RESEARCH ARTICLE

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Is Functional Vitamin B12 Deficiency a Risk Factor for the Development of Chemotherapy-Induced Peripheral Neuropathy in Cancer Patients?

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Abstract

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common, significant, debilitating symptom of anticancer treatment, and continues to plague patients and medical fraternity. This study aimed to explore the associations between CIPN and functional vitamin B12 deficiency, as well as other predictors including nutritional and non-nutritional factors among cancer patients. **Methods:** A prospective study design was conducted to achieve the study objectives, utilizing a non-probability purposive sampling technique. A consecutive case series of 64 adults (≥ 18 years) newly diagnosed cancer patients of various sites, registered and scheduled to receive the first cycle of chemotherapy were recruited from the Oncology Department of European Gaza Hospital (EGH). At two different points of time, at the baseline before the initiation of the first cycle of chemotherapy (pre) and after the completion of the chemotherapy regimen (post), vitamin B12 status was evaluated using serum vitamin B12 and it is related metabolites methylmalonic acid (MMA) and homocysteine (Hcy), and CIPN was evaluated using patient neurotoxicity questionnaire (PNQ). **Results:** The results reported the presence of a functional vitamin B12 deficiency, such that there is a drastic reduction in serum vitamin B12 levels (355.0(IQR 115.0) to 219.0(IQR 177.0) pg/mL, $P < 0.001$), accompanied by a significant increase in it is related metabolites MMA (3.9(IQR 3.0) to 49.7(IQR 32.0) ng/mL, $P < 0.001$) and Hcy (3.90(IQR 0.85) to 12.60(IQR 7.05) ng/mL, $P < 0.001$) after the completion of chemotherapy regimen. Increases in serum MMA levels significantly predicted increases in PNQ scores ($b = 0.02$, $R^2 = 0.30$, $P = 0.001$). **Conclusion:** Functional vitamin B12 deficiency as defined by increased MMA levels is a distinct risk factor in the development of CIPN in cancer patients undergoing chemotherapy. Further studies are required to evaluate the impact of vitamin B12 therapy in the management and/or prevention of CIPN.

Keywords: Cancer- chemotherapy- neuropathy- platinum compounds- vitamin B12

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Introduction

Cancer is currently a leading cause of mortality worldwide [1]. Chemotherapeutic drugs are used to block the progression of cancer owing to their ability to kill cancer cells, despite many side effects caused by damage affecting normal cell growth and function. Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most frequent side effects of many chemotherapeutic agents and a major cause of ongoing pain in cancer survivors [2]. As oncological treatments have advanced, cancer survival has increased significantly, with many patients either being cured of cancer or living for many years with cancer. Unfortunately, many modern, commonly used chemotherapeutic agents can cause both acute and chronic CIPN [3]. The primary classes of chemotherapeutic agents associated with CIPN are platinum-based antineoplastics (mainly oxaliplatin and cisplatin), vinca alkaloids (mainly vincristine and vinblastine), epothilones (ixabepilone), taxanes (paclitaxel and docetaxel), proteasome inhibitors (bortezomib), immunomodulatory drugs (thalidomide) and ifosfamide [4]. Given the prevalence of common cancers (colorectal, breast, lung) that these chemotherapeutics counteract, CIPN affects several million patients worldwide each year. During oncological treatment, the severity of the acute syndrome may require reducing the dose of chemotherapy or even stopping it, with a potential impact on tumor control, quality of life (QoL), and survival of cancer patients [5, 6]. CIPN also places a significant economic burden on patients as a result of work loss and on the healthcare system because of its prevalence [7].

The incidence of CIPN depends on chemotherapy agent administered but it is estimated to occur in one-third of all

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patients undergoing chemotherapy [8, 9]. In a systematic review of 31 studies (N =4179), CIPN prevalence was 68.1% in the first month after chemotherapy and 60.0% at 3 months. Although CIPN prevalence decreases with time, at 6 months 30% of patients continue to suffer from CIPN [10]. CIPN symptoms are primarily sensory (e.g., tingling, numbness, and pain in the extremities), but can be motoric (e.g., cramps and loss of strength), or autonomic (e.g., dizziness after standing up and blurry vision) as well [11].

There are currently no effective preventive and limited treatment options for CIPN [12]. Knowledge of CIPN predictors may help develop strategies for early identification with prevention and more efficacious management of CIPN. Various risk factors for CIPN have been identified, some of them treatment-related, such as the type of employed chemotherapeutic agent, cumulative dose, number of cycles, treatment duration, and combination therapies, and others related to patient's age, comorbid conditions like diabetes, pre-existing nerve damage and prolonged consumption of alcohol [13].

It's a known fact that neuropathies also commonly result from frank vitamin B12 deficiency, which is identified by the presence of low serum B12 levels accompanied by increased values of B12-related metabolites, methylmalonic acid (MMA), and/or homocysteine (Hcy) [14]. More recently, B12-responsive neuropathies have also been described in the setting of "functional" vitamin B12 deficiency, which is defined by the presence of elevated levels of MMA and/or Hcy despite normal serum vitamin B12 values [14, 15]. Cancer patients are vulnerable to vitamin B12 deficiency due to poor oral intake, malabsorption, GI surgeries, medications, and enteritis [8]. Vitamin B12 deficiency may develop during chemotherapy administration and may potentially predispose cancer patients to develop CIPN. Moreover, the neurotoxic effects of chemotherapy can be compounded by a pre-existing vitamin B12 deficiency. Consequently, diagnosing vitamin B12 deficiency early in the natural history of cancer can help identify patients who are at a greater likelihood of subsequently developing CIPN [16].

However, vitamin B12 deficiency can be difficult to diagnose. Diagnosis is typically based on the measurement of serum vitamin B12 levels (usually less than 200 pg/mL), however, about 50% of patients with the subclinical disease have normal vitamin B12 levels [17, 18]. Moreover, elevated serum levels of vitamin B12 can be accompanied by signs of deficiency as well, suggesting a functional deficiency from defects in tissue uptake and action of vitamin B12 at the cellular level [19]. Therefore, the measurement of metabolites that accumulate as a result of vitamin B12 deficiency is more sensitive indicator in the diagnosis of vitamin B12 deficiency than using serum vitamin B12 testing alone [16].

Over the past decade, there was a large interest in identifying factors that predict risk for developing CIPN, as this may help identify the most susceptible patients, will allow physicians to personalize treatment choices, and may guide new methods of treatment in the future. To the best of our knowledge, there is a lack of literature exploring the association between functional vitamin B12 deficiency and CIPN in cancer patients undergoing chemotherapy. Therefore, the present study aimed to explore the following in a cohort of cancer patients undergoing chemotherapy at the Oncology Department of EGH: 1) vitamin B12 and its related metabolites levels at the baseline before the initiation of the first cycle of chemotherapy (pre) and after the completion of chemotherapy regimen (post); 2) how strongly lab indicators of vitamin B12 deficiency predict CIPN severity. Covariates (e.g., age, gender, cancer type, cancer stage, chemotherapy type, diabetes diagnosis, patients' nutritional status, and serum HoloTC, folate, vitamin B6, and albumin levels) were also explored.

Materials and Methods

Study design and patient population

This study deployed a prospective (short cohort) design. All eligible patients were recruited between February and November of 2017 from the Oncology Department at EGH located in Khan Younis, Gaza Strip, Palestine. All adult (≥18 years) newly diagnosed cancer patients registered and scheduled to receive the first cycle of chemotherapy were considered eligible irrespective of their age, gender, cancer diagnosis, or any other clinical or demographic characteristic. Then, using a non-probability purposive sampling technique, a consecutive case series of 64 potential patients was properly informed of the study's objectives, procedures, and potential risks and benefits of the study in both verbal and written form and were asked for their willingness to participate in the study.

Exclusion criteria included patients who declined participation in the study, who had received pharmacological doses of vitamin B12, those with low serum vitamin B12 levels of less than 200 pg/mL, those who had received previous chemotherapy treatment, and patients who had a previous cancer diagnosis. Also, the exclusion criteria were extended to include end-stage renal disease (ESRD) patients.

In this study, the existing data were collected from patient's medical records or directly from patients or through identifiers linked to the patients during face-to-face interviews conducted by a researcher. Patient records/ information was anonymized and de-identified before analysis.

Measurements

Socio-demographic, clinical, and nutritional characteristics

Patients' socio-demographics (e.g., age, gender) and clinical information (e.g., cancer type, cancer stage, chemotherapy type, and diabetes) were obtained from patient's medical records. Body mass index (BMI) was calculated as kg/m^2. Patient's nutritional status was assessed with SGA, as described by Detsky et al. [20] at the baseline before commencing the first cycle of chemotherapy and after the completion of chemotherapy regimen.

Biochemical assessment

Venous whole blood samples, about 5.0 mL, were collected from recruited patients at the baseline and

after the completion of chemotherapy regimen, in ethylenediaminetetraacetic acid (EDTA)-coated anticoagulant tubes and plain vacutainers (BD vacutainer, NJ, USA). After collection of the whole blood, blood samples were centrifuged in a refrigerated centrifuge at 4◦C within one hour of sample collection and the separated plasma and serum were stored at -20◦C for subsequent analysis in batch. Laboratory values of MMA, Hcy, HoloTC, and vitamin B6 were determined using abbexa enzyme-linked immunosorbent assay (ELISA) Kits (Abbexa, Cambridge, UK) following the manufacturer's instructions. Vitamin B12 and folate were measured using a commercially available MyBioSource ELISA Kit (MyBioSource, California, USA). Albumin levels were measured using the bromocresol green method (DiaSys, Germany).

Neurological evaluation

The patient neurotoxicity questionnaire (PNQ) was used to quantify symptoms and severity of CIPN. Two PNQs were completed, one at the baseline and the second one after the completion of chemotherapy regimen.

The PNQ is a simple self-administered instrument that was designed and developed concerning the neurosensory and neuromotor components of the NCI-CTC (Version 2) by BioNumerik Pharmaceuticals, with input from the US Food and Drug Administration (FDA) and physicians and nurse's familiar with CIPN [21]. The PNQ is comprised of two clinically defined symptom areas relevant to CIPN, namely, sensory (numbness, tingling, and pain) and motor (weakness), with a clear demarcation between interference and non-interference in daily activities. These two items are rated 1-5 on the following scale: 1 = No, 2 = Mild, 3 = Moderate, 4 = Moderate to Severe, and 5 = Severe. The CIPN of each patient was assessed by summing the two items' scores, with the final score being called the PNQ total score, which ranges from 2 to 10, defined as grade A: 2, grade B: 3-4, grade C: 5-6, grade D: 7-8, and grade E: 9-10, with a high total score representing severe CIPN symptoms [22].

PNQ appears to have an applicable and practical level of feasibility and validity for CIPN diagnosis and grading in the clinical setting, not only for the identification of CIPN-related symptoms but also to aid treatment-related decisions [23, 24].

Statistical analysis

The statistical analysis was performed using SPSS Statistical Package for Social Sciences version 24.0 software (IBM Corp., Armonk, NY USA). Basic Descriptive data were used for reporting patient-related characteristics. For qualitative variables, absolute frequencies (n) and relative frequencies (%) were calculated, while for quantitative variables, mean, standard deviation (SD), median and interquartile range (IQR) were determined as descriptive measures. The conformity of the numerical variables to normal distribution was examined using Shapiro–Wilk test. The Wilcoxon Signed Rank test (non-parametric test) was used for finding the differences between at the baseline (pre) and after the completion of chemotherapy regimen (post).

Linear regression analyses were performed to explore the associations between CIPN symptoms severity and functional vitamin B12 deficiency. With PNQ score as a criterion variable, the predictor variables included the changes in biochemical values of lab indicators of functional vitamin B12 deficiency (vitamin B12 $_{\Delta pre\text{-}post}$, MMA $_{\Delta post\text{-}pre}$, Hcy $_{\Delta post\text{-}pre}$). As potential covariates, we considered the following: patient age, gender, cancer type, cancer stage (III and IV vs. other), chemotherapy type, diabetes, and patients' nutritional status "SGA $_{\Delta post\text{-}pre}$", in addition to Holo TC Δpre-post, folate $\Delta_{pre\text{-}post,}$ vitamin B6 $_{\Delta pre\text{-}post}$, and albumin $_{\Delta pre\text{-}post}$. First, bivariate linear regression analysis between the outcome and each potential independent variable were performed. Subsequently, a stepwise multiple linear regression model was created by employing those candidate variables showing values of $P < 0.05$ from bivariate regression or selected based on previous studies [10, 25]. For categorical data, a dummy variable is constructed whereby the value of '0' is for cases that don't have the category and the value '1' is for cases that have the certain category. The independent variables of the model were checked for multicollinearity. Linear regression was bootstrapped to account for non-normal distribution of the residuals and to produce robust confidence intervals. The value of R squared was calculated and P values below 0.05 were deemed "statistically significant".

Results

Patient characteristics

Table 1 displays the baseline characteristics of our patients. Patients' mean age was 48.58(SD 15.33) years and women were predominant in the study sample (37 women and 27 men). The most common cancers were breast (31.3%), colon and rectal cancer (18.8%), lung (6.3%), and gastric (6.3%), and platinum compounds were the most commonly received types of chemotherapy (46.9%), followed by taxanes (28.1%). Most patients in stage IV (51.6%), non-diabetic (87.5%), and well-nourished (64.1%) based on SGA.

Biochemical analysis at the baseline and after the completion of the chemotherapy regimen

In this study, 45 patients out of a total 64 enrolled patients were evaluated at the baseline before the initiation of the first cycle of chemotherapy and after the completion of chemotherapy regimen for vitamin B12, HoloTC, vitamin B6, folate, MMA, Hcy, and albumin. The median serum vitamin B12 concentration at the baseline was significantly higher 355.0 (IQR 115.0) pg/mL than that after the completion of chemotherapy regimen 219.0 (IQR 177.0) pg/mL. On the other hand, the median serum concentration of MMA after the completion of chemotherapy regimen was significantly higher 49.7 (IQR 32.0) ng/mL than that at the baseline 3.9 (IQR 3.0) ng/mL. Similarly, the median serum Hcy concentration after the completion of chemotherapy regimen was higher 12.6 (IQR 7.05) ng/mL than that at the baseline 3.90 (IQR 0.85) ng/mL (Table 2).

Table 1. Baseline Patient Characteristics (n = 64)

Variables	No. of respondents (%)	Mean (SD)
Age (years)		48.58 (15.33)
Gender		
Male	27 (42.2)	
Female	37 (57.8)	
Cancer type		
Breast cancer	20 (31.3)	
Colon and rectal cancer	12 (18.8)	
Lung cancer	4 (6.3)	
Gastric cancer	4 (6.3)	
Other	24 (37.5)	
Cancer stage		
Stage II	11 (17.2)	
Stage III	20 (31.3)	
Stage IV	33 (51.6)	
Chemotherapeutic agents		
Taxanes	18 (28.1)	
Platinum compounds	30 (46.9)	
Vinca alkaloids	3 (4.7)	
Proteasome inhibitors	1 (1.6)	
Diabetes		
Diabetic	8 (12.5)	
Non-diabetic	56 (87.5)	
BMI (kg/m2)		26.82(5.90)
SGA		
Well nourished	41 (64.1)	
Moderately malnourished	13 (20.3)	
Malnourished	10 (15.6)	

BMI, Body Mass Index; kg/m^2, kilogram per square meter; SGA, Subjective Global Assessment

Predictor factors of CIPN

Multiple linear regression showed that MMA, SGA, diabetes, other (types of cancer), platinum compounds, age, folate, and vitamin B6 were associated with worse CIPN. Increases in serum MMA levels was significantly associated with higher PNQ score (β = 0.02, 95% CI, 0.01, 0.03, P = 0.001). A higher score of SGA was associated with a higher PNQ score (β = 0.31, 95% CI, 0.11, 0.51, P = 0.004). Accordingly, patients with malnutrition developed more sever CIPN symptoms compared with well-nourished patients. Furthermore, other types of cancer were significantly associated with CIPN (β = 1.09, 95% CI, 0.75, 1.43, P < 0.001). As was diabetes diagnosis, with diabetic patients being more likely to experience more sever CIPN symptoms than non-diabetic patients (β = 0.38, 95% CI, 0.04, 0.73, P = 0.032).

Platinum compounds treatment was associated with worse CIPN (β = 0.51, 95% CI, 0.23, 0.80, P = 0.001). For age, older patients reported a worse CIPN (β = 0.02, 95% CI, 0.01, 0.03, P = 0.001). Decreases in serum folate levels "pre-chemotherapy minus post-chemotherapy levels" was associated with worse CIPN (β = 0.15, 95% CI, 0.02, 0.27, P = 0.021). Similarly for vitamin B6, decreases in serum vitamin B6 levels predicted increases in PNQ score (β = 0.01, 95% CI, 0.00, 0.02, P = 0.039) (Table 3).

Discussion

In line with the available literature, the current study hypothesis was that functional vitamin B12 deficiency is a risk factor for the development of CIPN in cancer patients receiving neurotoxic chemotherapeutic agents. This is confirmed, as we found a significant association between CIPN indicator (PNQ) and the best indicator of functional vitamin B12 deficiency (MMA) as well as other predictor factors of CIPN including nutritional and non-nutritional factors. The present study prospectively evaluated CIPN using a patient-based instrument, PNQ at the baseline before commencing the first cycle of chemotherapy and after the completion of chemotherapy regimen, seeking to identify the prognostic factors for CIPN, although a complete description of CIPN risk and protective factors has yet to be defined.

In our regression model, the PNQ score significantly increased with increasing serum MMA levels. It is important to note that MMA is more specific to vitamin B12 deficiency compared to Hcy. A deficiency of vitamin B12 at tissue level can lead to elevation of both MMA and Hcy even when serum vitamin B12 concentrations are within the reference range [17]. Meanwhile, inadequate levels of folate, vitamin B12, vitamin B6, and riboflavin may all result in high levels of Hcy [26]. In our current study, we evaluated vitamin B12 status by measuring serum levels of vitamin B12 and metabolites that accumulate as a result of vitamin B12 deficiency, MMA, and Hcy. Our results reported significant differences in serum vitamin

Table 2. Biochemical Analysis at the Baseline and after the Completion of Chemotherapy (n = 45)

Variables	Pre Median (IQR)	Post Median (IQR)	P value*
Vitamin B12 (pg/mL)	355.00 (115.00)	219.00 (177.00)	<0.001
HoloTC (ng/mL)	2.90 (2.85)	1.30 (3.15)	<0.001
Vitamin B6 (ng/mL)	83.40 (27.65)	70.70 (38.45)	<0.001
Folate (ng/mL)	6.60 (3.00)	5.30 (2.75)	<0.001
MMA (ng/mL)	3.90 (3.00)	49.70 (32.00)	<0.001
Hcy (ng/mL)	3.90 (0.85)	12.60 (7.05)	<0.001
Albumin (g/dL)	4.10 (0.70)	3.20 (0.85)	<0.001

*Wilcoxon Signed Ranks Test, p < 0.05; pg/mL, picogram per milliliter; ng/mL, nanogram per milliliter; g/dL, gram per deciliter; HoloTC, Holotranscobalamin; MMA, Methylmalonic Acid; Hcy, Homocysteine

Table 3. Predictor factors of CIPN

Variables	SLR[a]		MLR[b]			
	b (95%CI)	P Value	Adjusted b (95%CI)	t- Statistics	R^2	P Value
$MMA_{\Delta post-pre}$	0.03 (0.02, 0.04)	<0.001	0.02 (0.01, 0.03)	3.82	0.3	0.001
$SGA_{\Delta post-pre}$	0.64 (0.36, 0.93)	<0.001	0.31 (0.11, 0.51)	3.11	0.54	0.004
Diabetes	0.05 (-0.65, 0.74)	0.89	0.38 (0.04, 0.73)	2.24	0.61	0.032
Cancer type						
Breast cancer	-0.43 (-0.91, 0.06)	0.087				
Colorectal cancer	0.00 (-0.59, 0.59)	1				
Lung cancer	-0.79 (-1.86, 0.28)	0.143				
Gastric cancer	0.61 (-0.46, 1.69)	0.257				
Other	0.44 (-0.03, 0.92)	0.068	1.09 (0.75, 1.43)	6.51	0.65	<0.001
Chemotherapeutic agents						
Taxanes	0.62 (0.12, 1.12)	0.015				
Platinum compounds	0.25 (-0.22, 0.72)	0.287	0.51 (0.23, 0.80)	3.7	0.79	0.001
Vinca alkaloids	-0.44 (-1.52, 0.64)	0.419				
Proteasome inhibitors	0.93 (-0.90, 2.76)	0.312				
Age	0.01 (-0.01, 0.02)	0.38	0.02 (0.01, 0.03)	3.75	0.83	0.001
$Folate_{\Delta pre-post}$	0.07 (-0.20, 0.34)	0.59	0.15 (0.02, 0.27)	2.42	0.87	0.021
$Vitamin\ B6_{\Delta pre-post}$	0.02 (0.00, 0.04)	0.067	0.01 (0.00, 0.02)	2.15	0.86	0.039

[a], Simple linear regression; [b], Multiple linear regression; R^2, 0.86. The model reasonably fits well. Model assumptions are met. There is no interaction and multicollinearity problem; *, Regression p values are included only for variables in the final model; MMA, Methylmalonic Acid; SGA, Subjective Global Assessment

B12, MMA, and Hcy levels between the baseline and after the completion of chemotherapy regimen. Serum vitamin B12 levels reduced significantly after the completion of chemotherapy regimen, whilst vitamin B12 related metabolites, MMA and Hcy, significantly elevated after the completion of chemotherapy regimen. This key finding of our study asserts the presence of functional vitamin B12 deficiency among cancer patients.

Consistent with our study, Vashi et al.'s a cross sectional study conducted among cancer patients to evaluate the prevalence of vitamin B12 deficiency using serum vitamin B12, MMA, and Hcy [16], Vashi et al. [16] found that the prevalence of vitamin B12 deficiency was 8.9% using a cut-off point for vitamin B12 deficiency <300 pg/ml, whilst using MMA and Hcy levels, the respective prevalence rates were 10.8% and 17.4%, respectively, suggesting that using serum vitamin B12 testing alone can lead to an under-diagnosis of vitamin B12 deficiency by up to 16%. Additionally, Vashi et al. [16] suggested MMA has the best discriminatory power in predicting vitamin B12 deficiency, such as 8.5% of a total sample classified as B12 deficient based on MMA but vitamin B12 sufficient based on serum vitamin B12. The prevalence of vitamin B12 deficiency, using serum MMA in conjugation with serum B12 was 17.4% versus 8.9% using serum vitamin B12 alone.

In other words, functional vitamin B12 deficiency, as a consequence of our findings is a risk factor for CIPN in cancer patients who have completed or received their cycles of chemotherapy regimen and/ or even scheduled for the first cycle of chemotherapy. To our best knowledge, this is the first study and the first reported prognostic model that is based on MMA "the best sensitive indicator of functional vitamin B12 deficiency" to explore the association between CIPN and functional vitamin B12 deficiency in cancer patients of various sites.

The findings of this study highlight the fact that malnutrition negatively impacts clinical outcomes in cancer patients. It has been reported that malnutrition is associated with increased hospitalization, susceptibility to infection, and mortality [27]. It has a significant negative impact on QoL and survival [28]. Moreover, cancer-induced malnutrition is associated with a decreased response to chemotherapy, more frequent complications, and severe toxicity [29]. More importantly, our findings revealed that malnutrition (using SGA) is a significant prognostic factor for CIPN in cancer patients, which means malnourished patients showed a higher score of PNQ compared with well-nourished patients. Pointing to a higher incidence and more severity of CIPN symptoms in malnourished cancer patients compared with well-nourished patients. In concordance with our findings, Arrieta et al.'s [30] a prospective study conducted among 100 consecutive patients recently diagnosed with lung cancer to associate malnutrition and serum albumin levels with the occurrence of chemotherapy-induced toxicity[30]. Arrieta and his colleagues found that 51% of patients were malnourished before chemotherapy administration, and those who were malnourished had a higher incidence of chemotherapy-induced toxicity compared with well-nourished patients [30].

Moreover, Arrieta and his colleagues reported that overall toxicity development was significantly related to low albumin serum levels being more significant as the

levels decreased [30]. By contrast, our findings did not support the association between serum albumin levels and CIPN. The non-significant association between serum albumin levels and PNQ might be explained by the fact that the range of the difference between serum albumin levels at the baseline and after the completion of chemotherapy regimen was -0.7-2.6 g/dl, with a mean of 0.91 mg/dl, which is below the standard level of 3.5 g/dl, considering hypoalbuminemia among the majority of patients enrolled in the study.

In line with a previous study [10], another noteworthy finding is that diabetic patients tend to develop a higher grade of CIPN compared with non-diabetic patients, which means that diabetes is a significant predictor factor for CIPN among cancer patients. By far diabetic neuropathy is the most prevalent chronic complication of diabetes with prevalence rates ranging from 10-26% in newly diagnosed adults with diabetes [31]. In our regression model, platinum compounds are a significant predictor factor for CIPN. In other words, cancer patients treated with platinum compounds (47%, oxaliplatin, cisplatin, and carboplatin) as part of their scheduled chemotherapy regimen have a higher score of PNQ and/or a higher incidence and more severity of CIPN symptoms compared with patients treated with other neurotoxic chemotherapeutic agents such as taxanes (docetaxel and paclitaxel), vinca alkaloids (vincristine) or proteasome inhibitors (bortezomib). Our findings agree with the results of previous investigations, showing that the prevalence of CIPN is agent-dependent and is the highest in the case of platinum-based drugs (70-100%) with oxaliplatin evoking the most varied and unique neurotoxic effects [32].

In the current study, we also found a significant association between PNQ and other types of cancer. To our knowledge, based on our foregoing finding of "a significant association between PNQ and platinum compounds", cancer patients treated with platinum-based drugs, alone or in combination, as first-line treatments for their type of cancer exhibit a higher PNQ score compared with cancer patients treated with other neurotoxic chemotherapeutic agents. In dead, patients with colorectal, lung or gastric cancer were treated with platinum-based drugs, nonetheless, no significant association between these types of cancer and PNQ, showing in our model. The reasoning behind that would be, the proportion of heterogeneity accounted for by chemotherapy type, among patients of the same type of cancer. Accordingly, our findings are thus in keeping with Seretny and Currie et al.'s expectation, CIPN prevalence is more likely to be related to the type of chemotherapy than to cancer type [10].

In our regression model, aging increases the risk of having more aggressive CIPN symptoms and/or higher PNQ scores. Our findings concur with Seretny et al.'s study, which defined patient age among the predisposing risk factors of CIPN, specifying that older patients have a higher risk [10]. Our findings of significant differences in serum HoloTC, vitamin B6 and folate levels between at the baseline and after the completion of chemotherapy regimen is in agreement with a clinical study of a single breast cancer patient [9], which found a pronounced HoloTC deficiency after the completion of full chemotherapy regimen (107 pmol/l at the baseline to 29 pmol/l after the completion of chemotherapy regimen, reference range >35 pmol/l). Similarly, in this clinical study of a single breast cancer patient by Schloss and his colleagues, vitamin B6, and folate reduced after the completion of the chemotherapy regimen, but not less than the reference range [9].

Another noteworthy finding, was significant associations between PNQ score and the change (pre-chemotherapy minus post-chemotherapy levels) in serum folate as well as vitamin B6 levels, decreases in folate and vitamin B6 levels predicted increases in PNQ score and worse CIPN. To our knowledge, there has not been a published study investigating the association between CIPN and serum folate or vitamin B6 levels. Indeed, a thorough literature review identified a few published studies that focused on the role of B vitamins in the prevention of CIPN, indicating that there is a need for further studies to ascertain possible protection and treatment options [33, 34]. However, none of these studies assessed the association between CIPN and B vitamins.

In conclusion, functional vitamin B12 deficiency as defined by increased MMA levels is a distinct risk factor in the development of CIPN in cancer patients undergoing chemotherapy. The results of this study have emphasized the importance of MMA as the best indicator of functional vitamin B12 deficiency; using serum vitamin B12 alone to evaluate B12 status in cancer patients as well as in patients suspected to have risk factors for vitamin B12 deficiency may fail to identify those with functional deficiency. Thus, detecting and treating functional vitamin B12 deficiency, particularly in patients likely to receive neurotoxic chemotherapeutic agents, may reduce the incidence of CIPN or limit it and allow the use of chemotherapy for a longer period. This study also highlights serum folate and vitamin B6 levels as potential risk factors for CIPN. Lower serum folate and/or vitamin B6 levels were associated with CIPN, exacerbating CIPN as their levels decreased in cancer patients undergoing chemotherapy. In addition, CIPN was much more pronounced in older, malnourished, diabetic, and those cancer patients treated with platinum compounds as the first line of treatment for their cancer type.

Author Contribution Statement

All authors contributed to the study conception and design. Material preparation and data collection were performed by S.E.E. Data analysis was conducted by S.E.E., I.A.N. and K.M.A. The first draft of the manuscript was written by S.E.E. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethical approval

Study was approved by the Institutional Research and Ethics Board at Human Resources Development in Palestinian Ministry of Health, Faculty of Pharmacy and the Deanship of Postgraduate studies and Research at Al-Azhar University- Gaza. Besides, ethical approval was obtained from the Helsinki Committee in Gaza- Palestine with reference no PHRC/HC/183/16.

Availability of data

The datasets generated during and/or analyzed during the current study are not publicly available due to confidentiality but are available from the corresponding author on reasonable request.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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