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Staging of relapsing-remitting multiple sclerosis – the promising role of the BDNF/VEGF ratio

Стадијуми у релапсно-ремитентној мултиплој склерози – улога односа *BDNF–VEGF* која обећава

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Staging of relapsing-remitting multiple sclerosis – the promising role of the BDNF/VEGF ratio

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SUMMARY

Introduction/Objective Brain derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) may play important roles in development and monitoring of multiple sclerosis (MS). BDNF is a neuroprotective factor in the process of inflammation, degeneration, and demyelination of MS. Inflammatory cells stimulate angiogenesis in demyelinating lesions through the release of VEGF, which is a proinflammatory factor.

Methods The study included 86 subjects-20 healthy individuals and 66 patients with relapsing-remitting (RR) MS-who were divided into three groups: Patients in remission, patients in relapse from MS at the beginning and patients at the end of corticosteroid therapy due to disease relapse.

Results The study showed a statistical difference in BDNF concentration between patient groups at baseline and at the end of therapy due to disease relapse, as well as a difference in VEGF concentration between groups. The BDNF/VEGF ratio was increased in patients in remission compared with the control group, this ratio decreased significantly in patients at the onset of MS relapse compared with patients in remission.

Conclusion This study describes the BDNF/VEGF ratio for the first time as a biomarker that may be of interest in well-controlled longitudinal studies for staging RR-MS and evaluating the response to therapy during relapses.

Keywords: Relapsing-remitting multiple sclerosis; BDNF; VEGF; BDNF/VEGF; CRP; IL-6

САЖЕТАК

Увод/Циљ Неуротрофни моћдани фактор (*BDNF*) и васкуларни ендотелни фактор раста (*VEGF*) могу бити од значаја у развоју и праћењу тока мултипле склерозе (МС). *BDNF* има неуропротективну улогу у процесима инфламације, дегенерације и демијелинизације у МС. У демијелинизационим лезијама инфламаторне ћелије подстичу ангиогенезу ослобађајући *VEGF*, који је такође проинфламаторни фактор.

Методе У студију је било укључено 86 испитаника – 20 здравих испитаника који су чинили контролну групу и 66 болесника са релапсно-ремитентном мултиплом склерозом (РРМС). Пацијенти су били подељени у три групе: болеснике у ремисији, болеснике на почетку релапса болести и болеснике на крају кортикостероидне терапије.

Резултати Студија је показала статистички значајне разлике у концентрацији *BDNF* између болесника на почетку и на крају терапије релапса болести, као и значајне разлике у концентрацији *VEGF* између група испитаника. *BDNF*/*VEGF* однос је био виши код болесника у ремисији у поређењу са контролном групом, док је овај однос био значајно нижи код болесника на почетку терапије релапса МС у односу на болеснике у ремисији.

Закључак Ова студија први пут описује однос *BDNF*/*VEGF* као биомаркер који би могао бити од интереса у добро контролисаним лонгитудиналним студијама за одређивање стадијума РРМС и процену одговара на терапију током релапса.

Кључне речи: релапсно-ремитентна мултипла склероза; *BDNF*; *VEGF*; *BDNF*/*VEGF*; *CRP*; *IL*-6

INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated neurodegenerative disease of the central nervous system (CNS) characterized by demyelination and axonal degeneration [1]. There are several clinical forms of the disease: relapsing-remitting (RR-MS), primary progressive (PP-MS) and secondary progressive MS (SP-MS). The most severe form of the disease is PP-MS, which occurs in 15% of patients. In 85% of patients, the disease manifests as RR-MS. The processes of deterioration (relapse) and improvement (remission) occur at different intervals. However, on average, 50% of patients with RR-MS show clinical signs of SP-MS after a period of 10 years. Additionally, some patients experience progression independent of relapse activity

(PIRA), a form of disease progression in which disability worsens without relapses or inflammatory activity, highlighting the neurodegenerative nature of the disease even in the absence of acute flare-ups [2].

Inflammation is the basis of the pathogenesis of MS. Inflammation causes demyelination, and autoreactive T lymphocytes play a leading role in initiating the disease. Autoreactive T lymphocytes are activated in the peripheral circulation due to some pathogen, where clonal expansion occurs. Activated autoreactive T cells infiltrate the CNS, where they upregulate proinflammatory mediators and activate microglia/macrophages, leading to inflammation and demyelination [3]. However, besides clonal expansion, there is a significant imbalance in T cell subtypes. Th1 and Th17 subtypes become dominant and lead to microglia and macrophage activation, secretion of proinflammatory cytokines, and thus contribute to the initiation and maintenance of inflammation. The functional activity of Treg cells becomes significantly reduced, and there is no adequate inhibition of autoreactive cell activation. The lack of effective Treg cells leads to a state of chronic inflammation [4].

Various biomarkers of inflammation provide information about disease progression, remission, exacerbation, and response to therapy. Immune system response includes the production of peptides, cytokines, and free radicals, as well as increased activity of various immune cells. Proinflammatory cytokines (IL-2, TNF-alpha, IFN-gamma, IL-17) dominate and contribute to the inflammatory process, while anti-inflammatory cytokines (IL-4, IL-10, IL-13) limit the inflammatory response [5]. In addition to acquired immunity, the role of innate immune system should be emphasized. Microglia, the primary resident immune cells of the CNS, plays a pivotal role in neuroinflammation, tissue repair, and neural homeostasis, and their activity is altered in MS. However, under the influence of proinflammatory cytokines, microglia can also lead to neuron and oligodendrocyte damage. They increase the production of IL-6, IL-12, IL-23, and thus enhance the activation of Th1 and Th17 cell subtypes. Additionally, they begin to release reactive oxygen and nitrogen species, leading to oxidative stress [6]. Chronic inflammation leads to the overproduction of reactive oxygen and nitrogen species, which disrupt homeostasis and damage axons. Free radicals damage mitochondrial membranes, DNA, and respiratory chain enzymes. Damaged mitochondria, besides producing less ATP, produce increased amounts of free radicals, which in turn cause greater damage. Oxidative stress and metabolic dysfunction processes lead to neuronal damage and neurodegeneration [7].

Brain Derived Neurotrophic Factor (BDNF) and Vascular Endothelial Growth Factor (VEGF) may play important roles in the pathogenesis of MS and monitoring disease progression [8].

BDNF, produced primarily by neurons and glial cells, is essential for neurogenesis, differentiation, and neuroprotection and serves as a key mediator of synaptic plasticity. Changes in blood and central nervous system (CNS) levels of BDNF, along with the conversion of its precursor, proBDNF, into its active, mature form, have been linked to the pathogenesis of several neurological diseases, including MS [9]. Studies have shown that BDNF levels in the blood of MS patients are significantly lower than those in healthy controls [10]. Both neurons and immune cells, including lymphocytes, macrophages, and astrocytes, synthesize proBDNF. In MS, inflammatory factors increase the production of proBDNF. However, during inflammation, the conversion of proBDNF to its active form is impaired, as inflammatory mediators decrease the activity of the enzymes responsible for this process [11].

BDNF has been confirmed to play a neuroprotective role in the subsequent processes of inflammation, degeneration, and demyelination. BDNF promotes repair, regeneration, and remyelination and prevents clinical progression of the disease [12]. BDNF exerts its effects by binding to the TrkB (tyrosine kinase B) receptor with high affinity, promoting cell survival and various trophic effects. Oligodendrocytes and their progenitors also express the TrkB receptor, through which BDNF stimulates their differentiation and myelin production, playing a key role in remyelination [13]. However, in patients with MS, lower concentrations of BDNF have been shown, and its protective role is reduced as well [10]. Proinflammatory cytokines TNF-alpha, IL-1, and IL-6 decrease the concentration of BDNF. Cytokines inhibit its transcription in neurons and glial cells by activating signaling pathways (e.g., NF-kB) and increasing oxidative stress, there by damaging neurons and reducing BDNF production [11].

In MS, VEGF expression increases due to mitochondrial dysfunction and the higher metabolic demands of demyelinated axons. Damaged mitochondria become less efficient at producing ATP, while demyelination requires greater ATP consumption to maintain axonal conduction. As a result, even when oxygen levels are suficient, cells experience a state of “virtual hypoxia”. This condition triggers HIF-1α-dependent activation of VEGF gene transcription as a compensatory response to local metabolic stress [14]. The concept of "virtual hypoxia" and metabolic exhaustion in MS is supported by MRI spectroscopy [15] and metabolic profiling studies [7], which show altered energy metabolism in the brain.

Initiation of angiogenesis has been associated with the pathogenesis of many diseases, including MS. Previous studies have shown that proinflammatory factors within demyelinating lesions stimulate angiogenesis [16]. In the early stages of MS, VEGF acts as a proinflammatory mediator, contributing to lesion formation. Several studies have also reported significantly elevated

VEGF levels at all stages of MS compared to healthy controls, reinforcing its role in the disease process [17].

Considering the protective role of BDNF and the proinflammatory role of VEGF in the areas of inflammation and neurodegeneration during the alternating phases of the disease, the aim of this cross-sectional study was to evaluate the predictive value of the ratio of these parameters in the phase of remission, that is, in the phase of relapse in patients with RR-MS.

METHODS

Subjects

The study was conducted in 2022 as a cross-sectional study in the Department of Neurology, the Central Chemical Laboratory, and the Institute of Medical Research of the Military Medical Academy in Belgrade. The Ethics Committee of the Medical Faculty of the Military Medical Academy of University of Defense confirmed the ethical acceptability of all research procedures.

The study included 86 subjects, non-smokers–20 healthy individuals and 66 patients diagnosed with RR-MS by clinical, laboratory and radiological examinations. The participants were divided into four groups:

I-Group of healthy subjects (H; n = 20); formed for research purposes, mean age 35.95±8.98 years. Healthy controls were individuals without a diagnosis of multiple sclerosis or any other neurological, autoimmune, or chronic inflammatory disease, who were free from acute infection and not receiving any therapy that could affect immune function.

II-Group of patients in remission (MS REM; n = 23); patients diagnosed with RR-MS who were in remission at the time of the study, mean age 42.13±8.49 years. Remission is defined as the absence of disease relapse in a period of at least six months.

III-Group of patients at the onset of disease relapse (MS REL1; n = 23); this group comprised patients diagnosed with RR-MS who were experiencing the onset of a disease relapse at the time of inclusion. The mean age was 36.92±10.64 years. A relapse was defined with an increase of at least one point on the Expanded Disability Status Score (EDSS). Patients experiencing an acute relapse received high-dose intravenous methylprednisolone (typically 1g/day for five days) according to standard clinical practice. Blood samples for biomarker analysis were collected before the initiation of corticosteroid therapy.

IV-Group of patients at the end of disease relapse therapy (MS REL2; n = 20); the group comprised RR-MS patients who had completed a five-day course of high-dose intravenous methylprednisolone for relapse management at the time of evaluation. The mean age was 38.67±12.27 years. Sampling in this group occurred after completion of corticosteroid therapy.

Of the 66 patients enrolled in the study, 35 patients were untreated,while the remaining 31 received various forms of therapy. Specifically, 21 patients received interferon therapy (11 patients received Betaferon (interferon beta-1b, 250 µg every other day), 4 received Avonex (interferon beta-1a, 30 µg intramuscularly once weekly), and 6 received Rebif (interferon beta-1a, 22 µg subcutaneously three times per week). In addition, 6 patients were treated with dimethyl fumarate (240 µg twice daily), two patients received monomethyl fumarate (380 mg daily), one patient received fingolimod (Gilenya, 0.5 mg once daily), and one patient was treated with mitoxantronetherapy (12 mg/m^2 intravenously per clinical protocol). The therapy is prescribed by a clinical neurologist.

Medical history data were obtained from each subject's medical record at RR-MS, and EDSS determined by a clinical-neurologist.

Biochemical analyses

Biomarkers were measured in the blood of the subjects. Blood samples were collected by venipuncture in the morning, after 12-hours of fasting. Venipuncture was performed with a vacuum system (Becton Dickinson, Plymouth, England) in vacutainers containing clot activator (serum) or vacutainers containing heparin (plasma). Blood samples were centrifuged at 2500 rpm for 15 minutes. Plasma/serum was then divided into smaller aliquots and stored at -80 ºC until analysis.

In patients who were in the relapse phase of the disease, blood collection was performed before the start of therapy.

The concentration of the biochemical parameters: C-reactive protein (CRP) and ferritin were measured (CRP- Advia 1800, Clinical Chemistry Analyzer System, Siemens Healrhcare Gmbh, Germany; ferritin- Siemens, Dade Behring BN II Nephelometer, Siemens Healthcare Diagnostics Ltd. Erlangen, Germany). Serum BDNF, VEGF, and IL-6 concentrations were determined using commercially available ELISA kit, according to the manufacturer's instructions (BDNF-Elabscience Biotechnology Inc., sensitivity 3.9 pg/mL; VEGF- Invitrogen Thermo Fischer

Scientific, sensitivity < 5 pg/mL; IL-6-R&D Systems, Minneapolis, Minn, USA, sensitivity 0.70 pg/ml).

Statistical analysis

Statistical analyzes were performed using the SPSS statistical program (version 22.0). Results are presented as numbers, percentages, means and standard deviations. The Shapiro-Wilk test was used to test the normality of the data distribution. A statistically significant difference between parameters that had a normal distribution was determined using the ANOVA test, followed by a Bonferroni post hoc test. For parameters that did not have a normal distribution, the Kruskal–Wallis test and the χ^2 test were used. Spearman's and Pearson's correlations were used to determine the presence of a statistically significant correlation between variables, as a function of normal distribution. The significance level for all statistical test was set at $p < 0.05$.

Ethics: This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from patients or their representatives. The Ethics Committee of the Medical Faculty of the Military Medical Academy approved this study (No. 3/4/2023).

RESULTS

While no significant differences were found between groups in ferritin, CRP, and IL -6, a higher leukocyte count was measured in the MS REL2 (at the end of relapse treatment) than in the other three groups. Increased BDNF levels were observed in MS REL2 (after corticosteroid treatment) compared with patients in MS REL1. Significantly lower VEGF levels were observed in MS REM compared with healthy subjects. Although VEGF levels in MS REL1 were not different from those in MS REM, higher VEGF levels were measured in MS REL2 compared with MS REM after corticosteroid therapy (Table 1).

Avery weak positive correlation was recorded between VEGF with leukocyte count, and a negative correlation was observed between BDNF with CRP. A weak positive correlation was also found between CRP with ferritin and IL-6 (Table 2).

The BDNF/VEGF ratio is significantly increased in MS REM patients compared with healthy subjects (H). This ratio decreased significantly in MS REL1 patients at the onset of relapse compared with patients in remission (MS REM) (Figure 1).

In the receiver operating characteristic curve (ROC) for the BDNF/VEGF ratio, the area under the curve (AUC) was greater than 0.7, indicating a suitable predictive parameter for monitoring disease progression from MS remission (MS REM) to disease relapse (MS REL1) (Figure 2).

DISCUSSION

This pilot study investigated the correlation between clinical and biochemical parameters and tissue factors (BDNF, VEGF) in a group of RR-MS patients at different stages of the disease.

The patient group MS-REL2 (at the end of corticosteroid treatment) had a significantly higher leukocyte count than the other three patient groups, which is consistent with other publications [18]. Patients were treated with i.v. corticosteroids after diagnosis of MS relapse, so leukocytosis was a sign of the effect of corticosteroids. It is already known that leukocytosis can be induced by corticosteroids. High-dose corticosteroids have been associated with the extent and earlier onset of leukocytosis [19]. Leukocytosis in MS patients is usually a byproduct of the increase in neutrophil count, and the mechanism itself is not fully understood. However, the mechanism is thought to be based on the interaction of leukocytes and endothelial adhesion molecules [20]. Although, the patients from MS-REL2 received corticosteroid therapy at relapse onset of relapse, the potential immunological effects of corticosteroids on biomarker levels cannot be fully excluded.

Although an increase in inflammatory markers would be expected in MS patients, no significant differences were found between groups in ferritin, CRP, and IL-6 in this study. There was no statistically significant difference between the patients with RR-MS and the control group, and there was no difference in the concentration of these parameters during the different phases of the disease. This is in contrast to the results of other studies, in which a significantly higher concentration of ferritin [21], IL-6 and CRP was found in MS patients compared with the control group. CRP is not only an indicator of an acute phase of disease but can also indicate the location of a lesion. Studies show that the greatest increase in CRP occurs in patients with symptoms of cerebellar and brainstem damage [22].

Some other studies have shown that the concentration of BDNF decreases in MS lesions and that the concentration of this neuroprotective protein decreases with disease progression. However, in our study, no significant changes in BDNF were observed in MS REM patients and in patients at the onset of relapse compared with the control group. However, a significant increase in BDNF was observed after corticosteroid treatment compared with patients who had relapsed

before treatment. Although the patient cohort was small, the observed results are consistent with earlier reports showing a significant increase in the protein concentration after relapse [23].

The inflammatory process in MS lesions leads to an increase in the concentration of VEGF, which is responsible for angiogenesis, but is itself a proinflammatory factor [14]. The study found a significantly lower concentration of VEGF in patients in remission compared with healthy individuals. These data differ from published studies that have found higher VEGF concentrations at all stages of the disease [10]. In this study, significantly higher VEGF concentrations were found at the end of MS relapse therapy compared with patients in remission, which is consistent with published data from other studies [17]. Unexpectedly, VEGF levels at the beginning of the disease relapse were not significantly different from those in remission. Unchanged VEGF levels at the beginning of relapse compared with disease remission could be due to an insufficient time interval for the full extent of VEGF increase, and the significantly higher VEGF levels at the end of MS relapse therapy could also be due to the corticosteroids, especially from the aspect of the resulting leukocytosis. It has already been shown that in many diseases whose pathogenesis is based on the process of angiogenesis, there is a correlation between a higher VEGF concentration and leukocytosis [24]. One of the possible explanations for the presence of angiogenesis in MS lesions is because a large amount of ATP is needed at the sites of axon demyelination to conduct impulses and that, at the same time, ATP production at the damaged axons has been reduced. In this way, the state of hypoxia reflects the chronic demyelination of axons [14].

The data indicate that VEGF is necessary for BDNF to exert its effects. The study found that BDNF stimulates the release of VEGF, and that the effects of BDNF in the prefrontal cortex of mice depend on VEGF release. Additionally, BDNF-induced dendrite complexity is blocked by a selective VEGF-Flk-1 antagonist. VEGF infusion induced neurotrophic effects that were abolished by BDNF neutralization, indicating their reciprocal dependence [25]. The reciprocal dependence between BDNF and VEGF is based on the overlap of their signaling pathways (PI35/Akt and MAPK/ERK) and mutual regulation of expression, enabling a synergistic effect on neuroplasticity and neuronal survival [26, 27]. Considering the interaction of these two important factors, the BDNF/VEGF ratio can be considered as an anti-inflammatory indicator showing the neuroprotective properties of BDNF and the proangiogenic and proinflammatory properties of VEGF. Considering the limitations of the study, the data indicate that the BDNF/VEGF ratio is significantly higher in patients with RR-MS, who are in remission (MS REM) compared with healthy controls. In contrast, this ratio decreases at the onset of MS

relapse relative to patients in remission. All patients in the study who were in remission received therapy (17 patients received interferon therapy (Betaferon or Rebif) and six patients received dimethyl fumarate therapy) that could have anti-inflammatory and neuroprotective effects in the damaged areas. The neuroprotective and anti-inflammatory effects of this therapy have long been known. Interferon has been shown to affect the expression of certain genes, which has short- and long-term effects on the immune response MS [28]. However, previous studies have not shown any effects of interferon therapy on BDNF [29]. At the same time, a higher ratio of BDNF/VEGF in patients in remission (MS REM) was negatively correlated with the concentration of VEGF. Moreover, ROC curve analysis indicates that the BDNF/VEGF ratio has potential as a reliable indicator of progression of RR-MS progression from remission to relapse.

Limitations of the study

This study has several limitations. The sample size was small and included patients at different clinical stages of RR-MS, resulting in biological variability and limiting the generalizability of the findings. The cohort also exhibited therapeutic heterogeneity, with multiple DMTs represented, which restricted the ability to account for treatment effects. In addition, corticosteroid use, particularly in the MS REL2 group, may have affected BDNF and VEGF concentrations. The cross-sectional design further limits conclusions about temporal changes or predictive value, so the ROC results should be interpreted with caution. Finally, the BDNF/VEGF ration remains an experimental parameter and requires further validation.

Overall, these factors indicate that the findings should be considered preliminary and confirmed in larger, longitudinal, and treatment-stratified studies.

CONCLUSION

The BDNF/VEGF ratio could be important for the assessment of the MS stage in patients with RR-MS, especially with regard to the prediction of the transition from the remission phase to relapse. As this relationship was described for the first time in the study conducted, the relevance of its change during the disease stage remains to be clarified.

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Table 1. Demographic, clinical, and laboratory parameters of patients divided into the following groups: healthy, patients with multiple sclerosis in remission, patients with multiple sclerosis at the beginning of relapse, and patients with multiple sclerosis at the end of therapy during disease relapse

Demographic, clinical and laboratory parameters		**H n = 20**	**MS REM n = 23**	**MS REL1 n = 23**	**MS REL2 n = 20**	**p**
Sex (%)	Male	60	34.8	60.9	65	0.163
	Female	40	65.2	39.1	35	
Duration of illness (years)			11.77	7.91	6.05	0.00
EDSS#			2.22	3.52	2.35	0.00
Therapy MS (yes/no)			100%	17.4%	20%	0.00
Leukocytes × 10^9/L		5.8 ± 1.16	5.4 ± 1.65	6.57 ± 2.67	**11 ± 3.55*##&**	**0.000**
CRP mg/L		0.57 ± 0.8	0.75 ± 1.48	2.47 ± 9.66	0.4 ± 1.06	0.063
IL-6 pg/mL		3.49 ± 4.29	2.2 ± 0.96	4.45 ± 7.23	2.49 ± 1.76	0.799
Ferritin ug/L		54.23 ± 50.2	69.77 ± 46.18	54.68 ± 44.37	53.29 ± 50.9	0.355
BDNF ng/mL		7.83 ± 1.83	7.67 ± 1.76	6.19 ± 2.9	**9.09 ± 3.34&**	**0.004**
VEGF A ng/mL		0.22 ± 0.09	**0.13 ± 0.04***	0.16 ± 0.06	**0.27 ± 0.22#**	**0.002**

MS – multiple sclerosis; H – healthy; MS REM – patients with MS in remission; MS REL1 – patients with MS at the beginning of relapse; MS REL2 – patients with MS at the end of therapy during disease relapse; EDSS – Expanded Disability Status Score; CRP – C-reactive protein; IL-6 – interleukin 6; BDNF – brain-derived neurotrophic factor; VEGF – vascular endothelial growth factor;

*$p < 0.05$;

**$p < 0.01$ statistical significance compared to group H;

#$p < 0.05$;

##$p < 0.01$ significance compared to group MS REM;

&$p < 0.05$;

&&$p < 0.01$ significance compared to group MS REL1

Table 2. Spearman's correlation analysis between brain-derived neurotrophic factor, vascular endothelial growth factor A, white blood cell count, C-reactive protein, interleukin 6, and ferritin in multiple sclerosis

	BDNF	**VEGF A**	**Le**	**CRP**	**IL-6**	**Ferritin**
	Rho (ρ**)**	Rho (ρ)	Rho (ρ)	Rho(ρ)	Rho (ρ)	Rho (ρ)
BDNF	-	0.018	0.059	-0.177	-0.067	-0.047
IL-6	-0.067	-0.026	0.085	0.163	-	0.155
VEGF A	0.018	-	0.185	0.000	-0.026	0.006
Le	0.059	0.185	-	-0.035	0.085	0.049
CRP	-0.177	0.000	-0.035	-	0.163	0.254*
Ferritin	-0.047	0.006	0.049	0.254*	0.155	-

BDNF – brain-derived neurotrophic factor; VEGF – vascular endothelial growth factor; Le – white blood cells count; CRP – C-reactive protein; IL-6 – interleukin 6;
*$p < 0.05$

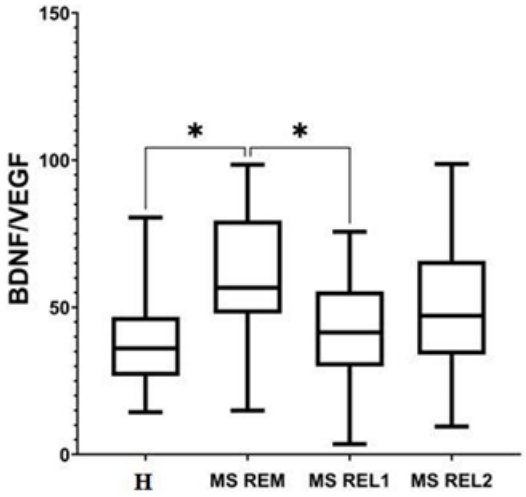

Figure 1. Brain derived neurotrophic factor / vascular endothelial growth factor serum ratio of patients classified into the following groups: healthy, multiple sclerosis patients in remission, multiple sclerosis patients at the beginning of relapse, and multiple sclerosis patients at the end of therapy during relapse;

MS – multiple sclerosis; H – healthy; MS REM – patients with MS in remission; MS REL1 – patients with MS at the beginning of relapse; MS REL2 – patients with MS at the end of therapy during disease relapse; BDNF/VEGF – brain derived neurotrophic factor / vascular endothelial growth factor ratio;

*$p < 0.05$

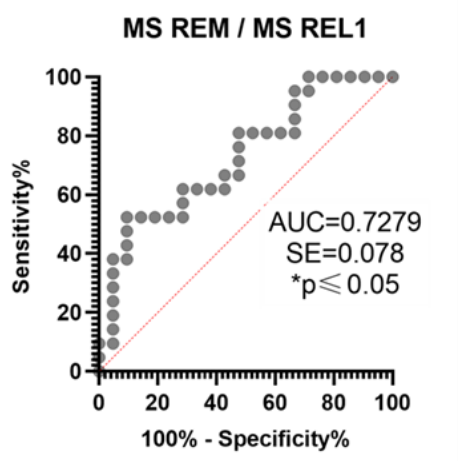

Figure 2. Receiver operating characteristic curve was analyzed to evaluate the significance of brain derived neurotrophic factor / vascular endothelial growth factor ratio in predicting disease stage; the figure shows the percentage of sensitivity and specificity; the measure of separability is expressed by the area under the curve, with a confidence interval of 95%; a ratio of AUC > 0.7 is suitable for predicting disease progression;
MS – multiple sclerosis; MS REM – patients with MS in remission; MS REL1 – patients with MS at the beginning of relapse; AUC – area under the curve; SE – standard error; p – statistical significance

