcomes in cancer survivors.

For this study, we investigated pretreatment blood-based biochemistry and clinical risk factors for developing TIPN following three kinds of taxane treatments, including paclitaxel, docetaxel and nab-paclitaxel. The factors most consistently associated with severe TIPN were higher cumulative chemotherapy dose, lower Na^+ and higher Cl^-. Although no single marker stood out as a strong prognostic factor for TIPN, multiple markers may be prognostic factors for TIPN risk.

We found that lower Na^+ and higher Cl^- were associated with higher TIPN severity among the whole cohort, paclitaxel and docetaxel-treated group. Alterations in neuronal ionic homeostasis can result in hyperexcitability and ectopic spontaneous activity in both peripheral and spinal neurons, as revealed by ion channel microarray [20]. Accumulated evidence indicates that the robust activation of voltage-gated Na^+ and K^+ ion channels plays a critical role in the pathology of painful TIPN [22,38]. In patients receiving taxane chemotherapy, alterations in Na^+ channel type and activity may contribute to the development of TIPN [39]. The expression and function of the voltage-gated Na^+ channel Nav1.7 are markedly increased in dorsal root ganglia neurons after paclitaxel treatment and contribute directly to the development of ectopic spontaneous activity in nociceptors [40]. Beyond the dorsal root ganglia, increased expression of voltage-gated Na^+ channels is also found in forebrain regions after paclitaxel treatment [41]. A caveat to this latter observation is that forebrain changes in Na^+ channel expression would be secondary to alterations occurring elsewhere, given the poor penetrance of paclitaxel to the central nervous system. The voltage-gated Na^+ channels can pump more Na^+ into neurons and cause less Na^+ outside the neurons. This may be indicative of lower Na^+ ions outside the neurons. Importantly, the relationship between the concentration of Na^+ outside neurons and in blood are needed in prospective cancer cohorts exposed to neurotoxic chemotherapies. These preclinical observations are supported by clinical findings that voltage-gated Na^+ channel blockers, such as carbamazepine, have successfully treated some neuropathic pain patients [42]. Moreover, increasing the Cl^- concentration in dorsal root ganglion neurons can enhance the excitability of dorsal root ganglion neurons and ultimately promote hyperalgesia and allodynia in a rat model [43]. The Cl^- concentration is regulated by Na^+-K^+-2 C l^- cotransporter 1 (NKCC1) and K^+- Cl^- cotransporter 2 (KCC2), which belong to the cation- Cl^- cotransporter family. The altered function of NKCC1/KCC2 can cause the transmission of peripheral pain [44,45], which may be associated with gamma-aminobutyric acid [46]. However, we did not find an association between K^+, Ca^{2+}, Mg^{2+} and TIPN severity, which highlights the complexity of TIPN development.

A higher cumulative chemotherapy dose was associated with higher TIPN severity among the whole cohort and three subgroups. A cumulative dose is generally associated with greater TIPN risk [47]. In most patients, TIPN develops in a dose-dependent fashion after several cycles of neurotoxic chemotherapy administration and is typically dependent on the administered dose [3]. Among 1725 Danish breast cancer patients receiving adjuvant treatment with docetaxel, 34% developed TIPN, with those developing TIPN receiving significantly lower cumulative doses of docetaxel than those who did not [48]. The results were confirmed for paclitaxel in a prospective self-controlled trial [49]. We did not find that the relative dose intensity was associated with developing TIPN. This may be due to the mean relative dose intensity reaching 99.9% for the whole cohort and all the subgroups.

Severe TIPN was associated with higher BMI only in the docetaxel-specific analysis. We did not find a significant association between BMI and TIPN in the whole cohort or paclitaxel- and nab-paclitaxel-treated patients. Although some studies demonstrated an association between BMI and greater taxane-induced TIPN prevalence and severity [19,50,51], other investigations failed to find any association [52–55]. This may be because, in the whole cohort, only 59 (5.8%) patients were obese (BMI $\geq$30 kg/m^2), including 29 (5.9%) patients in the paclitaxel-treated group, 18 (6.4%) patients in the docetaxel-treated group and 4 (3.9%) patients in the nab-paclitaxel-treated group. Obesity is associated with increased idiopathic neuropathy risk [56] and metabolic dysregulation, hyperinsulinemia, and insulin sensitivity, which can also predispose patients to neuropathy [57], so there is a mechanistic rationale for increased TIPN risk. The links between obesity and TIPN may be partially mediated via higher treatment doses administered to patients with higher BSA [51]. However, we did not find that BSA was associated with developing TIPN.

Metabolic syndrome and associated conditions have emerged as potential risk factors for peripheral neuropathy (88). However, we found that higher glucose was only associated with higher autonomic severity

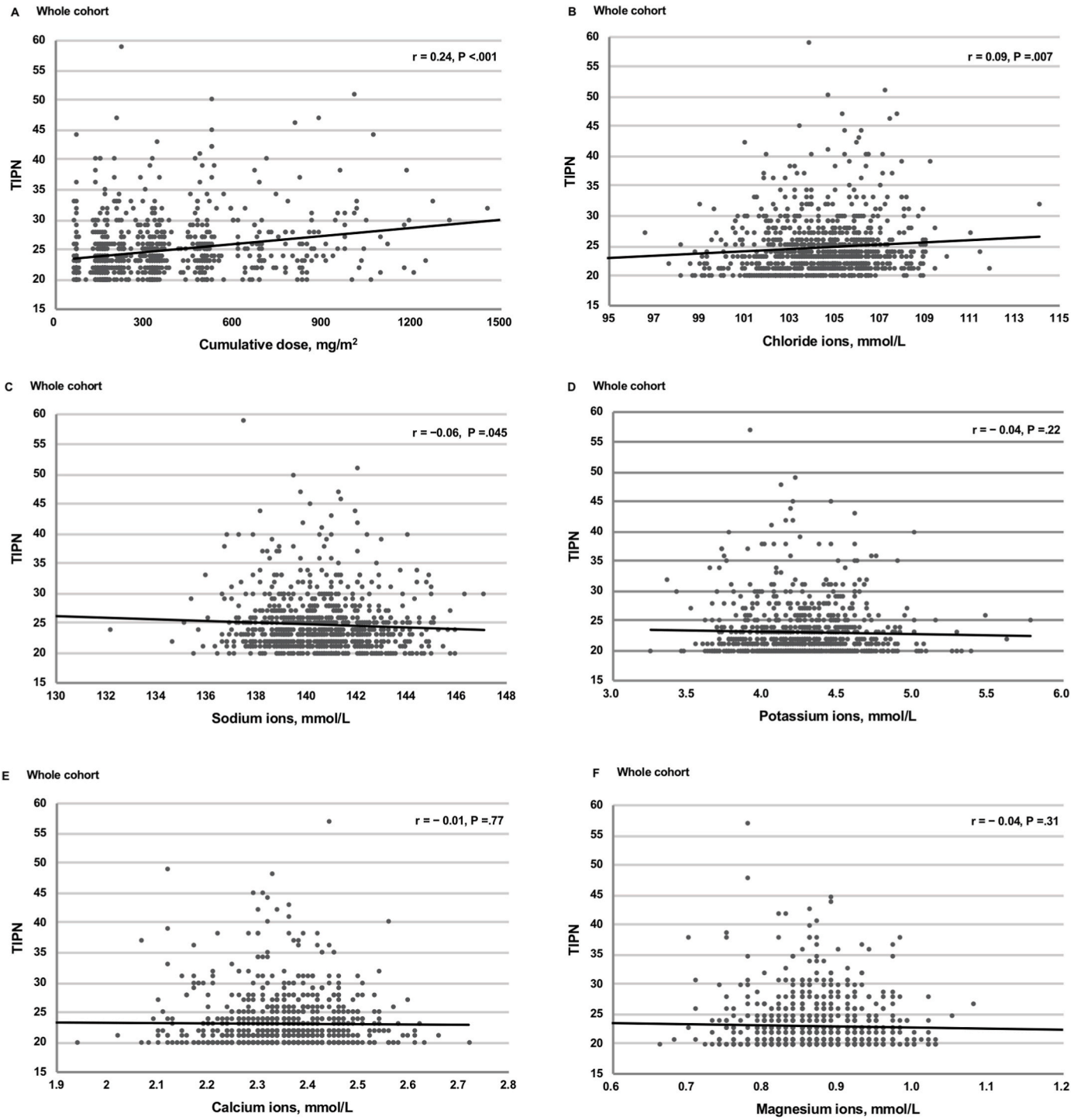

Fig. 1. Blood-Based and Clinical Factor Univariate Correlates of Taxane-induced peripheral neuropathy (TIPN) Toxicity Score Across the Whole Cohort
(A) Higher TIPN toxicity score was correlated with higher cumulative chemotherapy dose (B) Higher TIPN toxicity score was correlated with higher chloride ions (C) Higher TIPN toxicity score was correlated with lower sodium ions (D) TIPN toxicity score had no association with potassium ions (E) TIPN toxicity score had no association with calcium ions (F) TIPN toxicity score had no association with magnesium ions.

in the whole group. Moreover, we did not find an association between blood lipids and TIPN severity, including cholesterol, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol. We only selected the baseline blood test, so the glucose and lipid concentrations may not reflect blood glucose and lipid status.

The time point of the highest TIPN toxicity score was mostly towards the final few cycles. However, some patients reported the highest toxicity score in the first few cycles. On the one hand, the patients' subjective feeling was relatively strong when they began to receive treatments, and gradually adapt to symptoms. On the other hand, patients may take antidepressants or drugs for pain that could interfere in symptom evaluation. Besides, we used mean ± SD to define the outliers of the blood biochemistry indexes because the blood environment of patients with cancer are different from that of normal people. Moreover, the difference of some TIPN scores between the two groups was less than one point and may not reflect clinical important difference [58].

Table 4
Linear regression to determine univariate factors influencing the development of chemotherapy induced peripheral neuropathy contributing to the multivariable model in the whole cohort and paclitaxel, docetaxel and nab-paclitaxel subgroups.

	Total (n = 873)			Paclitaxel (n = 489)			Docetaxel (n = 282)			Nab-paclitaxel (n = 102)		
	Univariate	Multivariable		Univariate	Multivariable		Univariate	Multivariable		Univariate	Multivariable	
	P-value	B (95%CI)	*P*-value	*P*-value	B (95%CI)	*P*-value	*P*-value	B (95%CI)	*P*-value	*P*-value	B (95%CI)	*P*-value
Age	.16			.33			.11			.57		
Cumulative chemotherapy dose (mg/m^2)	<.001[a]	0.005 (0.004–0.006)	<.001[a]	<.001[a]	0.005 (0.003–0.006)	<.001[a]	.001[a]	0.010 (0.004–0.016)	.001[a]	<.001[a]	0.006 (0.003–0.009)	<.001[a]
Relative dose intensity	.17			.54			.71			.73		
Body surface area	.32			.40			.25			.59		
Body mass index	.032			.39			.009[a]	0.19 (0.04–0.35)	.015[a]	.58		
Potassium ions	.22			.077			.53			.73		
Sodium ions	.045[a]	−0.24 (−0.39 to −0.09)	.002[a]	.69			.008[a]	−0.40 (−0.60 to −0.10)	.008[a]	.82		
Chloride ions	.007[a]	0.30 (0.16–0.44)	<.001[a]	.003[a]	0.29 (0.13–0.45)	<.001[a]	.67			.60		
Glucose	.50			.24			.68			.35		
Total bilirubin	.52			.35			.75			.26		
Creatinine	.39			.14			.51			.40		
Calcium ions	.77			.74			.36			.13		
Magnesium ions	.31			.15			.91			.96		
Cholesterol	.17			.18			.22			.97		
Triglyceride	.50			.54			.37			.71		
High-density lipoprotein cholesterol	.46			.73			.53			.20		
Low-density lipoprotein cholesterol	.29			.13			.33			.57		
Albumin	.36			.15			.39			.76		

[a] Factors included in final backwards linear multivariable model. Univariate factors with $p < .10$ were included in the final model and removed during the backwards removal model process. Variables with $P < .05$ in the multivariable model were considered significant.

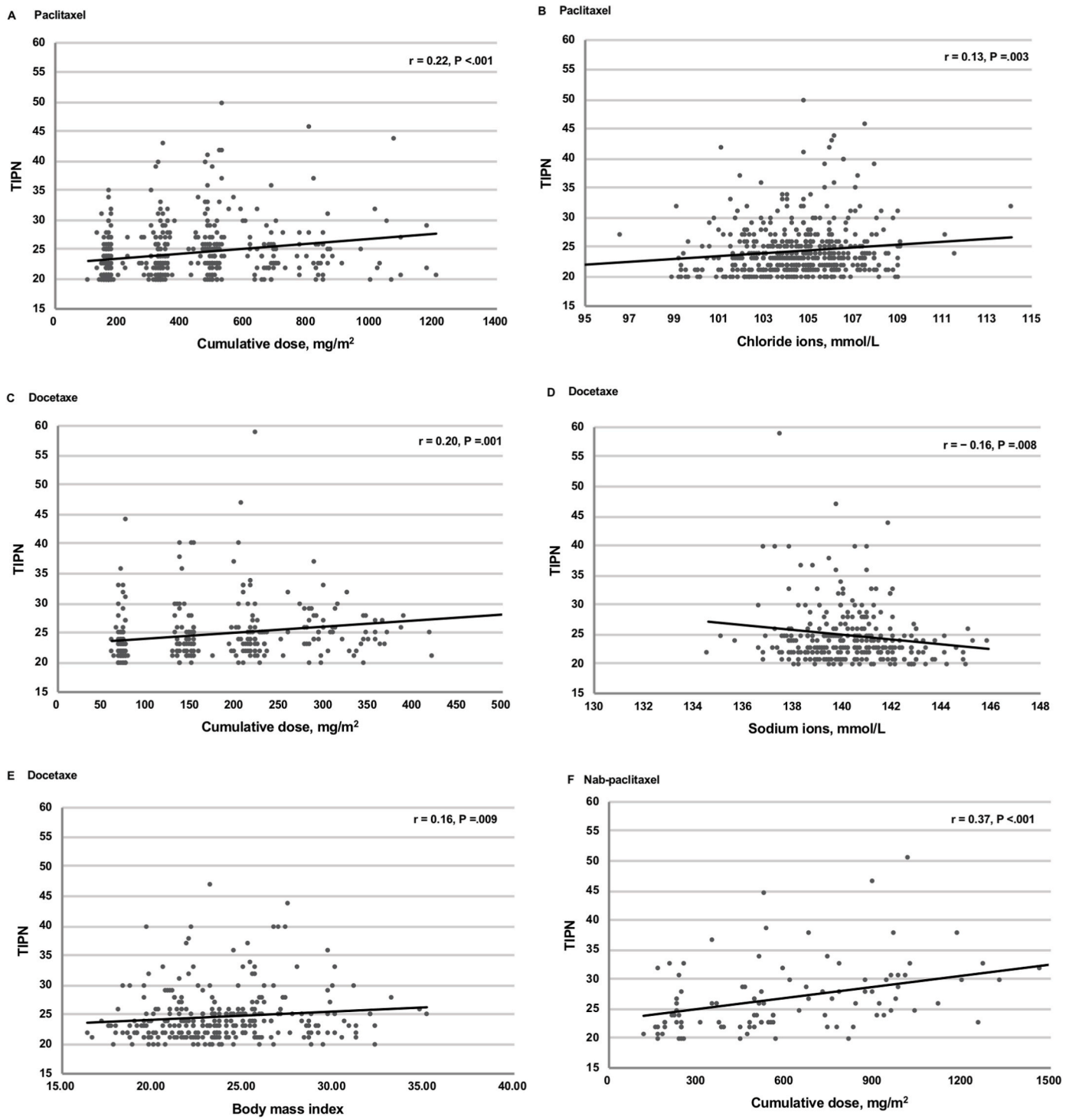

Fig. 2. Blood-based and clinical factor univariate correlates of taxane-induced peripheral neuropathy (TIPN) toxicity score in patients who received paclitaxel, docetaxel and nab-paclitaxel
(A) Higher TIPN toxicity score was correlated with higher cumulative chemotherapy dose in the paclitaxel-treated group (B) Higher TIPN toxicity score was correlated with higher chloride ions in the paclitaxel-treated group (C) Higher TIPN toxicity score was correlated with higher cumulative chemotherapy dose in the docetaxel-treated group (D) Higher TIPN toxicity score was correlated with lower sodium ions in the docetaxel-treated group (E) Higher TIPN toxicity score was correlated with higher body mass index in the docetaxel-treated group (F) Higher TIPN toxicity score was correlated with higher chloride ions in the nab-paclitaxel-treated group.

However, the difference indicated the risk factors related to TIPN.

5. Strengths and limitations

This multisite, large-scale study incorporated comprehensive TIPN assessment using numerous validated objective and patient-reported assessment tools [59]. Factors identified in our model using backward regression were validated using the hold-out method and consistent when using forward regression, reassuring the factors identified.

This study still had several limitations. First, our conclusions are

limited to the taxane chemotherapy drugs commonly associated with TIPN and may not apply to other TIPN-inducing therapies. Because of the large sample of taxane-treated breast cancer, our findings are predominantly generalized to women and this cancer type, which may limit the generalizability more broadly. Secondly, we did not collect data on nutritional supplementation, transfusions, or other interventions that may potentially affect TIPN development. For example, patients may take antidepressants or drugs for pain that could interfere in symptom evaluation. Besides, the work relied on a subjective patient-reported outcome measure and lacked of formal or objective assessment of TIPN. Moreover, the concurrent application of neurotoxic drug (carboplatin) and taxane may influence notably the incidence and severity of TIPN. This was an observational study without controls. Further studies with controls are needed to fully evaluate association of pretreatment blood-based biochemical factors with patient-reported TIPN severity. We acknowledge the inherent limitations of cross-sectional TIPN assessments, and these findings should be confirmed with objective evaluation method in prospectively assessed cohorts.

6. Conclusions

We found that the baseline electrolyte level is related to the severity of TIPN. Patients with a higher cumulative chemotherapy dose, lower Na^+ and higher Cl^- were more likely to develop TIPN posttreatment. Closer monitoring of those at higher risk to allow dose modification may mitigate the development of short-term and long-term TIPN among patients receiving taxane. Appropriate drug doses and symptomatic support treatment should improve patients' quality of life.

Author contribution statement

JZ, HM, FM and BX designed the study. JZ, XS, FZ, BP, HL, ZL, MC, and JZ collected and analyzed the data. JZ, XS and HM drafted the manuscript. FM and BX supervised the study and gave critical revision of the manuscript. All authors read and approved the final manuscript.

Ethics

This work was approved by the Ethics Committee of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Ref. 19/327–2111). Written informed consent was obtained from each participant. All data analyzed were in aggregate information and were stripped of any patient identifiers.

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Data availability statement

The original contributions presented in the study are included in this publication. Further inquiries can be directed to the corresponding authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2022.12.034.

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