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C-reactive protein/albumin ratio in patients with multiple sclerosis and its relationship with disease subtype and disability

Multiple skleroz hastalarında C-reaktif protein/albümin oranı ve hastalık alt tipi ve disabilite ile ilişkisi

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Abstract

Aim: Oxidative stress and inflammation are the cause of demyelination and axonal damage in patients with Multiple Sclerosis (MS). Serum C-reactive protein (CRP) and albumin levels are used as a marker of systemic inflammation and oxidative stress for many diseases. In this study, we aimed to determine the level of CRP/albumin ratio in patients with MS and its relationship with disease subtype and disability.

Methods: This cross-sectional study was conducted in patients treated for MS disease. One hundred twenty MS patients and 62 healthy controls were included. Sociodemographic characteristics were questioned. MS subtype was determined. Disability was calculated with Expanded Disability Status Scale (EDSS). Patients were divided into 3 groups: EDSS 0-3 (minor), 3.5-4.5 (moderate) and 5.0 or higher (major). Attack frequency, albumin and CRP serum levels were noted, and hemogram was analyzed with fluorescence flow cytometry.

Results: There were 71 (59.2%) female and 49 (40.8%) male patients in the study, and their mean age was 39.49 (11.47) years. Leukocyte value was higher and albumin was lower in patients with MS (P=0.046, P=0.006). In progressive MS patients, CRP and CRP/albumin ratio was higher and albumin level was lower compared to the relapse remitting subtype (P<0.01). Patients with high EDSS had higher CRP and CRP/albumin ratio and lower albumin levels (P<0.01). A low correlation was detected between the number of attacks and CRP/albumin ratio (P=0.032; r=0.196).

Conclusion: We detected that albumin level and CRP/albumin ratio are related with subtype and activity of MS disease.

Keywords: Multiple sclerosis, Hypoalbuminemia, CRP/albumin ratio

Öz

Amaç: Oksidatif stres ve inflamasyon Multiple Skleroz (MS) hastalarında demiyelinizasyon ve aksonal hasarın sebebidir. Serum C-reaktif protein (CRP) ve albümin düzeyleri birçok hastalıkta sistemik inflamasyon ve oksidatif stresin belirteci olarak kullanılmaktadır. Bu çalışmada, MS hastalığında CRP/albümin düzeyinin saptanması, hastalık alt tipi ve dizabilite ile ilişkisini değerlendirilmesi amaçlanmıştır.

Yöntemler: Bu kesitsel çalışma MS hastalığı nedeniyle tedavi edilen hastalarda yapıldı. Çalışmaya 120 MS hastası ve 62 sağlıklı kontrol alındı. Sosyodemografik özellikler sorgulandı. MS subtipi belirlendi. Dizabilite genişletilmiş özürlülük durum ölçeği (EDSS) ile hesaplandı. Hastalar EDSS 0-3 (hafif), 3,5-4,5 (orta) ve 5,0 veya üzeri (ağır) olmak üzere 3 gruba ayrıldı. Atak sıklığı belirlendi. Albümin ve CRP serum seviyesi belirlendi. Hemogram floresans akış sitometrisi ile ölçüldü.

Bulgular: Çalışmada 71 (%59,2) kadın ve 49 (%40,8) erkek hasta vardı. Yaş ortalamaları 39,49 (11,47) idi. MS hastalarında lökosit değeri daha yüksek, albümin ise düşüktü (P=0,046; 0,006). Progresif MS hastalarında relapsing remitting alt tipine göre CRP ve CRP/albümin oranı daha yüksek, albümin seviyesi daha düşüktü (P<0,01). EDSS yüksek olan hastalarda CRP ve CRP/albümin oranı daha yüksek, albümin seviyesi daha düşüktü (P<0,01). Atak sayısı ile CRP/albümin oranı arasında zayıf korelasyon saptandı (P=0,032; r=0,196).

Sonuç: Bu çalışmada albümin seviyesi ve CRP/albümin oranının MS hastalığında hastalık alt tipi ve aktivitesi ile ilişkili olduğu ortaya konulmuştur.

Anahtar kelimeler: Multiple skleroz, Hipoalbüminemi, CRP/albümin oranı

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Introduction

Axonal damage and neurodegeneration are present in the etiopathogenesis of many acute and chronic neurological diseases. Neurogenerative diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, etc.), inflammatory diseases (Multiple Sclerosis (MS) etc.) and traumatic brain diseases are examples of these [1, 2]. MS is a chronic disease of the central nervous system characterized by demyelination and different degrees of axonal degeneration [3]. There are many different immunological mechanisms in demyelination and axonal damage formation in this disease. Oxidative stress contributes directly and indirectly to this process [4].

Oxidative stress occurs when the balance between the production and destruction of reactive oxygen species (ROS) is disturbed. As ROS is released in cells, antioxidant molecules increase. Thus, neuronal damage is reduced. However, increased ROS release causes many diseases [5, 6]. Proinflammatory conditions (including oxidative stress) are important for MS disease and its progression [7, 8]. Myelin damage occurs because of immune hyperactivation in the early stage of disease. In the chronic period, structural and functional damage occur due to oxidative stress [9].

Serum C-reactive protein (CRP) and albumin are frequently used in routine clinical practice, for diagnosis of acute diseases and evaluation of treatment response. There are many studies which show that it can be used to evaluate prognosis in patients with coronary artery disease, ischemic stroke, sepsis, and cancer [10-13]. Serum albumin is a negative acute phase reactant. It is thought that albumin level may be associated with prognosis of many acute and chronic diseases [10, 14]. CRP/albumin ratio is used as a marker of systemic inflammation and oxidative stress for many diseases [15-17]. In our study, it was aimed to determine the level of CRP/albumin ratio in patients with MS and its relationship with disease subtype and disability.

Materials and methods

Participants and ethical procedure

The sample size was calculated with the G-power program before study. When patient /control ratio was kept at 2, a minimum 144 of samples (96 patients, 48 controls) were required for medium effect size in two-way variance analysis. One hundred twenty MS patients (between 18-65 years of age, treated for at least 1 year) and 62 healthy controls were included in the study between 1 January 2017 and 31 December 2019. The data were collected retrospectively. The study was approved by University of Health Sciences Turkey, Konya Training and Research Hospital, Ethics Committee (5/8/2020; 38-15). The principles of the Declaration of Helsinki and Guidelines for Good Clinical Practices were adhered to during the study. The diagnosis of disease was re-analyzed according to McDonald's criteria [18]. Patients with acute MS attack, active systemic infection (bacterial, viral, or fungal), endocrinological, metabolic, hematological diseases, smoking and alcohol abuse, recent abnormal weight gain or loss, and those who were pregnant, or breastfeeding were excluded from the study.

The duration (years) of MS disease, attacks, and frequency of attacks during the disease period were questioned. Patients were divided into two groups according to the number of attacks (<5: Rare attacks, ≥5: Frequent attacks), and into 3 main groups according to disease types: Relapsing remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS).

Data collection materials

Expanded disability status scale (EDSS)

The extended disability status scale (EDSS) is the most used test in the assessment of disability for MS patients. Total score varies between 0 and 10 (0: Normal neurological examination, 10: Death associated with MS). Disability increases with increasing values from 0 to 10 [19]. Disability due to disease was divided into 3 groups according to EDSS results: 0-3 (minor), 3.5-4.5 (moderate), 5.0 or higher (major).

Laboratory measurements

Blood samples were collected from the antebrachial veins of the patients admitted to outpatient clinic between 09:00-12:00. Separator gel tubes were used for serum tests and potassium-EDTA tubes were used for blood count. Blood was centrifuged at 5000 rpm for 10 minutes and separated to serum. Hemogram was tested with fluorescence flow cytometry. Albumin was measured with spectrophotometric measurement (Cobas 8000 series c702 modular analyzer). CRP level was determined using the immunoturbidimetric method (Wako Chemicals, Osaka, Japan) on a Hitachi 7600 chemistry analyzer (Hitachi, Tokyo, Japan).

Statistical analysis

Data were analyzed with SPSS® version 16.0 statistical package software (SPSS Inc., Chicago, IL, United States). Mean (standard deviation) and median (min-max) values were used to summarize the numerical data. Number (n) and percentage (%) were used to summarize the categorical data. Distribution of data was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Student T test (normally distributed) and Mann Whitney U test (non-normally distributed) were used for comparison of two groups, while one-way ANOVA and Kruskal Wallis tests were used for comparing three groups. The relationship between numerical data was evaluated by Spearman Correlation test. Correlation coefficients were as follows: 0-0.25 weak, 0.25-0.50 weak-medium, 0.50-0.75 strong, 0.75-1.00 very strong. *P*-value <0.05 was considered statistically significant.

Results

One hundred twenty MS patients, consisting of 59.2% (n=71) females, and 40.8% (n=49) males and 62 controls were included in the study. Disease characteristics and blood values of patients are summarized in Tables 1 and 2.

Albumin values were compared between patient and control groups. Leukocyte value was higher and albumin value was lower in MS patients (P=0.046, P=0.006, respectively). Blood values of patient and control groups are presented in Table 3. There was no difference in blood parameters between genders (P>0.05).

The number of attacks was divided into 2 groups, as <5, and ≥5, between which blood values of MS patients were compared (P> 0.05). MS patients in the study were divided into

3 groups according to EDSS results, as follows: EDSS 0-3.0: Minor disability, 3.5-4.5: Moderate disability, and 5.0 or higher: Major disability. Blood values of these 3 groups are summarized in Table 4. CRP values were higher and albumin levels were lower in the group with major disability compared to the other two groups (P<0.05 for both). Albumin level and CRP/albumin ratio significantly differed across all groups. Patients with high EDSS had low albumin levels and high CRP/albumin ratios (P<0.05).

Table 1: Disease subtype, attack, and disability in patients with multiple sclerosis

		Number (n)	Percentage (%)
	Female	71	59.2
	Male	49	40.8
MS type	PRMS	91	75.8
	SPMS	24	20.0
	PPMS	5	4.2
Attack number	<5	76	63.3
	≥5	44	36.7
Disability	EDSS 0-3	67	55.8
(0-10)	EDSS 3.5-4.5	33	27.5
	EDSS 5.0 or higher	20	16.7

RRMS: Relapsing remitting multiple sclerosis, SRMS: Secondary progressive multiple sclerosis, PPMS: Primary progressive multiple sclerosis, EDSS: Expanded Disability Status Scale

Table 2: Disease characteristics and blood parameters in patients with multiple sclerosis

	Mean (SD)	Median(min-max)
Age (years)	39.49 (11.47)	39.00 (19.00-64.00)
Disease duration (years)	8.60 (5.50)	8.00 (1.00-26.00)
Attack number	4.35 (2.99)	3.00 (1.00-20.00)
EDSS (0-10)	2.69 (1.84)	2.00 (0.00-7.00)
Leukocyte (10^3/mm^3)	7.00 (2.16)	6.82 (2.81-15.09)
CRP (mg/l)	4.02 (2.19)	3.11 (2.33-17.00)
Albumin (g/L)	40.77 (3.57)	41.00 (29.80-48.00)
CRP/albumin ratio	0.10 (0.05)	0.07 (0.05-0.43)

SD: Standard deviation, EDSS: Expanded Disability Status Scale, CRP: C-reactive protein, min: minimum, max: maximum

Table 3: Blood parameters in patients with multiple sclerosis and control group

	Control group (n=62) Mean (SD)	Patient group (n=120) Mean (SD)	P-value
Leukocyte (10^3/mm^3)*	7.86 (1.95)	7.46 (2.16)	0.056
Albumin (g/L)*	42.77 (3.47)	40.77 (3.57)	0.006
C-reactive protein (CRP) (mg/l)**	3.88 (1.72)	4.02 (2.19)	0.312
CRP/albumin ratio **	0.09 (0.03)	0.10 (0.05)	0.205

*: Independent sample T test, **: Mann Whitney U test

Table 4: Blood parameters in patients with multiple sclerosis according to disability group

	EDSS 0-3[a] (n=67) Mean (SD)	EDSS 3.5-4.5[b] (n=33) Mean (SD)	EDSS 5.0 or higher[c] (n=20) Mean (SD)	P-value
Leukocyte (10^3/mm^3)*	6.96 (2.29)	6.81 (2.20)	7.43 (1.58)	0.235
Albumin (g/L)**	42.46 (2.99)	39.59 (3.12)	37.05 (2.28)	<0.001$^{(a-b)}$ <0.001$^{(a-c)}$ 0.016$^{(b-c)}$
C-reactive protein (CRP) (mg/l)**	3.63 (1.77)	3.87 (1.80)	5.59 (3.18)	<0.001$^{(a-c)}$ 0.004$^{(b-c)}$
CRP/albumin ratio **	0.08 (0.04)	0.09 (0.05)	0.14 (0.07)	0.004$^{(a-b)}$ <0.001$^{(a-c)}$ <0.001$^{(b-c)}$

EDSS: Expanded Disability Status Scale, *: One-way Anova, **: Kruskal Wallis test

MS patients were compared according to disease subtypes (Table 5). Albumin values were higher, and CRP and CRP/albumin values were lower in patients with RRMS compared to those with SPMS (P<0.001, P<0.05, respectively).

CRP and CRP/albumin levels increased with increasing disease duration (P=0.038, P<0.001, r=0.190, r=0.321, respectively). A negative correlation was detected between disease duration and albumin level (P<0.001, r=-0.342), number of attacks and albumin level (P=0.032, P=0.011, r=0.196, r=-232, respectively), and EDSS and albumin level (P<0.001, r=-0.574), while a positive correlation was detected between the number of attacks and CRP/albumin level (P<0.001, P<0.001, r=0.375, r=0.586, respectively), and EDSS, CRP and CRP/albumin level (P<0.001, P<0.001, r=0.375, r=0.586, respectively).

Table 5: Blood parameters in patients with multiple sclerosis according to disease subgroup

	RRMS[a] (n=91) Mean (SD)	SPMS[b] (n=24) Mean (SD)	PPMS[c] (n=5) Mean (SD)	P-value
Leukocyte (10^3/mm^3)*	6.93 (2.35)	7.44 (1.32)	5.78 (1.31)	0.313
Albumin (g/L)*	41.43 (3.42)	38.30 (3.26)	40.59 (2.83)	<0.001$^{(a-b)}$
C-reactive protein (CRP) (mg/l)**	3.47 (1.41)	5.85 (3.37)	5.27 (1.36)	<0.001$^{(a-b)}$ 0.004$^{(a-c)}$
CRP/albumin ratio **	0.08 (0.03)	0.15 (0.08)	0.13 (0.04)	<0.001$^{(a-b)}$ 0.009$^{(a-c)}$

RRMS: Relapsing remitting multiple sclerosis, SRMS: Secondary progressive multiple sclerosis, PPMS: Primary progressive multiple sclerosis, *: One-way Anova, **: Kruskal Wallis test

Discussion

MS is a chronic disease characterized by demyelination of central nervous system, accompanied by axonal and neuronal degeneration. Demyelination is a complex process that includes inflammation and oxidative stress [3]. Oxidative stress and neuronal damage occur with exceeding the antioxidant capacity of metabolism [20]. ROS, which occurs with oxidative stress, causes neuronal degeneration with proinflammation. In many neurological diseases, the antioxidant capacity of the brain decreases, and it becomes more prone to inflammation [21,22]. Although many different parameters have been used to evaluate the inflammation and oxidative process, an objective measurement method has not been determined. CRP/albumin ratio is one of the parameters for evaluating oxidative stress and inflammation, which is used especially for acute diseases, along with evaluation of neurodegenerative diseases [15,17]. As a result of literature review, no study which evaluates the CRP/albumin ratio in patients with MS was found.

Hematological and biochemical tests (including CRP and albumin) provide qualitative and quantitative information. They are cheaper and easier to access than many inflammatory biomarkers such as interleukin 6 and tumor necrosis alpha (TNF-α). The ratio of these two parameters (CRP/albumin ratio) is a marker used to evaluate inflammation, oxidative stress, and prognosis [10,11,15,17].

CRP is an acute phase protein synthesized in hepatocytes secondary to cytokines during inflammation. Its serum level increases in acute inflammation. However, it is known to be associated with chronic inflammation [23]. Its level increases during the inflammatory process, in which it participates directly [24]. Molecular based studies have shown that the level of CRP increases in local neuronal tissues in some neurodegenerative diseases (Alzheimer's disease, etc.) [25,26].

Serum CRP level is higher in patients with neuromyelitis optica (NMO) than MS and healthy controls, and in MS patients compared to healthy controls. It is also increased in female NMO patients than female healthy controls. However, there is no difference between the genders in terms of CRP levels in patients with MS. There is a positive correlation between attack frequency, disease duration and EDSS with CRP level [27]. Some studies show that CRP level is not different between RRMS patients and the control group [28]. Neutrophil/lymphocyte ratio and CRP are higher in MS patients (especially with high EDSS scores). These markers are associated with a poor prognosis [29]. However, cerebral antioxidant capacity is lower in progressive MS disease [22]. In our study, serum CRP level and CRP/albumin ratio were similar between the patient and control groups, but they were higher in PPMS and SPMS patients compared to those with RRMS. There

was no difference between genders. A positive correlation was detected between attack number, CRP level and CRP/albumin ratio, all of which were similar in patients with different attack frequencies (over 5, 5 and below). Especially in groups with high EDSS, serum CRP and CRP/albumin ratio were higher. Inflammation is higher in patients with progressive MS and high EDSS values. CRP and CRP/albumin ratio are associated with disease activity and disability in patient with MS.

Serum albumin eliminates free oxygen radicals and has antioxidant activity. Hypoalbuminemia is associated with oxidative stress and inflammation. Some studies show that there is a negative correlation between CRP and albumin levels [30]. Albumin level is lower in MS patients than healthy controls (especially in PPMS and SPMS subgroups) [14]. In our study, albumin level was lower in patients with MS, especially in those with SPMS and high EDSS scores, akin to the literature.

Limitations

The fact that the number of PPMS and SPMS subgroup patients were low, and the study's cross-sectional nature are limitations which both restrict our causal conclusion. Prospective studies with larger patient groups are needed.

Conclusion

CRP/albumin ratio is related to the number of attacks, EDSS and disease duration in patients with MS. It is especially higher in progressive MS subgroups. CRP/albumin ratio may be important in evaluating disability, attack frequency and MS subtype in patients with MS.

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References

1. Coleman M. Axon degeneration mechanisms: commonality amid diversity. Nat Rev Neurosci. 2005;6(11):889-98. doi: 10.1038/nrn1788.
2. Coleman MP, Perry VH. Axon pathology in neurological disease: a neglected therapeutic target. Trends Neurosci. 2002;25(10):532-7. doi: 10.1016/s0166-2236(02)02255-5.
3. Lassmann H. Pathogenic mechanisms associated with different clinical courses of multiple sclerosis. Fronti Immunol. 2019;9:3116. doi: 10.3389/fimmu.2018.03116.
4. Su KG, Banker G, Bourdette D, Forte M. Axonal degeneration in multiple sclerosis: the mitochondrial hypothesis. Curr Neurol Neurosci Rep. 2009;9(5):411-7. doi: 10.1007/s11910-009-0060-3.
5. Rojo AI, McBean G, Cindric M, Egea J, López MG, Rada P, et al. Redox control of microglial function: Molecular mechanisms and functional significance. Antioxid Redox Signal. 2014;21(12):1766-801. doi: 10.1089/ars.2013.5745.
6. Moretti M, Fraga DB, Rodrigues A. Preventive and therapeutic potential of ascorbic acid in neurodegenerative diseases. CNS Neurosci Ther. 2017;23(12):921-9. doi: 10.1111/cns.12767.
7. Carvalho C, Moreira PI. Oxidative Stress: A Major player in cerebrovascular alterations associated to neurodegenerative events. Front Physiol. 2018;9:806. doi: 10.3389/fphys.2018.00806.
8. Lutton EM, Farney SK, Andrews AM, Shuvaev VV, Chuang GY, Muzykantov VR, et al. Endothelial targeted strategies to combat oxidative stress: Improving outcomes in traumatic brain injury. Front Neurol. 2019;10:582. doi: 10.3389/fneur.2019.00582.
9. Miller E, Wachowicz B, Majsterek I. Advances in antioxidative therapy of multiple sclerosis. Curr Med Chem. 2013;20(37):4720-30. doi: 10.2174/09298673113209990156.
10. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350(14):1387-97. doi: 10.1056/NEJMoa032804.
11. Kaptoge S, Di Angelan¬tonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of cor¬onary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375(9709):132-40. doi: 10.1016/S0140-6736(09)61717-7.
12. Matsuo R, Ago T, Hata J, Wakisaka Y, Kuroda J, Kuwashiro T, et al. Plasma C-reactive protein and clinical outcomes after acute ischemic stroke: a prospective observational study. PLoS One. 2016;11(6):e0156790. doi: 10.1371/journal.pone.0156790.
13. Windgassen EB, Funtowicz L, Lunsford TN, Harris LA, Mulvagh SL. C-reactive protein and high-sensitivity C-reactive protein: an update for clinicians. Postgrad Med. 2011;123(1):114-9. doi: 10.3810/pgm.2011.01.2252.
14. Oliveira SR, Kallaur AP, Reiche EMV, Kaimen-Maciel DR, Panis C, Lozovoy MAB, et al. Albumin and protein oxidation are predictors that differentiate relapsing-remitting from progressive clinical forms of multiple sclerosis. Mol Neurobiol. 2017;54(4):2961-8. doi: 10.1007/s12035-016-9860-z.
15. Yazar HO, Yazar T, Aygün A, Kaygisiz Ş, Kirbaş D. Evaluation of simple inflammatory blood parameters in patients with migraine. Ir J Med Sci. 2020;189(2):677-83. doi: 10.1007/s11845-019-02136-y.
16. Ju SY, Ma SJ. High C-reactive protein to albumin ratio and the short-term survival prognosis within 30 days in terminal cancer patients receiving palliative care in a hospital setting: A retrospective analysis. Medicine 2020;99(9). e19350. doi: 10.1097/MD.0000000000019350.
17. Yazar T, Yazar HO. Evaluation of C-reactive protein/albumin ratio according to stage in patients with idiopathic parkinson disease. Turkish J Neurol. 2019;25(3):123-8. doi: 10.4274/tnd.galenos.2019.13334.
18. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-73. doi: 10.1016/S1474-4422(17)30470-2.
19. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33(11):1444-52. doi: 10.1212/wnl.33.11.1444.
20. Frati A, Cerretani D, Fiaschi AI, Frati P, Gatto V, La Russa R, et al. Diffuse axonal injury and oxidative stress: A comprehensive review. Int J Mol Sci. 2017;18(12). pii: E2600. doi: 10.3390/ijms18122600.
21. Siotto M, Filippi MM, Simonelli I, Landi D, Ghazaryan A, Vollaro S, et al. Oxidative stress related to iron metabolism in relapsing remitting multiple sclerosis patients with low disability. Front Neurosci. 2019;13:86. doi: 10.3389/fnins.2019.00086.
22. Choi IY, Lee P, Adany P, Hughes AJ, Belliston S, Denney DR, et al. In vivo evidence of oxidative stress in brains of patients with progressive multiple sclerosis. Mult Scler. 2018;24(8):1029-38. doi: 10.1177/1352458517711568.
23. Luan YY, Yao YM. The clinical significance and potential role of C-reactive protein in chronic inflammatory and neurodegenerative diseases. Front Immunol. 2018;9:1302. doi: 10.3389/fimmu.2018.01302.
24. Vachatova S, Andrys C, Krejsek J, Salavec M, Ettler K, Rehacek V, et al. Metabolic syndrome and selective inflammatory markers in psoriatic patients. J Immunol Res. 2016;2016:5380792. doi: 10.1155/2016/5380792.
25. Yasojima K, Schwab C, McGeer EG, McGeer PL. Human neurons generate C-reactive protein and amyloid P: upregulation in Alzheimer's disease. Brain Res. 2000;887(1):80-9. doi: 10.1016/s0006-8993(00)02970-x.
26. Mancinella A, Mancinella M, Carpinteri G, Bellomo A, Fossati C, Gianturco V, et al. Is there a relationship between high C-reactive protein (CRP) levels and dementia? Arch Gerontol Geriatr. 2009;49(1):185-94. doi: 10.1016/j.archger.2009.09.028.
27. Shu Y, Li R, Qiu W, Chang Y, Sun X, Fang L, Kermode AG. Association of serum gamma-glutamyltransferase and C-reactive proteins with neuromyelitis optica and multiple sclerosis. Mult Scler Relat Disord. 2017;18:65-70. doi: 10.1016/j.msard.2017.09.021.
28. Hon G, Hassan M, van Rensburg SJ, Abel S, Marais DW, van Jaarsveld P, et al. Immune cell membrane fatty acids and inflammatory marker, C-reactive protein, in patients with multiple sclerosis. Br J Nutr. 2009;102(9):1334-40. doi: 10.1017/S0007114509382185.
29. Guzel I, Mungan S, Oztekin ZN, Ak F. Is there an association between the Expanded Disability Status Scale and inflammatory markers in multiple sclerosis?. J Chin Med Assoc. 2016;79(2):54-7. doi: 10.1016/j.jcma.2015.08.010.
30. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis. 2000;35(3):469-76. doi: 10.1016/s0272-6386(00)70200-9.

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