



# Chemotherapy-Induced Polyneuropathy and Neurofilaments

Olga A. Tikhonova<sup>1</sup>, Evgeniia S. Druzhinina<sup>2</sup>, Dmitry S. Druzhinin<sup>3</sup>

<sup>1</sup>Immanuel Kant Baltic Federal University, Kaliningrad, Russia;

<sup>2</sup>Pirogov Russian National Research Medical University, Moscow, Russia;

<sup>3</sup>Sechenov First Moscow State Medical University (Sechenov University), Russia, Moscow

## Abstract

**Introduction.** Chemotherapy (CT) with platinum and taxane drugs often leads to chemotherapy-induced peripheral neuropathy (CIPN), which significantly impairs patients' quality of life. CIPN is diagnosed based on symptoms and neurological examination, which underscores the need for objective biomarkers.

Promising criteria for peripheral nerve damage are neurofilaments, in particular the light chain (NfL) and peripherin. NfL is released during axonal damage but is not specific to the peripheral nervous system. Peripherin, in contrast, is expressed exclusively in peripheral neurons and is considered a more specific marker; however, its detection is challenging.

**The aim** of the study was to evaluate serum levels of neurofilament and peripherin using the ELISA method in patients with solid tumors undergoing CT.

**Materials and methods.** The study included 66 patients with newly diagnosed solid tumors before starting CT with platinum or taxanes. Patients with known risk factors for polyneuropathy and those taking medications with neurotoxic effects were excluded. After treatment, 51 patients were examined. Neurological examination with assessment using the NCI-CTCAE and NDS scales, nerve conduction study (SRAR index, amplitude of the sural nerve action potential), and assessment of intraepidermal nerve fiber density were performed. Serum levels of NfL and peripherin were measured using ELISA before and approximately 4.5 months after CT. Preanalytical sample processing was standardized.

**Results.** After the CT course all patients showed a significant increase in NfL levels ( $p < 0.0003$ ). The most pronounced increase in the indicator (~fivefold) was recorded in male patients ( $p < 0.001$ ) and in the group of patients with malignant neoplasms in the gastrointestinal tract ( $p = 0.001$ ). The concentration of peripherin in all analyzed samples was zero, likely due to the low ELISA sensitivity. In patients with developed CIPN, the NfL level after treatment was significantly higher ( $p = 0.001$ ); however, no prognostic value for predicting neuropathy was found ( $AUC = 0.526$ ;  $p = 0.803$ ). At the same time, a moderate negative correlation was found between the NfL level and the density of intraepidermal nerve fibers ( $r = -0.416$ ;  $p = 0.012$ ). No statistically significant association was found between NfL concentration and electrophysiological parameters (SRAR index and sural nerve action potential amplitude).

**Conclusion.** NfL is a promising but insufficiently specific biomarker for monitoring patients with CIPN. The absence of a detectable level of peripherin by ELISA limits its clinical application and suggests the use of more sensitive analytical methods.

**Keywords:** chemotherapy-induced peripheral neuropathy; cancer; biomarker; neurofilaments; peripherin

**Ethics approval.** All patients provided their written informed consent to participate in the study. The study protocol was approved by the Independent Ethics Committee of the Clinical Research Center at Immanuel Kant Baltic Federal University (Protocol No. 35 dated October 27, 2022) and met the Helsinki Declaration principles.

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**For correspondence:** 14 A. Nevskiy Str., Kaliningrad, Russia, 236041. Immanuel Kant Baltic Federal University.  
E-mail: [offelia78@mail.ru](mailto:offelia78@mail.ru). Olga A. Tikhonova.

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# Химиоиндуцированная полинейропатия и нейрофиламенты

О.А. Тихонова<sup>1</sup>, Е.С. Дружинина<sup>2</sup>, Д.С. Дружинин<sup>3</sup>

<sup>1</sup>Балтийский федеральный университет имени Иммануила Канта, Калининград, Россия;

<sup>2</sup>Российский национальный исследовательский медицинский университет имени Н.И. Пирогова, Москва, Россия;

<sup>3</sup>Первый Московский государственный медицинский университет имени И.М. Сеченова (Сеченовский Университет), Москва, Россия

## Аннотация

**Введение.** Химиотерапия (ХТ) препаратами платины и таксанами часто приводит к развитию химиоиндуцированной полинейропатии (ХИПН), которая значительно ухудшает качество жизни пациентов. Диагностика ХИПН основана на симптомах и неврологическом осмотре, что подчеркивает необходимость в объективных биомаркерах.

Перспективными критериями повреждения периферических нервов являются нейрофиламенты, в частности лёгкая цепь (NfL) и периферин. NfL высвобождается при аксональном повреждении, но не специфичен для периферической нервной системы. Периферин, напротив, экспрессируется исключительно в периферических нейронах и считается более специфичным маркером, однако его детекция затруднена. **Цель** исследования – оценить уровни сывороточных нейрофиламента и периферина методом ELISA у пациентов с солидными опухолями на фоне ХТ.

**Материалы и методы.** Включено 66 пациентов с впервые диагностированными солидными опухолями перед началом ХТ препаратами платины или таксанов. Исключались пациенты с известными факторами риска развития полинейропатии и приёмом лекарственных препаратов с нейротоксическим действием. После лечения обследован 51 пациент. Проводились неврологический осмотр с оценкой по шкалам NCI-CTCAE и NDS, электромиография (индекс SRAR, амплитуда потенциала действия икроножного нерва), оценка плотности интраэпидермальных нервных волокон. Уровни NfL и периферина в сыворотке измеряли методом ELISA до и через ~4,5 мес после ХТ. Преаналитическая обработка образцов стандартизирована.

**Результаты.** После курса ХТ у всех пациентов наблюдалось значительное повышение уровня NfL ( $p < 0,0003$ ). Наиболее выраженный рост показателя (~ пятикратный) был зафиксирован у пациентов мужского пола ( $p < 0,001$ ) и в группе пациентов с локализацией злокачественного новообразования в желудочно-кишечном тракте ( $p = 0,001$ ). Концентрация периферина во всех проанализированных образцах оказалась нулевой, вероятно из-за низкой чувствительности иммуноферментного анализа. У пациентов с развившейся ХИПН уровень NfL после лечения был достоверно выше ( $p = 0,001$ ), однако не выявлено прогностической ценности для предсказания развития нейропатии ( $AUC = 0,526$ ;  $p = 0,803$ ). При этом обнаружена умеренная отрицательная корреляция между уровнем NfL и плотностью интраэпидермальных нервных волокон ( $r = -0,416$ ;  $p = 0,012$ ). Статистически значимой связи между концентрацией NfL и электрофизиологическими параметрами (индекс SRAR и амплитуда потенциала действия икроножного нерва) не установлено.

**Заключение.** NfL является перспективным, но недостаточно специфичным маркером для наблюдения за пациентами с ХИПН. Отсутствие детектируемого уровня периферина методом иммуноферментного анализа ограничивает его применение в клинике и предполагает использование более чувствительных методов анализа.

**Ключевые слова:** химиоиндуцированная полинейропатия; рак; биомаркер; нейрофиламенты; периферин

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**Адрес для корреспонденции:** 236041, Россия, Калининград, ул. А. Невского, д. 14. Балтийский федеральный университет им. И. Канта. E-mail: offelia78@mail.ru. Тихонова О.А.

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## Introduction

Platinum-based drugs and taxanes are widely used in the treatment of malignant neoplasms, especially solid tumors. However, their use is often associated with chemotherapy-induced polyneuropathy (CIPN), the pathogenesis of which is complex and can be exacerbated by underlying diseases, paraneoplastic processes, and endogenous toxins. This complication can persist and progress even after completion of therapy, significantly worsening patients' long-term quality of life [1–5].

The diagnosis of CIPN is primarily based on symptom analysis and neurological examination, highlighting the need for objective and quantitative assessment methods. However, nerve conduction study (NCS) can only confirm damage to thick fibers, while invasive skin biopsy remains the gold standard for diagnosing small fiber neuropathy. These methods are labor-intensive and not always applicable in routine oncological practice. This stimulates the search for simpler and more accessible methods for diagnosing and predicting CIPN.

Particular interest lies in biomarkers capable of objectively reflecting the degree of peripheral nervous system damage [6–8], with neurofilaments being the most promising among them. They shape the neuronal cytoskeleton and are expressed exclusively in neurons. Modern neuroscience focuses greatest interest on neurofilament light chain (NfL) and peripherin in peripheral nervous system lesions, as they unlike medium and heavy subunits are decisive in polymerizing peripheral neuron filaments and shaping their structure. During neuronal and axonal damage, they are released into the extracellular space and blood [9].

Recent studies have shown that serum NfL levels increase during chemotherapy (CT) with platinum and taxanes, correlating with neuropathy severity [6–14]. Meanwhile, concentration returns to normal several months after treatment completion, potentially indicating halted damage progression and possible regeneration [15, 16]. However, unlike peripherin, NfL level may increase.

Peripherin, as a type III intermediate filament protein, plays a crucial role in neuronal growth and stability, axonal transport, and myelination. It demonstrates greater specificity in peripheral nervous system lesions, being expressed exclusively in peripheral neurons, and has recently emerged as a specific marker of axonal damage [17, 18]. In the study by S. Keddie et al., peripherin levels exceeded those of NfL in peripheral nervous system lesions [19]. However, its clinical application is limited by detection challenges, necessitating further research [20].

The study aimed to evaluate serum levels of NfL and peripherin biomarkers using ELISA in patients receiving chemotherapy for solid malignant neoplasms.

## Materials and Methods

The study was conducted in 2023–2024 in accordance with the ethical principles of the World Medical Association's

Helsinki Declaration and approved by the Independent Ethics Committee of the Immanuel Kant Baltic Federal University Center for Clinical Research (Protocol No. 35 dated October 27, 2022).

The study included 66 patients aged >18 years of age with newly diagnosed solid tumors, scheduled for planned neurotoxic CT using platinum-based and taxane-based treatment regimens. Exclusion criteria were complaints indicating peripheral nerve damage at the time of study inclusion; concomitant diseases and pathological conditions that might induce polyneuropathy (PNP); and the use of medications with potential neurotoxic effects. After CT, 51 patients were followed up; 15 patients withdrew from the study at the second visit and were subsequently excluded from the final analysis.

Platinum-based CT was administered to 35 patients (68.6%): oxaliplatin – 23 patients with gastrointestinal tract (GIT) cancer, cisplatin – 6 with respiratory system cancer and 6 with pelvic cancer; taxane-based chemotherapy – 16 patients (31.4%) (paclitaxel/docetaxel, predominantly for pelvic cancer).

All patients underwent neurological examination assessing neurotoxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE) scale and neuropathy severity using the Neuropathy Disability Score (NDS); NCS employing the SRAR (Sural/Radial Ratio) index and sural nerve action potential amplitude as highly sensitive and specific neurophysiological markers [21]; and intraepidermal nerve fiber density evaluation (IENFD) [22]. NfL and peripherin concentrations were measured in blood serum at baseline and at  $4.50 \pm 1.02$  months post-CT. Blood was collected followed by centrifugation at 1000g for 20 minutes at room temperature to obtain serum. The obtained serum was carefully aspirated to avoid cellular elements and aliquoted into 500  $\mu$ L volumes in low-adhesion Eppendorf tubes to minimize protein loss. Aliquoted samples were immediately frozen at  $-80^\circ\text{C}$  and stored until analysis. The entire preanalytical processing was strictly controlled, with documentation of time intervals and storage conditions to ensure result reproducibility.

Levels of NfL and peripherin were determined using solid-phase sandwich ELISA, employing Cloud-Clone Corp. test systems on a Bio-Rad 680 microplate photometer (Bio-Rad Laboratories). Optical density was measured at 450 nm.

Statistical processing was conducted using StatTech v. 4.2.8 (Stattech) and GraphPad Prism v. 9.3.1 (Insightful Science) software packages. Quantitative indicators were evaluated for normality of distribution using the Shapiro-Wilk test.

In cases of non-normal distribution, quantitative data were described using the median (Me) and lower and upper quartiles [ $Q_1$ ;  $Q_3$ ].

Group comparisons employed the Kruskal–Wallis, Wilcoxon, Pearson's  $\chi^2$  tests, and ROC analysis. Correlation analysis between two quantitative indicators was performed using Spearman's rank correlation coefficient (for non-normally

distributed indicators). A predictive model characterizing the dependence of a quantitative variable on factors was developed using linear regression. Differences were considered significant at  $p < 0.05$ .

## Results

A total of 51 patients completed the study: 23 with GIT cancer, 22 with pelvic cancer, and 6 with respiratory system cancer; the majority were women ( $n = 33$ ; 65%). The median age was 60 years, with 28 patients (55%) over 60 years old. The average disease duration from diagnosis to study inclusion was 6.06 months.

CIPN developed in 36 cases (70%). The neurological presentation corresponded to classic distal symmetric polyneuropathy. Sensory disturbances were the predominant clinical component, documented in 36 patients (71%). Motor deficits were rare ( $n = 3$ ; 6%), manifesting as diminished or absent Achilles and brachioradial reflexes. Autonomic dysfunction symptoms (e.g., sweating abnormalities) were observed in 12 patients (24%).

Patients were stratified by neurotoxicity grade using the NCI-CTCAE scale according to primary tumor site (Table 1).

The presented data indicate that the groups predominantly comprised patients with grade 1–2 NCI-CTCAE neurotoxicity. Nine patients showed no signs of neurotoxicity; patients with pelvic cancer prevailed. The highest frequency of neurotoxicity (any grade) was observed in GIT cancer (91.3%), and the lowest in the pelvic cancer (72.7%). No cases of grade 3–4 severity were recorded. Analysis of PNP severity according to the NDS scale, depending on tumor site and corresponding therapy, is presented in Table 2.

PNP was mostly moderate in all groups, particularly in pelvic cancer (68.2%). Severe PNP was more frequent in GIT tumors, though this was not statistically significant.

Serum analysis before and after CT revealed undetectable peripherin levels. The median serum NfL level increased significantly from 94.22 [33.24; 152.36] pg/mL before CT to 143.98 [87.91; 222.47] pg/mL after treatment ( $p < 0.0003$ ; Fig. 1).

NfL level changes showed dependence on the patient's sex: pre-CT levels were substantially lower in men ( $< 18.93$  pg/mL) compared to women (4.6-fold difference), but post-treatment analysis revealed a marked increase to 211.92 pg/mL specifically in male patients ( $p < 0.001$ ; Fig. 2).

Analysis of NfL level changes depending on the tumor site showed the most pronounced increase in NfL (~5-fold) specifically in patients with gastrointestinal cancer ( $p = 0.001$ ), unlike other sites (Table 3).

To analyze the sensitivity and specificity of NfL as a diagnostic marker for CIPN, ROC analysis was performed (Fig. 3). The sensitivity and specificity of the obtained predictive model were 90.9% and 35.7%, respectively. The NfL threshold after CT at the cut-off point using Youden's index was 95.37 pg/mL (AUC = 0.526; 95% CI 0.321–0.731;  $p = 0.803$ ).

No significant association was found between post-chemotherapy NfL levels and prediction of CIPN. However, in CIPN patients ( $n = 36$ ), serum NfL concentrations differed significantly ( $p = 0.001$ ) before versus after chemotherapy: 56.64 [13.01; 120.82] vs. 133.23 [68.58; 266.19], respectively.

No statistical relationship was observed between NfL levels and SRAR index ( $r = -0.259$ ;  $p = 0.112$ ) or gastrocnemius nerve action potential amplitude ( $r = -0.163$ ;  $p = 0.322$ ), but a negative correlation was found with IENFD ( $r = -0.416$ ;  $p = 0.012$ ; Fig. 4).

## Discussion

Results of a prospective study showed a significant increase in serum NfL levels after chemotherapy ( $p < 0.0003$ ); the median level was 143.98 pg/mL, particularly in male patients ( $p < 0.001$ ) and in those with GIT cancer treated with platinum-based regimens ( $p < 0.001$ ). Our data are generally consistent with the results of the study by S.-H. Kim et al., where oxaliplatin was also used in patients with GIT cancer [10]. The observed discrepancy of higher NfL levels in their study (mean 373.4 pg/mL) can be explained by the lack of strict selection criteria, inclusion of patients with risk factors for peripheral neuropathy, and the use of a more sensitive analytical method on the Simoa platform.

**Table 1. Assessment of the severity of neurotoxicity after chemotherapy according to the NCI-CTCAE scale depending on cancer site,  $n$  (%)**

Neurotoxicity severity	Number of patients post-CT ( $n = 51$ )		
	GIT cancer	pelvic cancer	respiratory system cancer
Total	23	22	6
No manifestations	2 (8.7)	6 (27.3)	1 (16.7)
1	12 (52.2)	7 (31.8)	2 (33.3)
2	9 (39.1)	9 (40.9)	3 (50.0)
3	–	–	–
4	–	–	–

Table 2. Severity of PNP after chemotherapy according to the NDS scale depending on cancer site, *n* (%)

Neuropathy severity	Number of patients post-CT ( <i>n</i> = 51)			<i>p</i> = 0.535
	GIT cancer	pelvic cancer	respiratory system cancer	
No (0–4 points)	6 (26.1)	2 (33.3)	6 (27.3)	
Moderate (5–13 points)	12 (52.2)	3 (50.0)	15 (68.2)	
Moderate (5–13 points)	5 (21.7)	1 (16.7)	1 (4.5)	

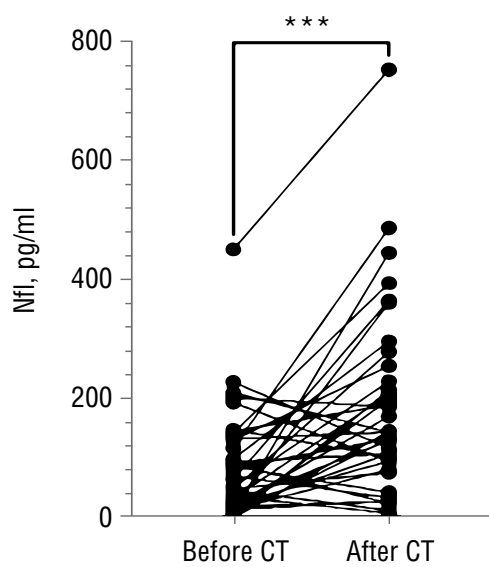


Fig. 1. Distribution of NfL before and after CT.

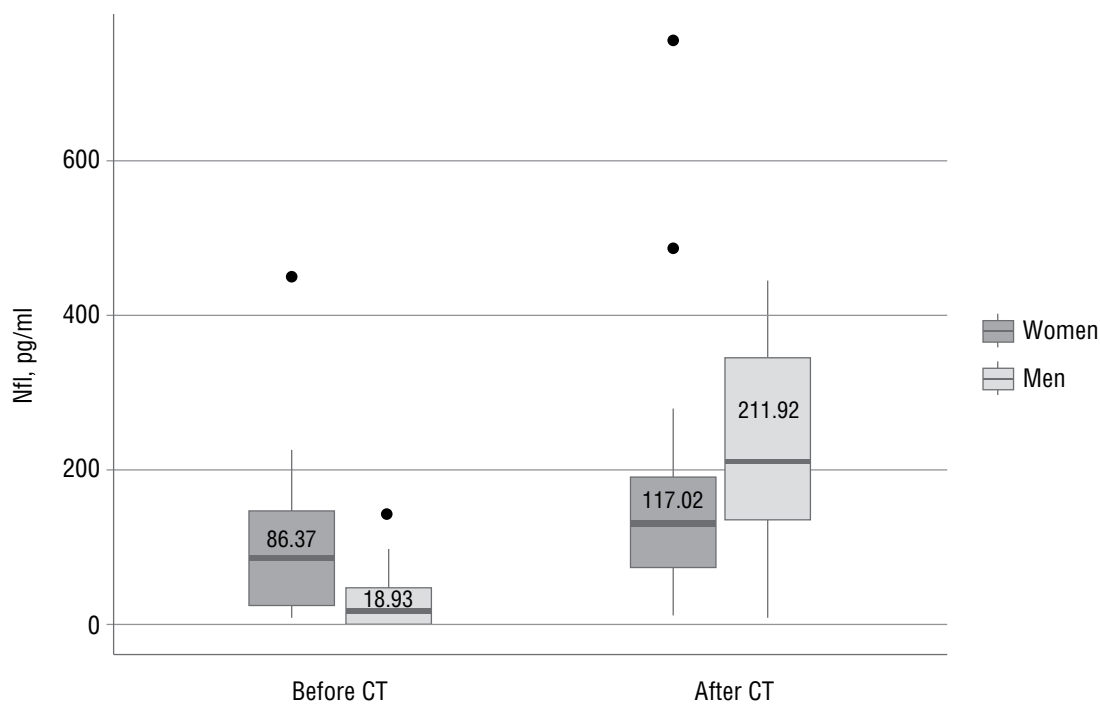
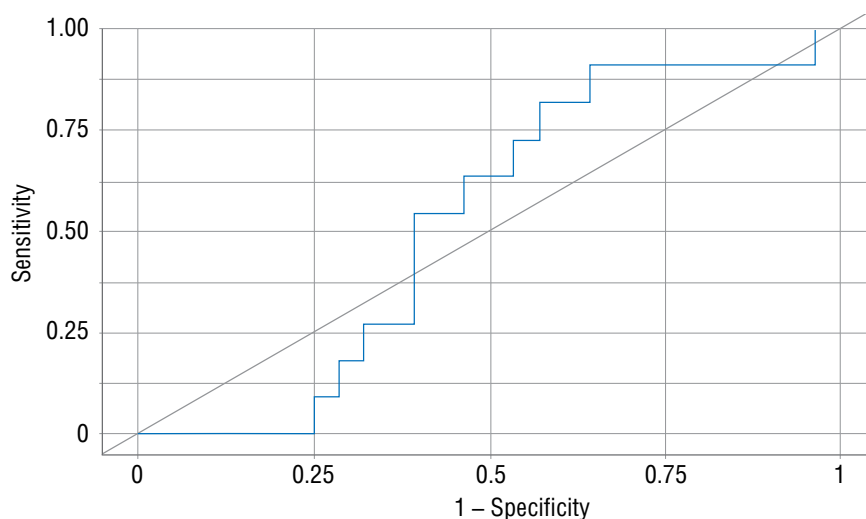


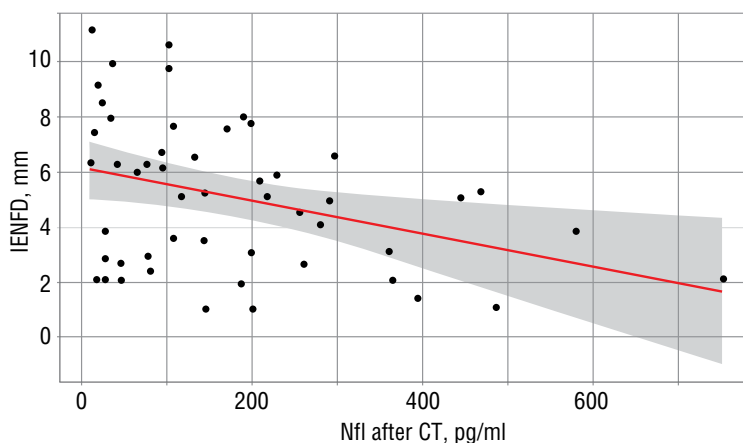
Fig. 2. Changes in NfL concentrations depending on the sex.

**Table 3. Changes in NfL levels (pg/mL) before and after CT depending on cancer site, median [Q<sub>1</sub>; Q<sub>3</sub>]**

Cancer site	Before CT	After CT	p*
GIT (n = 23)	41.13 [14.33; 87.53]	200.16 [107.60; 292.54]	< 0.001
Respiratory system (n = 6)	0.00 [0.00; 1.41]	133.43 [89.37; 139.66]	0.250
Pelvis (n = 22)	88.73 [40.44; 142.31]	112.40 [84.54; 178.70]	0.229



**Fig. 3. ROC analysis of sensitivity and specificity of NfL in CIPN.**



**Fig. 4. Negative correlation between NfL concentration and IENFD.**

Ultrasensitive single molecule array technology has enabled the detection of lower biomarker concentrations in serum compared to ELISA. However, this method has higher costs and limited availability in most medical institutions. The null result for peripherin in our study may be explained by concentrations below the detection threshold of ELISA using digital ELISA, unlike in previous studies [19], or by methodological limitations, for example, the selected antibodies in ELISA might not have captured serum peripherin.

Our data did not confirm changes in NfL levels in female patients with pelvic cancer, which contradicts the results of

other studies demonstrating the effect of taxane therapy on this indicator [6, 11]. This discrepancy may be associated not only with different research methodologies but also with the study design, specifically the time points, as well as the distinct mechanism of action of the neurotoxic agent, since platinum-based drugs primarily affect the neuron itself, while taxanes target microtubules [2, 23].

We also found no correlation with NCS data, unlike other studies [10], which may be explained by the absence of a more pronounced degree of neurotoxicity according to the NCI-CT-CAE scale and lower NfL concentrations in patients with grade

0–2, compared to previous research. NfL is a good screening marker for neuropathy due to its high sensitivity (85.7%), but it has low specificity (45.0%) and an AUC close to 0.5. Measuring NfL levels for severity monitoring may offer a significant advantage over NCS. Blood is frequently tested in cancer patients undergoing chemotherapy, unlike NCS, which is challenging to implement in daily practice, especially since electrophysiological changes may lag behind clinical manifestations and identify established axonal damage, whereas NfL levels can dynamically reflect this process. Thus, serum NfL can serve as a diagnostic biomarker for CIPN, as its significant association with this condition has been confirmed both in our study ( $p = 0.001$ ) and in other authors' work. However, more extensive studies are required to evaluate its prognostic value.

Our previous data demonstrated a significant reduction in IENFD after CT in patients with GIT cancer [22]. In the present study, we found that this reduction shows a significant negative correlation with increased NfL concentration. This finding is well explained by the cytotoxic mechanism of chemotherapeutic agents, which leads to nerve fiber degeneration. However, the absence of such correlation between NfL and IENFD in patients with idiopathic small fiber neuropathy, as demonstrated in the study by R. Baka et al. [24], indicates a distinct pathophysiology. This contradiction

underscores that the relationship between structural IENFD and biochemical (NfL) markers of nerve damage is not universal and depends on the etiology and mechanisms of neuropathy.

Our study had several limitations: small sample size ( $n = 51$ ); lack of a control group; short follow-up period with two control points; absence of long-term data on NfL changes after CT completion.

## Conclusion

Post-CT NfL is a promising, non-invasive, yet insufficiently specific CIPN biomarker. Its clinical application requires further investigation alongside clinical assessment and other biomarkers. Monitoring NfL levels during CT enables quantitative serial measurements with minimal patient burden and real-time tracking of ongoing neuronal damage, facilitating early CIPN prediction algorithms for personalized therapy. Extensive validation studies are needed to confirm the value of these data for both clinical trials and general practice. ELISA is less sensitive to changes in NfL and peripherin concentrations, while the implementation of highly sensitive analytical methods such as the Simoa platform immunoassay opens new avenues for its application.

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### Information about the authors

*Olga A. Tikhonova* – Cand. Sci. (Med.), senior lecturer, Department of psychiatry and neurosciences, Immanuel Kant Baltic Federal University, Kaliningrad, Russia, <https://orcid.org/0000-0002-1796-0193>

*Evgeniia S. Druzhinina* – Cand. Sci. (Med.), Associate Professor, Department of neurology neurosurgery and medical genetics named after acad. L.O. Badalyan, Institute of Neurosciences and Neurotechnology, N.I. Pirogov Russian National Research Medical University, Moscow, Russia, <https://orcid.org/0000-0002-1004-992X>

*Dmitry S. Druzhinin* – Dr. Sci. (Med.), deputy chief physician for research and innovation, University Clinical Hospital No. 3, First Moscow State Medical University (Sechenov University), Moscow, Russia, <https://orcid.org/0000-0002-6244-0867>

**Author contribution:** *Tikhonova O.A.* – conducting scientific research, analysing and interpreting the data, writing the text of the article; *Druzhinina E.S.* – analysis and interpretation of the data, writing the text of the article; *Druzhinin D.S.* – conceptualization and design of the article, justification and final approval of the manuscript for publication.

### Информация об авторах

*Тихонова Ольга Алексеевна* – канд. мед. наук, ст. преп. кафедры психиатрии и нейронаук Балтийского федерального университета им. И. Канта, Калининград, Россия, <https://orcid.org/0000-0002-1796-0193>

*Дружинина Евгения Сергеевна* – канд. мед. наук, доцент каф. неврологии, нейрохирургии и медицинской генетики им. акад. Л.О. Бадаляна Института нейронаук и нейротехнологий РНИМУ им. Н.И. Пирогова, Москва, Россия, <https://orcid.org/0000-0002-1004-992X>

*Дружинин Дмитрий Сергеевич* – д-р мед. наук, зам. главного врача по научной и инновационной работе Университетской клинической больницы № 3 Первого Московского государственного медицинского университета им. И.М. Сеченова, Москва, Россия, <https://orcid.org/0000-0002-6244-0867>

**Вклад авторов:** *Тихонова О.А.* – проведение научного исследования, анализ и интерпретация данных, написание текста статьи; *Дружинина Е.С.* – анализ и интерпретация данных, написание текста статьи; *Дружинин Д.С.* – разработка концепции и дизайна статьи, обоснование и окончательное утверждение рукописи для публикации.