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DN4 questionnaire as a useful tool for evaluating the pharmacotherapeutic response to opioid pharmacotherapy in malignant neuropathy

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Received February 25, 2024, accepted April 2, 2024

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Pharmazie 79: 109-113 (2024) *doi: 10.1691.ph.2024.4513*

Objective: Tapentadol is a drug of choice for neuropathic cancer pain. *DN4* questionnaire quickly determines neuropathic pain component. The aim of this study is to determine the correlation between neuropathic malignant pain component by applying tapentadol antidolorose pharmacotherapy in combination with palliative radiotherapy of osseous neuropathic metastatic changes in breast cancer patients before and after palliative radiotherapy. *Methods:* The first patients group comprised 30 patients with primary breast cancer and proved painful bone secondary deposits with neuropathy for which tapentadol was prescribed, and they underwent palliative radiotherapy. The second group comprised 30 patients with primary breast cancer and proved painful bone metastases with neuropathy treated only with palliative antidolorose radiotherapy. *Key findings*: After two-months-follow up, tapentadol group patients had lower DN4 score values (Z=2,021; p=0.043). Significantly lower number of tapentadol group patients was without neuropathic pain after a three-month-follow up (χ^2=5,711; p=0.017). Significantly greater number of tapentadol group patients had best ECOG score 0 (χ^2=7,486; p=0.023). There was statistically significant positive correlation between tapentadol dose and DN4 score in patients after a month (ρ=0,471; p=0.009) and three months after the radiotherapy completion (ρ=0,610; p<0.001). Tapentadol is an opioid analgesic efficient for neuropathy relief in these patients and DN4 questionnaire is an efficient pharmacotherapy tool.

1. Introduction

Breast cancer is the most often diagnosed malignant neoplasm worldwide. It is the most common cause of death in women and the fifth most common cause of death from malignant diseases in both sexes together, thus representing a global public health problem. The incidence of this malignant tumor is increasing in all contries (Nardin et al. 2020). Mortality rates vary widely from global region to region but are highest in socio-economically low areas, reflecting a lack of access to early screening and timely treatment (Sung et al. 2021).

Breast cancer can be divided into four principal molecular subtypes according to differences in immunohistological technique based on the expression of the estrogen receptor, the progesterone receptor, and the human epidermal growth factor receptor 2 (HER2): luminal A, luminal B, HER 2 positive non-luminal and triple-negative brast cancer (Ades et al. 2014). In addition to classical treatment modalities such as surgery, radiotherapy, hormone therapy and chemotherapy, a new approach in the treatment of breast cancer includes immunotherapy, the use of antibody-drug conjugates, as well as the targeted molecular therapy. Depending on the stage of the disease, these therapeutic modalities can be applied in a neoadjuvant, adjuvant or palliative approach (Gao et al. 2018). The 5-year relative breast cancer-specific survival rate is encouraging with 90.3%. However, for metastatic breast cancer the 5-year relative cancer-specific survival rate is still low: 29%. An additional challenge in the treatment of metastatic breast cancer are factors such as overtreatment, resistance to therapy, numerous side effects of previous therapeutic lines, but also the frequent presence of bone metastases, which are accompanied by severe cancer pain (Harbeck et al. 2019).

Bone pain is a common modality in oncology patients. Even 60-84 % of patients with advanced malignant diseases have experienced bone pain. The skeletal system is the third most common site of metastases after lungs and liver. Most bone metastases are diagnosed in the breast, prostate, lung cancer, as well as in thyroid cancer, renal and ovarian cancer. Out of all bone metastases in women, 65% develop as a consequence of breast cancer progression, and the incidence is the same in men due to prostate cancer spreading (Clézardin et al. 2021).

Localization of bone metastases is in 69% of cases in the vertebrae, in 41% of cases in the pelvic bones, in 25% in the long bones (proximal femur), and in 14% of cases in the skull bones. The location in the skeletal system and dissemination of bone metastases in oncology patients usually do not correlate with the severity and intensity of pain in these patients. Some patients with disseminated skeletal changes have subjective feeling of moderate pain intensity, while others having single lesion experience high intensity pain, and neuropathy degree in these patients is not the same as well. Based on these facts, an individualized therapeutic approach to these patients is needed regarding adequate pain relief and other co-analgesic and supportive therapies (Zajączkowska et al. 2019).

Bone pain in oncology patients is worse at night, and during the day when provoked by doing some activities and can be accompanied by fever. Pain provoked by palpation in certain areas is mostly caused by metastatic bone lesions in these areas (Fornetti et al. 2018). The main component of this pain is of neuropathic origin and standard nociceptive component as well, referred as mixed malignant pain syndrome.

Tapentadol (3-dimethylamino-1-ethyl-2-methyl-propyl-phenolhydrochloride) is a drug of choice for neuropathic cancer pain that is refractory to standard first-line opioid therapy with classic μ opioid agonists (Sugiyama et al. 2018). It should be given to oncology patients over a longer period of time at adequate doses to get an optimal pharmacotherapeutic response. Tapentadol is an opioid analgesic that provides adequate therapeutic response in oncology patients, with favourable safety profile (Homma et al. 2020). It is also effective as a pharmacological solution for patients who were on previous opioid treatment and who require conversion to some other opioid, such as tapentadol, due to its good safety profile (Sazuka and Koitabashi 2020).

In neuropathy of malignant etiology, long-lasting basal opioid analgesia is indicated to relieve both neuropathic and nociceptive pain components. Tapentadol is an opioid analgesic with strong analgesic potential and dual mechanism of action (it also inhibits noradrenaline reuptake, thus relieving neuropathy), so adequate mixed pain relief can be expected without the need for adjuvant co-analgesics that could potentially result in adverse effects, that is in mutual interaction of these drugs, and with drugs the patients have been using for other comorbidities.

Radiation therapy reduces pain in 60-80% patients with bone metastases, in 15-40% patients complete pain relief is achieved. Response to radiotherapy is usually within the first 4-6 weeks after completion of the radiotherapy treatment. Complete pain relief is more often achieved in radiation for bone metastases in breast and prostate cancers than in lung cancer metastases or tumors of other localizations, especially in cases where palliative therapy is combined with systemic therapy and supportive opioid pharmacotherapy (Le Fèvre et al. 2018).

The physician should make a decision and choose the optimal regime of radiotherapy dose fractionation to achieve optimal palliative effects. The physicians themselves, not the patients, should assess analgesics response, by using questionnaires and pain assessment scales for pain assessment before and after radiotherapy. Efficacy of radiotherapy in achieving antidolorose effect is higher in patients with mild or moderate pain than in patients with severe pain, so synergistic effect of opioid pharmacotherapy and radiation therapy is required.

Radiotherapy itself does not affect malignant cell integrity nor size reduction of metastatic origin, since analgesic effect is mostly the same in short-course and prolonged radiotherapy regime (Nakata et al. 2018).

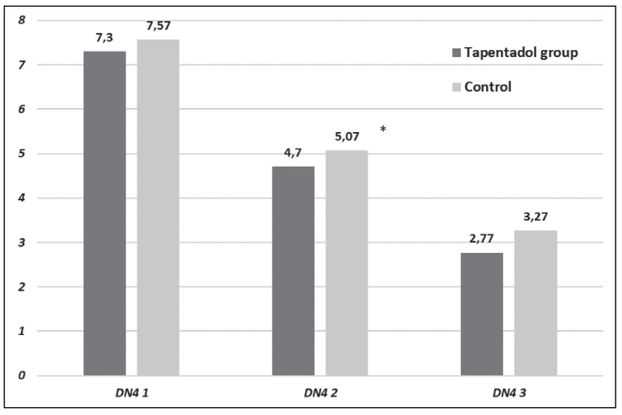
Neuropathic Pain Diagnostic Questionnaire (DN4 questionnaire) – taking patient's anamnestic data enables the physician to easily and quickly determine neuropathic pain component by four simple questions and ten possible responses which help in further pharmacotherapy for treating painful condition of a patient. The total score a patient can achieve is 10 and, with great statistical significance, a cut-off value for diagnosing the presence of neuropathic pain is a total score of 4 (Van Den Kerkhof et al. 2018).

ECOG score (*Eastern Cooperative Oncology Group score*) is also a significant parameter in everyday clinical practice for making decisions on further treatment, treatment response prediction and general prognosis for oncology patients. If the practicing oncologist rates patient's ECOG score 0, it means that the patient is fully active, or slightly restricted in performing physical strenuous activities, but capable in performing almost all everyday activities independently. Patient with ECOG score 1 is ambulatory and capable of selfcare but unable to do any work activities in less than 50% of waking hours. If the patient is capable of limited self-care and confined to bed more than 50% of waking hours, their ECOG score is 2. When a patient is completely disabled, not capable of any self-care and fully confined to bed, practicing physician gives them the ECOG score 3. If a patient is on deathbed, ECOG score is 4, and if a patient is dead the score is 5 (Quinn et al. 2020).

The aim of the paper is to determine the correlation between neuropathic malignant pain component by applying opioid antidolorose pharmacotherapy of long-lasting strong opioid analgesic formulation – tapentadol, in combination with palliative radiotherapy of osseous neuropathic metastatic changes, in oncology patients with primary breast cancer and proven bone metastases before and after palliative radiotherapy of bone metastases. Apart from that, patients were followed for general status by using the ECOG score before and during prescribed pharmacotherapy and palliative radiotherapy, and for possible new adverse reactions to tapentadol in post-registration phase of tapentadol monitoring, all of that by the physician subspecialist in pain medicine.

2. Investigations and results

Determining neuropathic pain component in these patients was performed by using the DN4 questionnaire. Comparison of mean values in two experimental groups is shown in Fig. 1, and patients' distribution according to pain severity can be seen in Table 1.



* $p < 0.05$

Fig. 1: Average values of the DN4 questionnaire score in the examined groups.

Table 1: Patients' distribution according to the values of DN4 questionnaire score

	Tapentadol group n (%)	**Control** n (%)	**p**
DN4 1			
≥4 neuropathic pain	30 (100.0)	30 (100.0)	1.000[a]
DN4 2			
1-3	0 (0.0)	1 (3,3)	
≥4 neuropathic pain	30 (100.0)	30 (96,7)	1.000[a]
DN4 3			
1-3	23 (76.7)	14 (46.7)	
≥4 neuropathic pain	7 (23.3)	16 (53.3)	0.017[b]

[a] Fisher test, [b] Chi square test

At first measurement there was no significant difference in mean values of DN4 questionnaire between the groups (Z=0.957; p=0.339). All the patients from both groups had neuropathic pain component (p=1,000).

After a month there was no significant difference in the mean values of DN4 questionnaire between the groups (Z=1,825; p=0.068). Only one patient from the control group was without neuropathic pain component (p=1,000).

Two months later patients from the tapentadol group had lower DN4 scores (Z=2,021; p=0.043). A significantly lower number of patients from the tapentadol group was without neuropathic pain component after a three-month-follow up (χ^2=5,711; p=0.017).

ECOG score for the patients is shown in Table 2. There was no statistically significant difference in the distribution of score values between the two groups at first measurement (χ^2=1,714; p=0.501) nor at the measurement after a month (χ^2=1,529; p=0.466). After three months a significantly greater number of patients from the tapentadol group had best ECOG performance status 0 (χ^2=7,486; p=0.023).

Table 2: Values of ECOG score of patients in all studied groups

		Tapentadol group n (%)	**Control** n (%)	**p**[a]
ECOG 1	*1*	15 (50.0)	10 (33.3)	
	2	15 (50.0)	20 (66.7)	0.190
ECOG 2	*0*	8 (26.7)	8 (26.7)	
	1	17 (56.7)	20 (66.7)	
	2	5 (16.7)	2 (6.7)	0.466
ECOG 3	*0*	22 (73.3)	12 (40.0)	
	1	6 (20.0)	16 (53.3)	
	2	2 (6.7)	2 (6.7)	0.023

[a] Chi square test

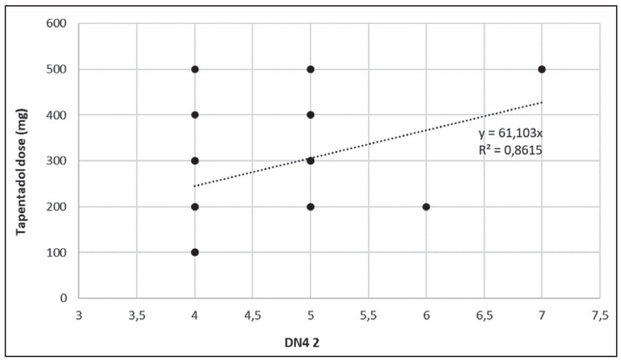


Fig. 2: Correlation of tapentadol dose and DN4 score in the second measurement point.

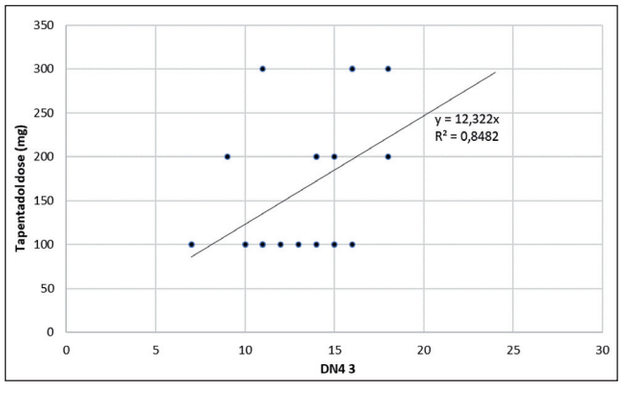


Fig. 3: Correlation of tapentadol dose and DN4 score in the third measurement point.

There was a statistically significant positive correlation between tapentadol dose and DN4 score (Fig. 2) in patients after one month (ρ=0,471; p=0.009) and three months after the completion of radiotherapy (ρ=0,610; p<0.001) (Fig. 3). There was no statistically significant correlation at first measurement.

3. Discussion

An efficient tool in assessing neuropathic pain component is the DN4 questionnaire (Sykioti et al. 2014). The results of the study suggest that, according to this questionnaire, patients from both groups had neuropathy from the start, but at the last point of pain intensity reevaluation patients receiving tapentadol were without neuropathic pain component, what is statistically significant (p=0.017). Thus, the results obtained by using this tool for evaluating neuropathy in this category of patients show that tapentadol, due to its dual mechanism of action, adequately reduced neuropathic pain component as well, what could not be achieved only by palliative radiotherapy in the control group of patients.

An important factor in total *performance score* (PS) in these patients is pain relief, as reported in this study and illustrated in Table 2 showing that the ECOG score was statistically significantly better in patients from the group receiving long-lasting tapentadol at the third point of neuropathy reevaluation. Since the ECOG score is an indicator of patients' overall status and a significant predictor of survival in metastatic breast cancer (Laohavinij et al. 2017), it can certainly be suggested that survival rate in patients receiving tapentadol along with palliative radiation will be significantly better in comparison to radiation treatment only. Of course, a longer follow-up time interval is required to obtain reliable data on their survival after this modality of supportive treatment in bone metastatic changes.

ECOG PS used in this study is very important to determine the further prognosis of oncology patients and evaluate further application of specific oncology treatment, so it serves as a quick tool to doctors for oncology treatment and for supportive oncology therapy as well (Sok et al. 2019). It has been proved that scoring oncology patients by using ECOG PS is best because of the possible subjective responses, comorbidities and multimorbidities in this type of patients, polypharmacy, frequent side-effects in all oncology treatment modalities (Simcock and Wright 2020). It is just for these reasons why this study also employed a scoring system for general status of all included patients.

Recent global recommendations for therapy of neuropathic cancer pain comprise coanalgesics administration (antidepressants and anticonvulsants), reporting that traditional analgesics, such as paracetamol, nonsteroidal anti-inflammatory drugs and opioids are only addressing one part of neuropathic pains, that is mixed malignant pain (Yoon and Oh 2018). Guidelines from the World Health Organization recommend combination of opioids and adjuvant analgesics as a therapeutic option for this type of pain and adequate solution for neuropathic cancer pain relief (WHO 2018). Problem that may arise in clinical practice regarding combination of these drugs are related to side/effects of these combinations including oversedation, dizziness, nausea, vomiting, cardiovascular side effects, or hepatotoxicity.

For these reasons tapentadol as a strong opioid analgesic may be an adequate pharmacological option for the treatment of mixed pain in this category of patients. Considering the fact that it has a dual mechanism of action and that it does not only act by classical mechanisms of opioid receptor agonization, but also acts by selective inhibition of noradrenaline reuptake, similar to antidepressants. In such a way it adequately relieves both nociceptive and neuropathic pain components, patients are suffering from due to bone metastases, so adjuvant coanalgesics treatment is not required (Kress and Coluzzi 2019).

In our study, a statistically significant positive correlation was also reported between tapentadol dose and DN4 score in patients after one month (p=0.009) and after three months after radiotherapy (p<0.001), while there was no statistically significant correlation at first measurement.

Coluzzi et al. carried out a study in patients suffering from multiple myeloma, experiencing mixed cancer pain like the patients in our study. The method used for assessing pain and neuropathy was the DN4 questionnaire and the score was compared at different time points of patient's pain reevaluation. Patients were treated with a long-lasting tapentadol formulation due to mixed pain. It has been proved by means of the DN4 questionnaire that tapentadol at a daily dose of only 100 mg is effective for analgesia and neuropathy of these patients who experience moderate to severe mixed cancer pain. It is also adequately tolerated, so it can be considered a first choice opioid for this type of pain in oncology patients (Coluzzi et al. 2015).

A recent Spanish study assessed pain and quality of life in cancer patients with moderate to severe neuropathic pain due to the presence of bone metastases, who underwent palliative radiotherapy and tapentadol opioid pharmacotherapy. It has been proven that palliative radiotherapy in combination with a long–lasting tapentadol formulation shows excellent therapeutic response in this category of patients with mixed pain and it also improves their quality of life. One of the diagnostic tools used in this study was the DN4 questionnaire (Cacicedo et al. 2020).

The DN4 questionnaire was also a useful tool in an Italian study to assess tapentadol efficacy for neuropathic pain in oncology patients. These patients, who had chemotherapy-induced neuropathy and received tapentadol pharmacotherapy, were assessed by this diagnostic test at multiple points of neuropathy reevaluation. The authors of this study concluded that tapentadol can be considered a first-line choice in treating chemotherapy-induced neuropathic pain in oncology patients, since the DN4 score showed reduction in neuropathic pain and overall status of patients, as well as improvement of their quality of life (Galiè et al. 2017).

The efficacy of the DN4 questionnaire as a screening tool for estimating neuropathy has also been proven in an Indian study about pharmacological treatment of cancer therapy-induced neuropathy. Most commonly used drugs in this study were pregabalin and amitriptyline, and the DN4 questionnaire was a fundamental tool to assess the success rate of this therapy (Singh et al. 2020).

This questionnaire primarily exhibited its growing popularity as a rapid diagnostic tool used by neurologists dealing with diabetic polyneuropathy treatment. An Italian study also used it for mixed pain assessment in this indicated area, but in patients who received a long lasting tapentadol formulation without adjuvant coanalgesics. Although the nociceptive pain component was assessed by NSB, the DN4 score had a significant role in neuropathy reevaluation in these patients in whom tapentadol was proven to be an adequate pharmacological solution (Tedeschi et al. 2018).

A German study compared the efficacy of tapentadol and oxycodone/naloxone fixed combinations regarding analgesia, functionality, neuropathy and quality of life. This study also used the DN4 questionnaire as a diagnostic tool for neuropathy. The authors showed results indicating that patients who were primarily on fixed combination oxycodone/naloxone, then rotated from opioids to tapentadol prolonged release, had adequate pain relief – analgesia – better functionality, better symptom control for neuropathy according to DN4 score, and better quality of life (Kern et al. 2014). This study also proved that tapentadol prolonged release maximally reduced administration of coanalgesics, what is of extreme importance regarding polypharmacy and potential interactions by the concomitant use of these drugs.

Another German study examined analgesia and quality of life in patients with chronic pain who exceeded analgesics potential of 300 mg tramadol daily. All these patients were switched to tapentadol prolonged release by rotation from opioids and pain intensity was assessed by NSB, and neuropathy by DN4 score. The results showed that patients have multiple benefits if being treated with tapentadol prolonged release regarding nociceptive pain relief and neuropathy and quality of life as well (Richter et al. 2015).

The clinical and practical importance of this study was a foundation of modern pharmacotherapy for cancer mixed pain – prescribing and dispensing strong opioid analgesics in oncology patients with bone metastases and consequent neuropathy, in whom their application was indicated. The results of this study confirmed a real need for prescribing strong opioids and also requirements for reducing or increasing, that is correcting the dosage regimen of opioid analgesics depending on applied dose of bone metastases radiotherapy and their synergistic antidolorose effect on neuropathy in these patients. This study is meant to explain the importance of reducing other coanalgesics prescription in mixed cancer pain if tapentadol was prescribed as a new opioid analgesic of dual mechanism of action because of polypharmacy and potential drug to drug interaction, based on good results of neuropathy relief.

Neuropathy relief in mixed cancer pain can adequately be achieved only by synergistic action of radiotherapy and opioid pharmacotherapy with peroral tapentadol prolonged release. Synergism of adequate dosage regimen of opioid analgesics tapentadol and multi-dose radiotherapy palliative treatments is a gold standard in relieving this type of pain in oncology patients.

Tapentadol is an opioid analgesic efficient in neuropathy relief in these patients with minimal side effects and adequate relief of both nociceptive and neuropathic component of this pain, thus adjuvant coanalgesics can be used minimally and in such a way polypharmacy can be avoided in these patients. The DN4 questionnaire is an efficient diagnostic tool for neuropathic pain component assessment and follow-up of the treated patients.

ECOG PS in these oncology patients is a proven to be an excellent tool also used for orientation in supportive oncology therapy and evaluation of the general status of patients and response to prescribed therapy.

Neuropathy reevaluation in these patients during radiotherapy treatment can adequately be achieved with the DN4 questionnaire and by following-up DN4 score. DN4 score is in positive correlation with tapentadol dosage, what is expected since they are parameters of neuropathy follow-up and tapentadol is an adequate pharmacotherapy.

4. Experimental

4.1. Ethical approval

This prospective study was conducted at the Clinic for Oncology, University Clinical Center Nis, Nis, Serbia during a three-month-time interval of follow up. The study was approved by the Ethical board of University Clinical Center Nis and all the participants gave informed consent before participating in this study. This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained from all patients for experimentation with human subjects.

4.2. Subjects and exclusion criteria

This study included only patients with established diagnosis of primary breast cancer with proved metastatic disease by using skeletal scintigraphy method, with painful bone metastatic secondary deposits with symptoms of neuropathy. Patients with proven histopathological diagnosis of breast cancer but without the presence of osseous secondary deposits since there is no neuropathy component of the pain, patients with breast cancer with proven soft tissue secondary deposits causing only nociceptive pain component, patients with moderate and severe kidney/liver failure, what is contraindicated for administration of this opioid, and patients intolerant to opioid pharmacotherapy were excluded from the study. All the patients from the first group received opioid analgesic pharmacotherapy comprising a long–lasting peroral tapentadol formulation in adequate dosees. As for opioid analgesics, besides tapentadol, a quick-acting peroral formulation of morphine sulfate was prescribed to the patients to treat breakthrough pain if needed, up to maximum four times a day. A need for rescue doses of fast-acting opioids for breakthrough pain more than four times daily was an indication for increasing the dose of basal long-acting opioid tapentadol. Patients from the second group were only on radiotherapy antidolorose treatment to painful, neuropathic bone metastatic changes and neuropathy intensity monitoring.

4.3. Evaluation of pharmacotherapeutic response

All the patients were interviewed by using the DN4 questionnaire. ECOG score was also determined in all the patients before the treatment and at pain intensity re-evaluation.

There were three time points of patients' pain evaluation, scoring and correction of antidolorose pharmacotherapy treatment as follows: first – before radiotherapy initiation when opioid pharmacotherapy was introduced to patients from the first group by using long-acting tapentadol and morphine-sulfate if needed in breakthrough pain; second – one month after radiotherapy to painful neuropathic metastatic changes, and third – two months after completion of radiotherapy. Depending on the tolerance to possible side-effects, patients' tapentadol dose was corrected or replaced by an opioid analgesic by opioid rotation strategy and they were excluded from the study.

4.4. Statistical analysis

The results of statistical analysis are shown in the forms of tables and graphs. Statistical calculations were performed using the programme SPSS version 22.

CRediT authorship contribution statement: The work was done through the contributions of all the authors. All authors have approved the final version of the manuscript.

Declaration of competing interests: The authors declare that they have no conflicts of interest or personal relationships that could have appeared to have influenced the work they report in this paper.

Acknowledgements: This research was supported by the Ministry of Education and Science of the Republic of Serbia (Grant No. 451-03-65/2024-03/200113) and the Faculty of Medicine University of Nis Internal Scientific Project No. 41.

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