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ORIGINAL ARTICLE

Predictive clinical factors of chronic peripheral neuropathy induced by oxaliplatin

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Abstract

Purpose We aimed to identify potential clinical parameters that can be easily obtained by a pre-treatment clinicopathological evaluation and whole blood test to estimate the development of oxaliplatin-induced peripheral neuropathy (OIPN).

Methods This study was conducted retrospectively. For the FOLFOX regimen, patients received oxaliplatin, 85 mg/m^2, every 2 weeks for 12 courses, and with the XELOX regimen, oxaliplatin was 130 mg/m^2, every 3 weeks for 6–8 courses. The incidence and degree of neuropathy (NCI-CTCAE v.3) were recorded.

Results A total of 186 patients were included in the study. There were 108 (58%) patients in the grade 0–1 (G0–G1) neuropathy group (mean age 50.5 ± 11.5; 63% men), and 78 (42%) patients in the grade 2–3 (G2–G3) neuropathy group (mean age 58.0 ± 10.8; 46.2% men). The relationship between G2–G3 OIPN development and age ($p < 0.001$), gender ($p = 0.02$), and ECOG performance status ($p = 0.007$) was statistically significant. In the G2–G3 neuropathy group, serum gamma-glutamyl transferase (GGT) ($p < 0.001$) and glucose ($p = 0.007$) levels were higher, whereas vitamin D ($p < 0.001$), hemoglobin (Hgb) ($p < 0.001$), serum albumin ($p = 0.001$), and serum magnesium ($p = 0.035$) levels were lower compared with the G0–G1 neuropathy group. G2–G3 neuropathy was observed in 88% of patients with mucinous carcinoma pathologic type ($p < 0.001$).

Conclusion This study demonstrated that age, histopathologic type, albumin, GGT, glucose, vitamin D, and Hgb levels were the effective factors in prediction of the development of OIPN. In addition, GGT, vitamin D, and Hgb levels were the most effective factor to predict development of OIPN.

Keywords Oxaliplatin · Peripheral neuropathy · Gastrointestinal system cancers · Treatment · Toxicity

Introduction

Oxaliplatin, a third-generation platinum-based agent, is the main chemotherapeutic agent for the treatment of colorectal cancer (CRC), stomach, pancreatic cancer, and many other cancers types [1, 2]. Oxaliplatin with 5-fluorouracil and leucovorin (FOLFOX regimen) or capecitabine (Xelox regimen) is one of the important drugs in the adjuvant and metastatic stage treatment of gastrointestinal system cancers. Oxaliplatin-induced peripheral neuropathy (OIPN) is one of the main problems associated with the use of this drug. In fact, oxaliplatin may cause acute neuropathy (transient, distal paresthesia during the first minutes of infusion or shortly after) and chronic sensory neuropathy (distal paresthesia and numbness may lead to functional disability in case of grade 3 toxicity) [3]. Nearly all patients develop some degree of OIPN, and in about two-thirds, symptoms may persist for 1 year or longer after the treatment [4, 5]. OIPN has been reported to be dose-dependent, more likely to occur when the cumulative dose exceeds 780–850 mg/m^2. These neuropathic symptoms intensify at cumulative doses, remain between cycles, and may affect quality of life in most patients [6, 7].

OIPN remains a limiting factor in treatment, although oxaliplatin has improved overall survival in studies [8, 9]. Although there is no evaluation of such management approaches in clinical studies, there may be cases of dose reduction, postponement of treatment, and discontinuation of

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medication to reduce the severity of OIPN and prevent irreversible nerve damage [10, 11]. Despite some promising efforts in recent years, an effective treatment for OIPN is not yet available.

Although the chemotherapy treatment program, cumulative drug dose, and pre-existing peripheral neuropathy have been identified as predictors of OIPN, there are currently no identified potential clinical parameters for OIPN and an effective strategy for its prevention [12, 13]. Attal et al. described the presence of hyperalgesia against cold and warm stimuli as an early reliable clinical marker of oxaliplatin neurotoxicity [14]. In a prospective study published by Won et al., several polymorphisms associated with severe OIPN were identified in two independent data sets, and these polymorphisms were evaluated as potential clinical markers [15]. However, due to lack of consensus in these studies, there is no validated marker to distinguish high-risk patients. The aim of this study was to investigate the incidence of oxaliplatin-induced chronic peripheral neuropathy and the clinical parameters predicting the development of neuropathy.

Materials and methods

Patient population

Patients with locally advanced or metastatic gastrointestinal cancer who received chemotherapy with oxaliplatin between September 2016 and July 2019 were evaluated retrospectively, and clinicopathological features of the patients were enrolled. The study and written informed consent documentation were reviewed and approved by the Independent Ethics Committee of Firat University, Medical Faculty.

Inclusion criteria were as follows: patients > 18 years of age, both sexes, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, histologically proven cancer, receiving oxaliplatin regimen, and also these patients did not have previous neuropathy history, polymyositis. Patients were treated with FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) or XELOX (capecitabine plus oxaliplatin) regimen. In FOLFOX regimen, patients received oxaliplatin, 85 mg/m^2 every 2 weeks for 12 courses and in XELOX regimen, 130 mg/m^2 every 3 weeks for 6–8 courses. Some patients received additional molecular-targeted therapies concurrent with the oxaliplatin, such as an antibody vascular endothelial growth factor (VEGF) and an anti-epidermal growth factor receptor (EGFR) drug.

Exclusion criteria were as follows: diabetes mellitus (DM), unstable psychological conditions, previous platinum-based or neurotoxic chemotherapy, patients with brain or leptomeningeal metastasis, history of alcohol dependency or concurrent use of other drugs known to influence serotonin levels, use of antiepileptics, antidepressants, or lithium, and use of opioids (concomitant use of selected analgesics like nonsteroidal anti-inflammatory drugs was allowed). In addition, patients with gamma-glutamyl transferase (GGT) and bilirubin elevation due to diffuse liver metastasis were not included in the study.

Assessment of neurotoxicity

Diagnosis of OIPN was evaluated based on symptom history, loss of deep tendon reflexes, and the presence of symmetrical "stocking-glove" numbness and burning–tingling after chemotherapy. While getting chemotherapy, all visits afterwards and post-treatment evaluation for sensorial neurotoxicity was evaluated based on the form of the neuropathic pain symptom inventory (NPSI). OIPN was assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.03 grading scale (0 = normal; 1 = asymptomatic, weakness on physical examination, loss of reflexes, or paresthesias not interfering with daily function; 2 = weakness and sensory alterations interfering with daily function; 3 = weakness and sensory alterations interfering with activities of daily living or requiring bracing or assistive devices; and 4 = life threatening, paralysis, disabling). Patients were divided into two groups: cases with grade 0–1 (G0–G1) neuropathy and cases with grade 2–3 (G2–G3) neuropathy. The relationship between the severity of neuropathy and clinicopathological factors was investigated.

Data collection

Age, sex, height, weight, body mass index, body surface area (BSA), diagnosis, treatment period, ECOG performance status, pathological, and laboratory data were obtained from patient files and hospital automation system. Pre-treatment, sodium, potassium, magnesium, calcium, urea, creatinine, albumin, glucose, GGT, bilirubin, low density lipoprotein cholesterol, triglyceride, folate, vitamin B12, vitamin D, C reactive protein, uric acid levels and white blood cell, lymphocytes, neutrophils, hemoglobin (Hgb), hematocrit, platelet, mean platelet volume values, and blood groups were recorded. Hematological toxicities secondary to chemotherapy developed during 6 months of treatment were determined.

Statistical analysis

The normal distribution of the data was tested using the one-sample Kolmogorov–Smirnov test. Continuous variables are presented as mean ± SD. Categorical variables are presented as counts. All statistical comparisons were performed using the two-sided Student's *t* test. Categorical variables were compared using the Chi-square test or Fisher exact test for small samples. Multivariate logistic regression model was performed to determine the effect of parameters for neuropathy. To evaluate the diagnostic accuracy, we carried out receiver

operating characteristic (ROC) curve analysis. ROC curves were plotted to see the power of parameters to differentiate the grade 0–1 neuropathy from grade 2–3 neuropathy. The area under the curve (AUC) was then estimated with 95% confidence interval. Values of $p < 0.05$ were considered to be statistically significant. The statistical analyses were performed using the SPSS 20.0 software (SPSS, Chicago, IL, USA) for Windows.

Results

Of the 230 patients evaluated, 186 patients who met the study criteria were included in the study. In this study, 56% of the cases were male patients (104/186) and 44% were female patients (82/186). Baseline clinical characteristics of all study patients are listed in Table 1.

There were 108 (58%) patients in the G0–G1 neuropathy group (mean age 50.5 ± 10.2; 63% men), and 78 (42%) patients in the G2–G3 neuropathy group (mean age 58.0 ± 11.5; 46.2% men). No grade 4 peripheral neurotoxicity was observed in any patient. The relationship between G2–G3 OIPN and age ($p < 0.001$) and gender ($p = 0.02$) was statistically significant. Sixty-eight (36.6%) patients received treatment in winter, while 118 (63.4%) patients received treatment in summer. There was no correlation between the groups in terms of season of treatment and development of G2–G3 neuropathy ($p = 0.09$). While 61% of the patients in the low-risk group had ECOG performance status of 0, approximately 60% of the patients in the high-risk group consisted of patients with ECOG performance status 1, which was statistically significant ($p = 0.007$). There was a significant relationship between the height of the patients ($p < 0.001$) and BSA ($p = 0.005$) and the development of G2–G3 neuropathy, but no correlation was found between body mass index. Patients in the G2–G3 group were shorter and had lower BSA. In the G2–G3 group, serum GGT ($p < 0.001$) and glucose ($p = 0.007$) levels were higher, whereas vitamin D ($p < 0.001$), hemoglobin ($p < 0.001$), hematocrit ($p < 0.001$), serum albumin ($p = 0.001$), and serum magnesium ($p = 0.035$) levels were lower compared with the G0–G1 group.

The clinicopathological features of the patients in the G2–G3 and G0–G1 groups are shown in Table 2. There was no difference between primary tumor location, T stage, stage, and tumor diameter between groups, whereas lymph node involvement was higher in G0–G1 group. In addition, 92% of the patients in the G0–G1 group had adenocarcinoma pathologically, only 1.9% had mucinous carcinoma type, but the rate of mucinous carcinoma was 20% in the G2–G3 group ($p < 0.001$).

The relationship between the treatment received by the patients and hematologic toxicities and the development of peripheral neuropathy is shown in Table 3. A total of 162 patients (87%) were treated with FOLFOX-based regimen, while 24 patients were treated with XELOX (13%) regimen. There was no correlation between neuropathy development and treatment regimens ($p = 0.739$). In addition to these regimens, 62 (33%) patients received target-aimed drugs. There was no difference between G0–G1 neuropathy and G2–G3 neuropathy in patients taking these drugs ($p = 0.248$). In the same way, there was no relationship between treatment with adjuvant treatment or metastatic stage treatment and previous chemotherapy experience with neuropathy development. Neutropenia and thrombocytopenia due to medications used during treatment were not found to be significantly correlated with neuropathy, whereas G2–G3 neuropathy was more observed in patients with treatment-related anemia ($p = 0.003$).

The results of multivariate logistic regression analysis for each of the independent predictors are presented for G2–G3 neuropathy in Table 4. Age, histopathology, GGT, vitamin D, and Hgb levels were related to G2–G3 neuropathy in the study groups.

A comparison of the ROC curves with sensitivity, specificity, AUC, cut-off, and asymptotic significance of Hgb, serum albumin, GGT, magnesium, and vitamin D levels between the study groups is given in Table 5 and Fig. 1.

Discussion

In this study, we aimed to identify potential clinical parameters that can be easily obtained by pre-treatment clinicopathological evaluation and whole blood test to predict the development of peripheral neuropathy. In this study, the incidence of G2–G3 neurotoxicity in patients receiving oxaliplatin-based chemotherapy was 42% and consistent with previous reports [3, 4]. The probability of neuropathy increased significantly with age. In some previous studies, age and sex were not detected as a predictive marker, whereas in our study, the development of G2–G3 neuropathy was more common in female patients [3, 13, 16, 17].

In our study, we observed that the risk of peripheral neuropathy decreased as height and BSA increased, and a finding consistent with the fact that oxaliplatin was first removed by dispensing into tissues [18]. Unlike height, body weight was not an informative factor; furthermore, BMI did not predict neuropathy as effectively as the BSA. In a study conducted in the literature, while weight and BSA were not a predictive factor for neuropathy [17], in another study, it was reported that the risk of neuropathy decreased with increasing body weight and that length was not correlated with neuropathy [13]. In this study by Alejandro et al., BSA > 2.0 m^2 and higher BMI, which aimed to predict OIPN in cancer patients, was associated with neurotoxicity in univariate analysis, and BSA > 2.0 m^2 was shown as an independent risk factor. It can be considered that chemotherapy doses are calculated according to BSA, so the larger the BSA, the higher the doses of neurotoxic drugs, and the observed effect of BSA and BMI on neuropathy may be due to this situation. In our patient population, there were only 7

Table 1 Baseline characteristics and laboratory measurements of the study population

Variables	Grade 0–1 neuropathy, $n = 108$	Grade 2–3 neuropathy, $n = 78$	p
Age (years)	50.5 ± 11.5	58.0 ± 10.8	< 0.001
Gender (F/M)	40/68	42/36	0.02
BSA (m^2)	1.77 ± 0.18	1.69 ± 0.16	0.005
BMI	24.9 ± 4.4	26.0 ± 5.3	0.131
Height (centimeter)	167.4 ± 11.5	161.2 ± 6.8	< 0.001
Winter/non-winter	34/74	34/44	0.09
ECOG (0/1)	66/42	32/46	0.007
Laboratory			
Creatinine (mg/dl)	0.72 ± 0.34	0.79 ± 0.38	0.191
eGFR (ml/min)	124 ± 38	103 ± 40	0.404
WBC count (μl)	7345 ± 2041	7940 ± 2919	0.111
Hemoglobin (g/dl)	12.4 ± 1.2	11.1 ± 1.3	< 0.001
Hematocrit	38.4 ± 3.9	35.4 ± 3.6	< 0.001
Lymphocyte count (μl)	1596 ± 585	1824 ± 994	0.058
Neutrophil count (μl)	4950 ± 1801	5152 ± 2616	0.543
Neutrophil-to-lymphocyte ratio	3.62 ± 2.1	3.73 ± 3.3	0.079
Platelet count (10^3/μl)	332 ± 130	381 ± 176	0.36
MPV	8.2 ± 1.0	8.1 ± 0.8	0.783
CRP (mg/L)	9.8 ± 13.2	16.9 ± 30.4	0.070
Uric acid (mg/dl)	4.7 ± 1.2	4.6 ± 1.6	0.693
Vitamin D (ng/mL)	17.2 ± 11.4	10.2 ± 7.2	< 0.001
Serum albumin (g/dL)	4.10 ± 0.4	3.90 ± 0.3	0.001
GGT (U/L)	37 ± 28.1	69 ± 61.6	< 0.001
Total bilirubine (mg/dl)	0.5 ± 0.38	0.4 ± 0.45	0.119
Glucose (mg/dl)	104 ± 41	120 ± 35	0.007
Triglyceride (mg/dl)	164 ± 57	169 ± 43	0.659
LDL-C (mg/dl)	117 ± 42	114 ± 38	0.670
Calcium (mg/dl)	9.21 ± 0.57	9.20 ± 0.67	0.066
Magnesium (mg/dl)	2.06 ± 0.2	1.93 ± 0.4	0.035
Sodium (mEq/L)	139 ± 3.3	138 ± 3.6	0.056
Potassium (mEq/L)	4.4 ± 0.54	4.4 ± 0.56	0.828
Vitamin B_{12}	398 ± 263	337 ± 171	0.121
Folate acid	11.1 ± 6.4	10.8 ± 6.9	0.168
Blood groups (A/non-A) − (*n*)	44/52	32/44	0.453
Rh +/ Rh − (*n*)	92/4	72/4	0.735
Comorbidity			
CAD (%)	4 (3.7)	8 (10.3)	0.730
Hypertension (%)	18 (16.7)	18 (23.1)	0.275
Dyslipidemia (%)	10 (9.3)	4 (5.1)	0.292

BSA, body surface area; *BMI*, body mass index; *ECOG*, Eastern Cooperative Oncology Group; *MPV*, mean platelet volume; *eGFR*, estimated glomerular filtration rate; *GGT*, gamma-glutamyl transferase; *CRP*, C reactive protein; *LDL-C*, low density lipoprotein cholesterol; *WBC*, white blood cell; *CAD*, coronary artery disease

patients with BSA > 2 m^2, and drug doses of these patients were calculated according to 2. In addition, the physical activity level of the patients was not assessed in this study. Evidence in the literature has shown that exercise plays an important role in reducing peripheral neuropathy caused by chemotherapy [19, 20]. Perhaps in previous studies, they had a lower level of physical activity, although this should be confirmed in patients with a higher BMI.

The incidence of OIPN was higher in anemic patients ($p < 0.001$) and those with low levels of albumin ($p = 0.001$) and magnesium ($p = 0.035$) before treatment. Very few data are available on the possible relationship between anemia or

Table 2 The clinicopathological features of patients of the grade 0–1 neuropathy and grade 2–3 neuropathy groups

Variables	Grade 0–1 neuropathy, *n* (%)	Grade 2–3 neuropathy, *n* (%)	*p*
Origin			
Rectum	30 (27.8)	18 (23.1)	0.120
Colon	58 (53.7)	52 (66.7)	
Gastric	16 (14.8)	4 (5.1)	
Pancreas	4 (3.7)	4 (5.1)	
T			
2	4 (4.1)	6 (8.1)	0.093
3	66 (67.3)	38 (51.4)	
4	28 (28.6)	30 (40.5)	
Lenf node			
0/1–3	10 (10.9)/82 (89.1)	24 (31.6)/52 (68.4)	0.061
Stage			
2–3	60 (55.6)	44 (56.5)	0.190
4	48 (44.4)	34 (43.6)	
Tumor size, mm	5.1 ± 2.2	5.3 ± 2.0	0.755
Histopathology			
Adenocarcinoma	100 (92.6)	58 (74.4)	< 0.001
Ringed cell carcinoma	6 (5.6)	4 (5.1)	
Mucinous carcinoma	2 (1.9)	16 (20.5)	

serum albumin levels and the development of peripheral neuropathy. Bosman et al. investigated the symptoms and signs of peripheral neuropathy in a total of 27 T1DM patients with diabetic neuropathy and reported that the anemia group had a more severe thermal perception than the non-anemia group. In addition, they found that severe ankle reflex, vibration sensation, and pinprick sensation were more severe in the anemia group [21]. In this study, the incidence of neuropathy was significantly higher also in patients with anemia during treatment. Pre-treatment anemia and hypomagnesemia were associated with OIPN in 2 studies in the literature on patients receiving oxaliplatin [3, 16]. In the study by Vincent et al., hypoalbuminemia was found to be a clinical predictive factor consistent with our study [3]. The role of magnesium supplementation in the prevention of peripheral neuropathy with different etiologies has been extensively investigated.

Table 3 The treatment modalities and toxicities of patients of the grade 0–1 neuropathy and grade 2–3 neuropathy groups

Variables	Grade 0–1 neuropathy, *n* (%)	Grade 2–3 neuropathy, *n* (%)	*p*
Regimen			
FOLFOX/CapeOX	94 (87)/14 (13)	68 (88.2)/10 (12.8)	0.739
Molecular-targeted therapy			
Yes/no	32 (30.2)/74 (69.8)	30 (38.5)/48 (61.5)	0.243
Original lesion			
Removed/remnant	84 (77.8)/24 (22.2)	72 (92.3)/6 (7.7)	0.008
Toxicities during treatment			
Neutropenia (yes/no)	64 (64)/36 (36)	40 (67.1)/30 (42.9)	0.180
Anemia (yes/no)	42 (42)/58 (58)	44 (62.99/26 (37.1)	0.003
Trombositopenia (yes/no)	46 (46)/54 (54)	32 (45.7)/38 (54.3)	0.122
Treatment			
Adjuvant	64 (59.3)	48 (61.5)	0.754
Metastatic	44 (40.7)	30 (38.5)	
Previously chemotherapy			
Yes	18 (16.7)	14 (17.9)	0.819
No	90 (83.3)	64 (82.1)	

FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; *CapeOX*, capesitabin plus oxaliplatin

Table 4 Multivariable logistic regression analyses with independent predictors of grade 2–3 neuropathy

Variables	Multivariable analysis	
	OR (95% CI)	*p*
Age	0.062 (1.006–1.126)	0.031
Gender	− 1.311 (0.070–1.042)	0.057
BSA	− 0.055 (0.010–26.706)	0.745
ECOG	0.794 (0.119–1.723)	0.245
Histopathology (mucinous carcinoma)	− 0.732 (0.253–0.913)	0.025
GGT, U/L	0.038 (1.017–1.061)	<0.001
Hemoglobin (g/dl)	− 0.954 (0.213–0.698)	0.003
Vitamin D, ng/mL	− 0.110 (0.834–0.962)	< 0.001
Serum albumin (g/dL)	1.355 (0.635–23.684)	0.142
Glucose (mg/dl)	0.007 (0.995–1.018)	0.268
Magnesium (mg/dl)	− 0.146 (0.202–3.696)	0.843

BSA, body surface area; *ECOG*, Eastern Cooperative Oncology Group; *GGT*, gamma-glutamyl transferase

Administration of intravenous CaMg before and after oxaliplatin has been the most studied approach for the prevention of OIPN, and Gamelin et al. claimed that it was effective in preventing OIPN in a retrospective study of 161 patients. These findings were supported by the hypothesis that the reason for the difference between the neurotoxicity of oxaliplatin and cisplatin was that oxalate was metabolized from oxaliplatin and known to chelate Ca and Mg, elements involved in the function of ion channels in nerve membranes [22]. This was supported in particular by a randomized controlled study of Grothey et al. [23] and a retrospective study by Knijn et al. [24]. However, Ishibashi et al. [25] and Loprinzi et al. [26] did not show a beneficial effect of CaMg infusions.

Neuropathy develops in up to 50% of patients with DM, and its probability is associated with both duration and severity of DM [27]. Retrospective analysis in the literature shows that the presence of DM is not associated with an increased risk of developing peripheral sensory neuropathy in patients receiving oxaliplatin therapy [3, 16, 28]. It should be noted, however, that diabetic patients registered in these series are newly diagnosed patients who receive diabetic or antidiabetic treatment, and therefore, serum glucose levels generally remain within the normal range. Patients with a previous diagnosis of diabetes and a history of peripheral neuropathy were not included in our study. However, pretreatment fasting blood glucose levels were statistically higher in G2–G3 neuropathy group.

GGT is a membrane-dependent enzyme involved in the extracellular catabolism of the antioxidant glutathione (GSH). GGT hydrolyses the gamma glutamyl linkage between glutamic acid and cysteine, which is the first step in the extracellular hydrolysis of GSH, and induces the formation of cysteine required for the resynthesis of GSH in the cell [29]. In the event of exposure to oxidative stress, the link between Ras-mitogen-activated protein kinase (MAPK) pathways and GGT expression has been shown [30]. Reactive oxygen species have been implicated in the process of carcinogenesis, and the redox regulation of many genes in response to ROS seems to modulate GGT expression [31]. Data on the possible relationship between serum GGT level and the development of peripheral neuropathy are not available in the literature. In this study, one of the most effective factors in predicting the development of G2–G3 neuropathy was serum GGT level. Increased levels of GGT may be the result of a defense mechanism against oxidative stress.

In the literature, low serum vitamin D is commonly found in multiple myeloma patients treated with bortezomib and/or thalidomide and has been associated with severe neuropathy [32]. In another study, vitamin D was significantly lower in patients receiving paclitaxel in the group in which

Table 5 Sensitivity, specificity, AUC, cut-off, and asymptotic significance of Hgb, Serum albumin, GGT, magnesium, and vitamin D in study group

Variables	Sensitivity (%)	Specificity (%)	AUC	Cut-off	*p*
Hemoglobin	65.7	70.4	0.754	12.2	< 0.001
Serum albumin	51.4	77.8	0.661	4.05	0.002
GGT	64.9	79.6	0.685	46	< 0.001
Magnesium	82.9	25.9	0.599	1.9	0.058
Vitamin D	74.3	59.3	0.701	9.05	< 0.001

AUC, area under the curve; *Hgb*, Hemoglobin; *GGT*, gamma-glutamyl transferase

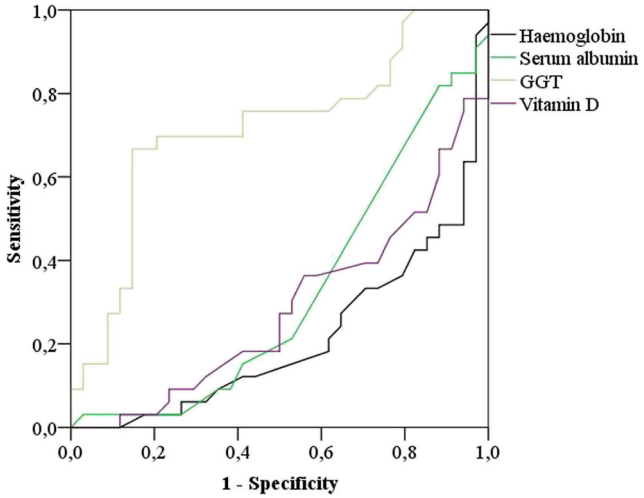

Fig. 1 Receiver operating characteristic curves for hemoglobin, serum albumin, GGT, and vitamin D in study groups

chemotherapy-associated neuropathy (CIPN) was observed. In this study, it was argued that vitamin D supplementation before chemotherapy may be an effective neuroprotective in CIPN prophylaxis [33]. In our study, vitamin D was found to be low in most patients, whereas vitamin D was significantly lower in the group with G2–G3 neuropathy development. Being one of the most effective factors predicting the G2–G3 neuropathy development, the relationship between OIPN and vitamin D has been shown for the first time.

In this study, although the number of patients with mucinous carcinoma type was low, 88% of the patients with this pathological type had G2–G3 neuropathy. In addition, primary tumor was removed in 92% of patients with high-grade neuropathy. Neuropathy was more likely to develop in operated patients than non-operated patients. This may be related to postoperative nutritional and electrolyte disturbances and anemia.

This study has several limitations. These limitations include the retrospective design of the study, the number of patients, and the absence of a uniform cancer type.

Conclusion

In conclusion, this study demonstrated that age, histopathologic type, GGT, glucose, albumin, vitamin D, and Hgb levels were the effective factors in prediction of the development of OIPN. In addition, vitamin D, GGT, and Hgb levels were the most effective factors to predict development of OIPN. Further comprehensive, prospective, and randomized controlled clinical trials are warranted to confirm our results for clinical practice.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Independent Ethics Committee of Firat University, Medical Faculty.

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