Analysis of the albumin level, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio in Guillain-Barré syndrome

Análise do nível de albumina, da relação neutrófilo-linfócito e linfócito-plaquetas na síndrome de Guillain-Barré

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ABSTRACT

The purpose of this study was to investigate the prognostic value of the pretreatment and post-treatment albumin level, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) in subtypes of Guillain-Barré syndrome (GBS). A retrospective analysis of 62 patients with GBS treated between 2011 and 2015 in Dicle University Hospital, Turkey, was carried out. The pretreatment and post-treatment albumin, NLR, and PLR were documented, together with acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy, motor sensory axonal neuropathy, and Hughes' scores. Post-treatment albumin levels in GBS were significantly reduced, and albumin level was negatively correlated with the Hughes scores. Elevated pretreatment NLRs and PLRs were significantly associated with AIDP. There were no correlations between the Hughes scores, NLR, and PLR. The results point to a negative correlation between albumin levels and GBS disability and suggest that the NLR and PLR may be promising blood biomarkers of AIDP.

Keywords: Guillain-Barré syndrome; albumin; neutrophil-lymphocyte ratio; platelet-lymphocute ratio.

RESUMO

O objetivo deste estudo foi investigar o valor prognóstico dos níveis pré e pós-tratamento de albumina , da relação neutrófilo/linfócito (RNL) e da relação plaqueta/linfócito (RPL) em subtipos de síndrome de Guillain-Barré (SGB). Realizou-se uma análise retrospectiva de 62 pacientes com GBS, tratados entre 2011 e 2015 no Hospital da Universidade Dicle, na Turquia. Os valores pré e pós-tratamento de albumina, RNL e RPL foram documentados, juntamente com polirradiculoneuropatia desmielinizante inflamatória aguda, (PDIA) neuropatia axonal motora aguda, neuropatia axonal sensorial motora e pontuações de Hughes. Os níveis de albumina reduziram significativamente pós-tratamento e correlacionaram-se negativamente com as pontuações de Hughes. RNLs e RPLs pré-tratamento elevados foram significativamente associados à PDIA. Não houve correlação entre as pontuações de Hughes, RNL e RPL. Os resultados apontam uma correlação negativa entre os níveis de albumina e a deficiência na SGB e sugerem que a RNL e a RPL possam ser promissores biomarcadores sanguíneos para PDIA.

Palavras-chave: síndrome de Guillain-Barré; albumina; relação neutrófilo/linfócito; relação linfócito-plaquetas.

Guillain-Barré syndrome (GBS) is an acute immune-mediated inflammatory disease of the peripheral nervous system. It is characterized by acute onset and rapid progressive symmetric weakness and areflexia[1]. Human and animal studies have provided convincing evidence that GBS, at least in some cases, is caused by an infection-induced aberrant immune response that damages peripheral nerves[1,2]. Molecular mimicry of pathogen-borne antigens, leading to the generation of cross-reactive antibodies that also target gangliosides, is part of the pathogenesis of GBS, and the nature of the antecedent infection and specificity of such antibodies partly determine the subtype and severity of the syndrome[3]. The most common type of GBS is acute inflammatory demyelinating polyradiculoneuropathy (AIDP). In AIDP, the immune response damages myelin, which is the covering that protects axons and promotes the efficient transmission of nerve impulses. In acute motor axonal neuropathy (AMAN), only the axons of motor neurons are damaged, whereas the axons of sensory neurons are also damaged in acute motor sensory axonal neuropathy (AMSAN).

Neurological disorders can stimulate the production of a high level of inflammation, resulting in an increase or decrease in acute phase reactans[4]. Some acute phase proteins, such as albumin, decrease during inflammation, and albumin

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levels may be related to the course and outcome in GBS[4]. The neutrophil-to-lymphocyte ratio (NLR) is calculated from the white blood cell count and is a novel prognostic and inflammatory marker in patients with neurological diseases[5,6]. The platelet-to-lymphocyte ratio (PLR) is a new biomarker of inflammation[7]. The PLR is thought to be a sensitive marker and to be a prognostic factor in many malignancies[8]. Changes in the levels of acute phase reactants, such as albumin, the NLR, and the PLR have not been well studied in patients with GBS. In this study, we aimed to evaluate the albumin level, NLR, and PLR in patients with GBS. We also evaluated the association between disease prognosis and the albumin level, NLR, and PLR.

METHODS

This study was conducted retrospectively in the Neurology Department of Dicle University, Diyarbakir, Turkey. The data for the study were extracted from the medical records of patients who attended the hospital between January 2011 and January 2016. The study included 62 patients with GBS. Demographics, age, sex, clinical features, electrophysiology, subtype, and treatment-related outcomes were assessed. A diagnosis of GBS was based on the criteria of the Brighton Collaboration GBS Working Group[9]. The strength of the proximal and distal muscles of the upper and lower limbs was classified as 0–5, according to the criteria of the Medical Research Council. Each patient was evaluated according to Hughes et al.'s disability score at the time of hospital admission and discharge[10].

All the patients underwent physical and neurological examinations, liver and kidney function tests, and lipid profiling. In all cases, a complete blood count was also obtained, and electrolyte levels were tested. Electromyography (Nihon-Kohden) was performed in each patient. The classification of the patients as having an axonal or demyelinating subtype was based on the electrodiagnostic criteria of Hadden et al.[11], and an AMSAN diagnosis was based on the criteria of Rees et al.[12].

Exclusion criteria included severe heart failure, autoimmune disease, diabetes mellitus, malignant hypertension, Cushing's syndrome, central nervous system vasculitis, congenital vascular disease, trauma, dissection, thyroid and kidney dysfunction, liver failure, and local and systemic infection.

Venous blood samples were collected when the patient initially presented to the emergency department or intensive neurology care unit (pretreatment-1) and 96–120 h after the first observation (post-treatment-2). The serum albumin levels were measured using a Beckman Coulter CX9 (Beckman Coulter, Inc., Brea, CA) chemistry analyzer. At our hospital, a serum albumin range of 3.5–5.5 gr/dL is considered normal. Hematologic indices were measured using an automated hematology analyzer system (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, ILs). All subsequent analyses were based on absolute cell counts. The baseline NLR was measured by dividing the neutrophil count by the lymphocyte count, and the PLR was measured by dividing the platelet count by the lymphocyte count.

Statistical analysis

The statistical analyses were performed using SPSS software, version 20.0 (SPSS Inc., Chicago, IL). Continuous data are presented as mean ± standard deviation (SD). Between-group differences in continuous variables were determined by a Student's t test or the Mann–Whitney U test for variables, with or without a normal distribution, respectively. To test whether the data showed a normal distribution, the Kolmogorov–Smirnov test was used. Categorical variables were summarized as percentages and compared with a one-way ANOVA test. Relationships between the variables were examined by calculating Pearson's and Spearman's correlation coefficients. To find independent associates of the Hughes' score, variables with a p value of ≤ 0.05 in a bivariate correlation analysis and univariate analysis were selected for multiple linear regression analyses. The cut-off values and corresponding sensitivity and specificity values for the prediction of the AIDP based on the serum albumin level, NLR, and PLR were estimated by receiving operator characteristic (ROC) curve analysis. A p value of < 0.05 was accepted as the threshold for determining statistical significance.

RESULTS

Sixty-two patients were enrolled in this study. Of the patients with GBS, 36 were men (58.1%), and 26 were women (41.9%). The mean age of the patient group was 48.0 ± 19.84 (17–89). Four of the patients died. Intravenous immunoglobulin was administered to all the patients.

The mean serum albumin levels were 3.58 ± 0.55 (2–4.6) at the first observation (albumin-1), and 30.6% of the patients (n = 19) had hypoalbuminemia. The mean serum albumin levels after 96–120 h (albumin-2) were 3.32 ± 0.59 (1.5–4.5), and 54.8% of the patients (n = 34) had hypoalbuminemia. Three patients were treated with 100 ml of 25% albumin via intravenous infusion. The albumin-1 (baseline/pretreatment) levels were significantly lower than the albumin-2 (post-treatment) levels (p < 0.05). The albumin-1 and -2 levels were negatively correlated with the Hughes' scores (admission/discharge). Thirty-five of the patients had AIDP, 12 had AMAN, and 15 had AMSAN. The Table shows the comparisons of the demographic features and laboratory findings among the subgroups. In the patients with AIDP, the neutrophil-1 and -2 levels (pre- and post-treatment levels, respectively) and NLR-1 (pretreatment) were significantly higher than those of the patients with AMAN and AMSAN. (p < 0.05). The pretreatment PLR (PLR-1) was significantly higher in the patients with AIDP when compared with those with AMAN (p < 0.05) The neutrophil-1 and -2 and lymphocyte-1 (pretreatment)

and -2 (post-treatment) levels were significantly higher in the patients with AIDP, as compared to those of the patients with AMSAN (p < 0.05). When the results of the pre- and post-treatment measurements were compared, there were no correlations between the Hughes' scores (admission/discharge) and neutrophil-1 and -2, lymphocyte-1 and -2, platelet-1 and -2, NLR-1- and 2, and PLR-1 (p > 0.05).

A cut-off NLR-1 of 3.275 predicted AIDP, with 83% sensitivity and 93% specificity (ROC area under the curve [AUC] of 0.928, 95% CI, 0.860–0.995, p < 0.001). A cut-off PLR-1 of 121.8 predicted AIDP, with 74% sensitivity and 70% specificity (ROC AUC of 0.761, 95% conficende interval [CI] 0.638–0.883, p < 0.001; Figure)

DISCUSSION

This study demonstrated that serum albumin levels decreased in GBS patients in the subacute period and that there was a negative correlation between albumin levels and Hughes' scores (admission/discharge). The NLR and PLR increased in AIDP during the acute period. To the best of our knowledge, this is the first clinical study to evaluate the association of GBS subtypes with serum albumin levels and the NLR and PLR.

The serum albumin concentration depends on various factors, such as the synthesis, rate of degradation, distribution, and exogenous loss of albumin, as well as nutritional intake and colloid oncotic pressure changes. The presence of systemic inflammation affects the synthesis of albumin[13,14,15,16]. Albumin is a late-reacting negative acute-phase protein[17].

The present study demonstrated the following: hypoalbuminemia is common in patients with GBS, it decreases after the subacute period, and there is a negative correlation between albumin levels and GBS disability. The mean pre- and

post-treatment serum albumin levels of the AIDP group were lower than those of the other groups. Such decreases in mean albumin levels in AIDP are thought to be mainly due to inflammation, hemodilution, or an acute phase response.

Pathophysiological changes in GBS depend upon the subtype. Immune reactions directed against epitopes in Schwann cell surface membrane or myelin can cause AIDP[18]. Cellular and humoral immune responses participate in these pathophysiological processes, with infiltration of epineural and endoneural small vessels by lymphocytes and monocytes causing segmental myelin degeneration throughout the nerve[19]. In demyelination forms of GBS, Berciano et al.
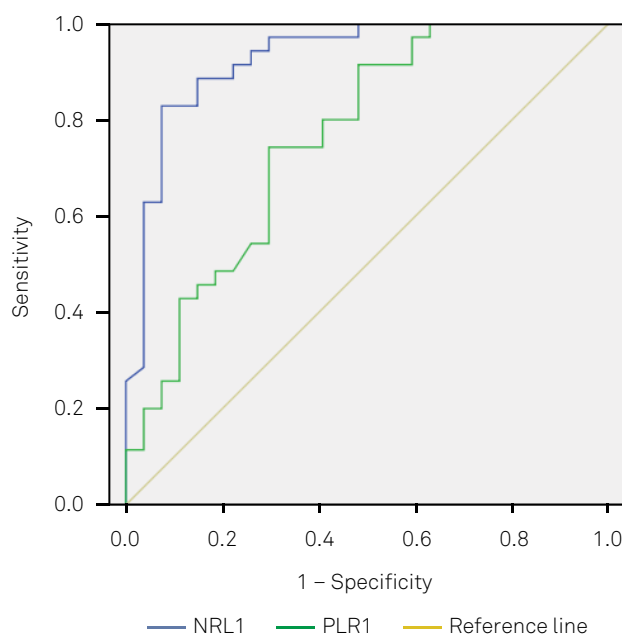
NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio.
Figure. The Receiving Operator Characteristic (ROC) curve analysis of NLR and PLR for prediction Guillain-Barre syndrome (GBS).

Table. The demographic and laboratory characteristics of the patients with Guillain-Barré syndrome (GBS).

Variables	AIDP (n = 35)	AMAN (n = 12)	AMSAM (n = 15)	p	p1	p2	p3
Age	50.23 ± 20.63	41.08 ± 18.24	48.33 ± 19.17	0.393	0.360	0.949	0.616
Hughes' score	3.29 ± 0.96	3.25 ± 0.75	3.47 ± 1.06	0.792	0.993	0.811	0.826
Albumin-1 (gr/dl)	3.52 ± 0.61	3.70 ± 0.48	3.63 ± 0.50	0.597	0.613	0.806	.946
Neutrophil-1 (10^3/mL)	9.07 ± 4.53	5.36 ± 2.23	5.30 ± 2.00	0.001	0.011	0.005	0.999
Lymphocyte-1 (10^3/mL)	1.910 ± 0.740	2.361 ± 0.498	2.570 ± 1.160	0.028	0.239	0.032	0.792
Platelet-1 (10^3/mL)	289.57 ± 82.52	233.00 ± 84.28	288.40 ± 87.67	0.124	0.119	0.999	0.213
NLR-1	5.78 ± 5.23	2.36 ± 1.20	2.15 ± 0.54	0.004	0.035	0.013	0.990
PLR-1	177.48 ± 104.97	98.58 ± 32.22	124.91 ± 46.70	0.012	0.018	0.115	0.699
Hughes'score*	3.37 ± 1.33	2.92 ± 0.67	2.87 ± 1.36	0.321	0.521	0.391	0.994
Albumin-2 (gr/dl)	3.18 ± 0.64	3.471 ± 0.526	3.52 ± 0.47	0.105	0.302	0.142	0.969
Neutrophil-2 (10^3/mL)	7.60 ± 5.10	4.31 ± 1.30	4.45 ± 1.93	0.011	0.046	0.037	0.996
Lymphocyte-2 (10^3/mL)	1.81 ± 0.81	2.14 ± 0.74	2.44 ± 0.87	0.046	0.460	0.041	0.611
Platelet-2 (10^3/mL)	252.88 ± 94.50	232.50 ± 73.34	262.53 ± 55.50	0.638	0.744	0.925	0.621
NLR-2	6.66 ± 9.93	2.34 ± 1.31	1.90 ± 0.73	0.070	0.210	0.112	0.988
PLR-2	173.09 ± 109.83	120.65 ± 64.22	117.20 ± 40.13	0.070	0.199	0.118	0.995

Data are presented as mean standard deviation. NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; AIDP: acute inflammatory demyelinating polyradiculoneuropathy; AMAN: acute motor axonal neuropathy; AMSAN: acute motor sensory axonal neuropathy;*after discharge; p: ANOVA test significance value. p1: significance between AIDP and AMAN. p2: significance between AIDP and AMSAN. p3: significance between AMAN and AMSAN.

showed that spinal root sections had extensive and almost pure macrophage-associated demyelination, with the occasional presence of T lymphocytes and neutrophil leukocytes[20]. On the other hand, immune reactions against epitopes in the axonal membrane cause AMAN and AMSAN[21]. In these variants of GBS, the axon is affected, without an inflammatory response[21]. The primary immune process is directed at the nodes of Ranvier, leading to functional axonal involvement with conduction block caused by paranodal myelin detachment, node lengthening, sodium channel dysfunction, and altered ion and water homeostasis[22]. These pathophysiological processes may be rapidly reversed in some patients or it may progress to axonal degeneration. Acute motor axonal neuropathy involves the motor nerves of the ventral roots, peripheral nerves, and preterminal intramuscular motor twigs[23]. In AMSAN, sensory nerves are also affected. These pathophysiological processes may increase the importance of lymphocytes and neutrophils as diagnostic features of GBS subtypes. In this study, neutrophilia was detected in AIDP.

According to some studies, the NLR and PLR are new biomarkers of the presence of inflammation[24,25]. Alan et al.[24] showed that the NLR and PLR might be associated with the presence and severity of Behçet's syndrome. Kokcu et al.[26] reported that the NLR, platelet count, and PLR were elevated in late stages of ovarian cancer. They also claimed that the PLR was an independent prognostic factor of the stage of epithelial ovarian cancer. In the present study, NLR-1 was a statistically significant biomarker in AIDP, and PLR-1 was a statistically significant biomarker in AIDP but not AMAN. When the results of the pretreatment and post-treatment measurements were compared, there were no correlations between the Hughes' scores (admission/discharge) and neutrophil-1 and -2, lymphocyte-1 and -2, platelet-1 and -2, NLR-1 and -2, and PLR-1. The data demonstrated that a pretreatment NLR value of 3.275 predicted the presence of the acute period of AIDP with 83% sensitivity and 93% specificity. A pretreatment PLR of 121.8 predicted the presence of the acute period of AIDP, with 74% sensitivity and 70% specificity.

In conclusion, decreased albumin levels may exacerbate GBS-related disability. Decreased NLRs and PLRs may indicate the presence of AIDP, but they are not associated with the severity of the disease. The NLR may be a useful diagnostic marker of AIDP. Larger prospective studies are needed to support the findings of the present study.

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