http://www.medscidiscovery.com
OPEN ACCESS JOURNAL

ISSN: 2148-6832

MSD Medical Science and Discovery
2016; 3(8):305-11

Original Article Doi: 10.17546/msd.90383

The Clinical Significance of the Neutrophil-to-Lymphocyte Ratio in Patients with Guillain-Barré Syndrome Independent of Infection

Sirma Geyik[1*], Hakan Bozkurt[2], Munife Neyal[1], Remzi Yigiter[1], Samiye Kuzudisli[3], Seval Kul[4]

Abstract

Objective: In the present study, we aimed to determine the predictive value of neutrophil-to-lymphocyte ratio (NLR) in the diagnosis of Guillain-Barré Syndrome (GBS).

Material and Methods: This retrospective study enrolled 94 GBS patients and a control group of 101 healthy subjects.

Results: GBS patients had significantly higher NLR, C- Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) values at presentation than the healthy control group ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively). Patients unresponsive to IVIg therapy had significantly higher NLR values at the time of admission in comparison to responsive patients ($p=0.001$). NLR was significantly and positively correlated with the disease severity, CRP and ESR. A receiver operating characteristic (ROC) analysis of the ability of NLR to predict GBS showed a cutoff value of 3.5 (sensitivity 62.8%, specificity 90.1%). The cutoff value was 11 for CRP (sensitivity 52.7%, specificity 86%) and 12.3 for ESR (sensitivity 51.3%, specificity 82%). Exclusion of patients with signs of infection at presentation gave a NLR value of 3.2, which had a sensitivity of 61.6% and a specificity of 89.8% for predicting GBS.

Conclusion: Whereas ESR and CRP lost their significance in predicting GBS. Unlike ESR and CRP, NLR might be a promising marker in GBS regardless of infection.

Keywords: Guillain-Barré Syndrome, neutrophil-to-lymphocyte ratio, C-reactive protein, erythrocyte sedimentation rate

Introduction

Guillain-Barre Syndrome (GBS) is a progressive immune-related polyradiculoneuropathy that is the most common cause of acute and progressive generalized paralysis (1). There is still little knowledge on the biochemical and immunological markers that can be used to support the diagnosis of GBS. Most patients (60% to 70%) have a history of surgical intervention, vaccination or infections, such as an upper respiratory or gastrointestinal infection, that often predate the onset of neurological symptoms by 4 weeks (2).

Several clinical subtypes of GBS have been identified, such as including acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), Miller Fisher Syndrome (MFS), acute pandysautonomia and acute sensory neuropathy (3).

Both cell-mediated immunity and humoral mechanisms are involved in the pathogenesis (4, 5).

The effectiveness of plasmapheresis and intravenous immunoglobulin (IVIg) was demonstrated in randomized trials (6, 7).Recently, the blood neutrophil-to-lymphocyte ratio (NLR) has been studied as a biomarker for systemic inflammation in a number of neurological disorders (8-10) and was found to be associated with a poor prognosis in certain diseases (11). Considering the integral role of inflammation in the development of GBS, we focused on three systemic inflammation markers in affected patients, namely the neutrophil-to-lymphocyte ratio, C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR). To our best knowledge, NLR has not been previously studied in GBS patients.

Received 17-06-2016 **Accepted** 21-06-2016 **Available Online** 15-08-2016
1Gaziantep University, Department of Neurology Gaziantep, Turkey
2 Medical Park Hospital, Neurology Clinic Gaziantep, Turkey
3 Emine-BahaeddinNakiboglu Medical Faculty, Zirve University, Department of Neurology Gaziantep, Turkey
4Gaziantep University, Department of Biostatistics Gaziantep, Turkey
* Corresponding Author :Sırma Geyik: E-mail: drsirmageyik@hotmail.com Phone: +905324830677

Thus, in the current study, we aimed to determine the predictive value of NLR, CRP and ESR in the diagnosis of GBS during the acute phase and to investigate the correlation of NLR with the severity and subtype of the disease, as well as the role of the response to IVIg treatment in GBS patients.

Material and Methods

Study population:

This study is a hospital-based retrospective investigation. Study approval was obtained from the Ethics Committee of Gaziantep University Faculty of Medicine, Turkey. Electronic medical records of 124 patients who were diagnosed with GBS (according to Asbury and Cornblath's diagnostic criteria)(12). 19 at an inpatient clinic of neurology (Department of Neurology, Gaziantep University Sahinbey Research Hospital, Gaziantep/Turkey) between January 2008 and January 2015 were reviewed retrospectively. Patients who were subsequently diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) during follow-up visits after being hospitalized with GBS were excluded. Additionally, patients with a history of alcoholism, diabetes mellitus or exposure to toxic substances, metals or drugs that could cause acute neuropathy and patients with inadequate data were excluded.

Thus, 94 eligible patients not meeting these exclusion criteria were enrolled. The data reviewed for study patients included age, gender, history of antecedent infections, signs of infection at the time of admission (based on clinical and blood parameters), electrophysiological findings, clinical features, information related to treatment, and duration of hospitalization. All GBS patients were classified electro physiologically as AIDP, AMAN or AMSAN using motor nerve conduction criteria (13). The GBS disability score (Hughes grade scale) was used to evaluate the disease severity during hospitalization and the first outpatient appointment (ranging from 3 weeks to 1 month after discharge)(14). Venous blood values at the time of presentation (within a mean period of 5.4±2.7 days after the onset of symptoms (min: 1, max: 15) and those obtained at the first occasion following administration of IVIG (0.4 g/kg/day continuously for 5 days) treatment (min: 2 and max: 10 days) for any reason were recorded for all patients. Sixteen (17%) patients treated with plasmapheresis after IVIg treatment because of a worsened neurological examination, despite receiving IVIg treatment.

A second set of blood samples were taken before the plasmapheresis. Post-treatment hemogram values were available for all 94 patients, but only 22 patients had both CRP and ESR values available; thus, only post-treatment NLR values were recorded. Healthy controls (n=101) matched for age and gender who were admitted to our hospital for routine check-up were randomly chosen from the hospital database if they did not have any symptoms of peripheral neuropathy, clinical signs or laboratory findings suggestive of an infection or a history of chronic illnesses, malignancy or rheumatic disorders.

ESR was measured using the traditional Westergren method. CRP levels were quantified using a nephelometric assay on a Dade Behring Nephelometer BN II device (Siemens Healthcare GmbH, Erlangen, Germany). CBC analysis was performed with a Beckman Coulter (High Wycombe, UK) Gen-S automated analyser within 2 hours of blood sampling. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count in a complete blood count taken before and after IVIg treatment.

Statistical Method:

Student's t-test was used to compare normally distributed numerical variables in two independent groups, and the Mann–Whitney U test was used for non-normally distributed numerical variables. An ANOVA and Fisher's least significant difference (LSD) multi-comparison test were employed to compare normally distributed variables in more than two groups, whereas the Kruskal–Wallis test was used for non-normally distributed variables. Pearson's coefficient of correlation was used to test correlations between numerical variables, and a chi-square test was used for the analysis of correlations between categorical variables.

Receiver operating characteristic (ROC) curves were used to determine the cutoff values for NLR. For descriptive statistics, data are presented as the mean ± standard deviation for numerical variables and the number and percentage for categorical variables. SPSS for Windows version 22.0 software package was used for statistical analyses, and a p value less than 0.05 was considered statistically significant.

Results:

The study enrolled a total of 94 GBS patients, including 32 females and 62 males with a mean age of 48.7±20.6 years (18-86). The control group consisted of a total of 101 healthy individuals (47 females, 54 males) with a mean age of 50.63±19.025 years (18-80). The demographic data, clinical characteristics and blood biochemistry values of the study population are summarized in Table I.

Electrophysiological classification of the GBS patients revealed the following subtypes: AIDP (n = 64), AMAN (n = 16) and AMSAN (n = 14). The mean duration from the onset of symptoms to the confirmed diagnosis of GBS was 5.4±2.7 days (1-15). The mean Hughes score of patients at the initial examination was 3.53±0.49.

Table 1: Demographic Data, Clinical Characteristics, and Blood Biochemistry Values of the Study Population (mean ± SD)

Variable	Controls (n=101)	Patients (n=94)	p value
Age (year)	50.63±19.025	48.7±20.6	0.497
Gender **Female (n %)** **Male (n %)**	 47 (46.5) 54 (53.5)	 32(34) 62(66)	 0.076
BMI	26.53±2.19	26.231±2.35	0.062
NLR **At presentation** **After IVIg treatment**	 2.53±0.94	 5.43±3.98 2,61±0.69	0.001*∞ 0.699° 0.001*≠
WBC (10^9/l) **At presentation** **After IVIg treatment**	 8.78±1.3	 9.42±2.32 8.99±1.9	0.089∞ 0.078≠ 0.081°
Hgb (/µ) **At presentation** **After IVIg treatment**	 13.67±1.32 -	 13.12±1.12 13.06±1.06	 0.127∞ 0.106° 0.118≠
CRP (mg/dl), median (min-max) **At presentation**	 3.7±1.2 (0.05-6.5)	 16.3±14.2 (2.2-86)	 0.001*∞
ESR (mm/h), median (min-max) **At presentation**	 6.4 (1-12)	 16.13±14.3 (4-110)	 0.001*
Hughes score **At presentation** **At 1 month** **Reduction**	 - -	 3.53±0.49 2.09±0.72 1.44	 0.001*≠

*p<0.005 ∞ comparison between GBS patients and controls before treatment
≠ pre-treatment/post-treatment comparison in GBS patients
° pre-treatment/post-treatment comparison between GBS patients and controls

Table 2. Associations between clinical characteristics and pre-treatment/post-treatment NLR values

Variable	n (%)	NLR[1]	NLR[2]	p value
Response to IVIG treatment **Yes** **No** **p value**	 78 (83) 16 (17)	 4,67±3,57 9,10±3,89 0.001*	 2,48±1,58 3,23±2,11 0.171	 0.001* 0.001*
Clinical subtypes **AIDP** **AMAN** **AMSAN** **P value**	 64 (68) 16(17) 14 (15)	 5,41±3.09 5.82±3.09 7,04±3.98 0.252	 3.61±1.41 3.12±1.07 4.46±2.01 0.345	 0.001* 0.001* 0.001*
Signs of infection at presentation **Yes** **No** **P value**	 11(11.7) 83(88.3)	 9.54±5.98 5.15±3.594 0.001*	 4.12±3.13 3.98±2.89 0.135	 0.001* 0.003*
History of infection **Yes** **No** **P value**	 48 46	 6.16±4.3 4.60± 3.8 0.009	 5.04±2.3 3.57±1.8 0.012	 0.360 0.302

1 values of GBS patients at admission at hospital, 2 values of GBS patients after IVIg treatment, * p<0.005

All 94 patients were given IVIg as the baseline therapy. Of these 94 patients, 78 (83%) benefited from this therapy and 16 (17%) continued their treatment with plasmapheresis therapy due to deterioration of their neurological findings, despite IVIg treatment. Six patients (6.4%) receiving both therapies died as a result of clinical deterioration.

Among these 6 patients, the cause of death was sepsis in 4 patients, pulmonary embolism in 1 patient, and 1 patient developed sudden cardiac arrest that was possibly associated with severe autonomic involvement. The mean duration of the hospital stay for all patients was 16.9± 5.4 days (12-90 days). Seventeen patients (18.08%) received antibiotherapy for treatment of intercurrent infections both at presentation and during hospitalization. The mean Hughes score of patients was 2.09±0.72 at the follow-up examination conducted within 3 weeks to 1 month after discharge. There was no significant difference between patient and control groups with respect to age, gender and BMI (Table I). The mean NLR value for patients at presentation (5.43±3.98) was significantly higher than that for the control group (2.53±0.94) (p=0.001), but the values for patients after IVIg treatment (2.61±0.69) were not significantly different from those for controls (p=0.699).

Significantly reduced NLR values were found after IVIg treatment among patients (p=0.001) (Table I).

The mean CRP value for patients at presentation (16.3±14.2 mg/dl) was significantly higher compared to that for the control group (3.7±1.2 mg/dl; p=0.001). Similar findings were also observed for ESR (Table I). When patients were divided into two subgroups based on the IVIg treatment response, the patients unresponsive to IVIg therapy showed significantly higher NLR values at presentation compared with the treatment-responsive patients (p=0.001) (Table II).

At presentation, the mean Hughes score was 3.48±0.38 for patients responding to IVIg and 3.69±0.72 for non-responsive patients, but the difference was not statistically significant (p=0.149). When we classified the patients according to the demyelinating form (AIDP) and axonal form (AMAN and AMSAN) subtypes, we observed the application HGS was higher in the axonal form (p=0.001). NLR values at presentation did not differ significantly between the disease subtypes (p=0.252). Eleven (11.7%) patients had signs of infection (both clinical and laboratory) at presentation, and a significant difference was found between the mean NLR values of infected patients (9.54±5.98) and non-infected patients (5.15±3.94) at presentation (p=0.001). CRP and ESR showed similar findings (Table III).

Based on the medical history, among the patients with clinical signs of infection at presentation, 31 patients (32.9%) had experienced an URTI and 17 (18.1%) patients had experienced diarrhoea within the last month. Patients with a history of infection had a mean NLR of 6.16±4.3, which did not differ significantly from the mean NLR of patients without such a history (4.60±3.80; p=0.009).

Analyses for the correlation between the disease severity and NLR revealed a significant positive correlation for patients between HGS at presentation and NLR values at presentation (r=0.383, p=0,000). A significant positive correlation was also found between the HGS at the follow-up visit within 3 weeks to 1 month after discharge and NLR at presentation (r=0.363 p=0,000). There was a mean improvement of 1.44 points in the HGS following treatment, and a significant negative correlation was observed between the magnitude of improvement in HGS and NLR values at presentation and post-treatment (r=-0.312 p= 0.002 and r=-0.288, p= 0.005, respectively). The application NLR was positively correlated and significantly associated with the length of the hospital stay (r=0.296; p=0.004). NLR at presentation was significantly associated and positively correlated with CRP and ESR at presentation (r=0.351, p=0.001 and r=0.338, p=0.001, respectively).

As determined by the ROC analysis, a NLR value of 3.5 had a 62.8% sensitivity and 90.1% specificity for predicting GBS (the area under curve (AUC), 0.772±0.035; p<0.001). A CRP value of 11 had a 52.7% sensitivity and an 86% specificity for predicting GBS (AUC=0.717±0.0374; p<0.001). An ESR value of 12.3 had a 51.3% sensitivity and an 82% specificity for predicting GBS (AUC=0.698±0.312; p=0,003) (Figure I).

Exclusion of 11 patients with signs of infection at presentation yielded a NLR value of 3.2, which was associated with a 61.6% sensitivity and an 89.8% specificity for predicting GBS (AUC= 0.752±0.031, p<0.001). In these patients, A CRP value of 7.5 had a 48.7% sensitivity and 63% specificity for predicting GBS (AUC=0.645±0.0305; p=0.105). An ESR value of 8.3 had a 46.3% sensitivity and 61% specificity for predicting GBS (AUC= 0.612±0.0317; p=0.137) (Figure II).

Discussion

Based on the results of this study, we found that NLR values were significantly higher in GBS patients than in healthy controls. A NLR value of 3.5 predicted the presence of GBS with a 62.8% sensitivity and 90.1% specificity. The cutoff value for the NLR for predicting GBS, regardless of infection, was 3.2 with a 61.6% sensitivity and an 89.8% specificity.

GBS is an acute inflammatory process that involves the peripheral nerves and nerve roots, and both humoral and cell-mediated immunity mechanisms play an integral role in its pathogenesis (5).

http://dx.doi.org/x10.17546msd.90383

Recently, NLR has been recognized as a simple and cost-effective peripheral biomarker that indicates the inflammatory status because it is believed to reflect the numerical balance between neutrophils and lymphocytes in the blood (9,10,15,16). CRP and ESR are elevated in the event of systemic inflammation, and combined use of ESR and CRP was considered to be more appropriate as inflammatory markers (17).

In the present study, GBS patients had significantly higher NLR, CRP and ESR values compared to healthy controls at presentation. These parameters are known to be influenced by infection (18). Therefore, when we removed the patients with clinical or laboratory signs of infection, the predictive significance of CRP and ESR disappeared, but an NLR value of 3.2 showed a 61.6% sensitivity and an 89.8% specificity for predicting GBS that remained significant.

Recent studies demonstrated that NLR can be used as a marker of disease, but it may also predict the disease severity and a poor prognosis (9,10,11,15,19). Similarly, positive correlations were found among the

initial NLR, the initial Hughes scores, and the length of hospital stay. However, it was expected that patients with a high HGS would have a long hospital stay. There was a 1.44-point average improvement after treatment. NLR at presentation showed a significant negative correlation with an improvement in the Hughes scores. Thus a high NLR may be correlated with a slow recovery. Also, the NLR values of IVIg treatment-resistant patients were higher regardless of the disease severity.

Especially in the axonal form, more cranial nerve involvement and a more rapid and severe need for mechanical ventilation was reported (20). In our study, patients with the axonal form had higher HGS at initiation and discharge.

Despite the current positive correlation with disease severity and NLR, there were no significant differences between subgroups. This may be due to different pathogenesis of subtypes of disease.

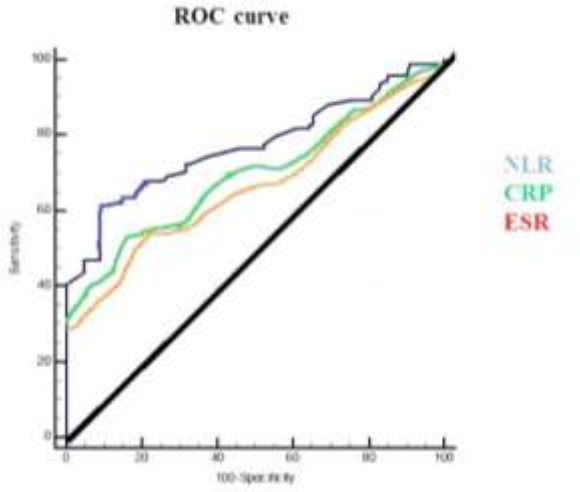

Figure 1.The ROC curve analysis of NLR, CRP and ESR for predicting GBS.

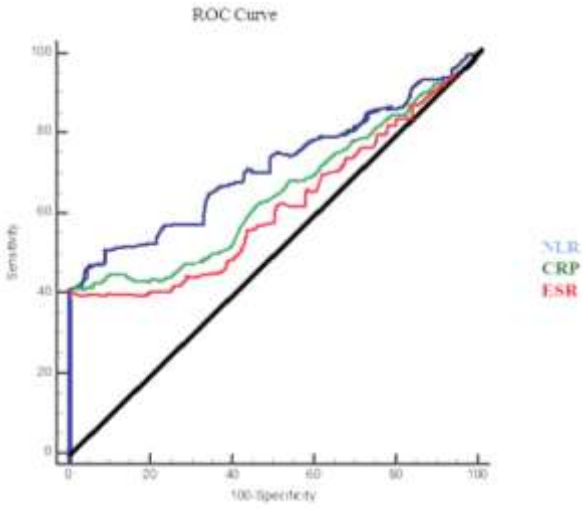

Figure 2.The ROC curve analysis of NLR, CRP and ESR for predicting GBS without infection.

Conclusion

Our study has several limitations. This study used a retrospective design and a small sample size. A major limitation of our study was the failure to obtain follow-up blood samples from all patients at a prespecified time point because they differed in the time of admission and transport to the emergency room. Nevertheless, to the best of our knowledge, the present study is the first to investigate the relationship between NLR and GBS. Unlike ESR and CRP, NLR might be a promising marker in GBS, regardless of infection. Another value, the average for NLR, is an inexpensive, quick and easy measure to obtain, and it might be associated with the severity of the disease..

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical issues: All Authors declare that Originality of research/article etc... and ethical approval of research, and responsibilities of research against local ethics commission are under the Authors responsibilities. The study was completed due to defined rules by the Local Ethics Commission guidelines and audits.

Acknowledgement: Role of Authors:: SG, HB, MN conceived and designed the study;. SG, RY and HB were responsible for data acquisition. SG, HB, MN, SaK, RY and SeK were in charge of data analysis and interpretation and drafted the manuscript. MN and SG were responsible for critical revision of this manuscript. All authors approved the final version of this manuscript.

References

1. Hiraga A, Mori M, Ogawara K, Kojima S, Kanesaka T, Misawa S, Hattori T, Kuwabara S. Recovery patterns and long term prognosis for axonal Guillain-Barre syndrome. Journal of neurology, neurosurgery, and psychiatry.2005; 76(5):719-722.

2. van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barre syndrome. The Lancet Neurology.2008; 7(10):939-950.

3. Van der Meche FG, Van Doorn PA, Meulstee J, Jennekens FG, Centre GB-cgotDNRS.Diagnostic and classification criteria for the Guillain-Barre syndrome.European neurology .2001; 45(3):133-139.

4. Kieseier BC, Kiefer R, Gold R, Hemmer B, Willison HJ, Hartung HP. Advances in understanding and treatment of immune-mediated disorders of the peripheral nervous system. Muscle & nerve.2004; 30(2):131-156.

5. Hughes RA, Hadden RD, Gregson NA, Smith KJ.Pathogenesis of Guillain-Barre syndrome.Journal of neuroimmunology.1999; 100(1-2):74-97.

6. Hughes RA, Raphael JC, Swan AV, van Doorn PA.Intravenous immunoglobulin for Guillain-Barre syndrome.The Cochrane database of systematic reviews.2006(1);CD002063.

7. Efficiency of plasma exchange in Guillain-Barre syndrome role of replacement fluids. French Cooperative Group on Plasma Exchange in Guillain-Barre syndrome.Annals of neurology .1987; 22(6):753-761.

8. Akil E, Bulut A, Kaplan I, Ozdemir HH, Arslan D, Aluclu MU.The increase of carcinoembryonic antigen (CEA), high-sensitivity C-reactive protein, and neutrophil/lymphocyte ratio in Parkinson's disease.Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology .2015; 36(3):423-428.

9. Demirci S, Demirci S, Kutluhan S, Koyuncuoglu HR, YurekliVA.The clinical significance of the neutrophil-to-lymphocyte ratio in multiple sclerosis. The International journal of neuroscience.2015;126(8)1-7.

10. Gokhan S, Ozhasenekler A, Mansur Durgun H, Akil E, Ustundag M, Orak M. Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack. European review for medical and pharmacological sciences.2013; 17(5):653-657.

11. Tokgoz S, Kayrak M, Akpinar Z, Seyithanoglu A, Guney F, Yuruten B. Neutrophil lymphocyte ratio as a predictor of stroke. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association.2013; 22(7):1169-1174.

12. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barre syndrome. Annals of neurology.1990; 27 Suppl:S21-24.

13. Hadden RD, Cornblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV, Swan AV. Electrophysiological classification of Guillain-Barre syndrome: clinical associations and outcome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. Annals of neurology.1998; 44(5):780-788.

14. van Koningsveld R, Steyerberg EW, Hughes RA, Swan AV, van Doorn PA, Jacobs BC.A clinical prognostic scoring system for Guillain-Barre syndrome.The Lancet Neurology.2007; 6(7):589-594.

15. Dirican N, Anar C, Kaya S, et al. The clinical significance of hematologic parameters in patients with sarcoidosis.The clinical respiratory journal. 2014;doi: 10.1111/crj.12178.

16. Sen BB, Rifaioglu EN, Ekiz O, et al. Neutrophil to lymphocyte ratio as a measure of systemic inflammation in psoriasis. Cutaneous and ocular toxicology. 2014;33(3):223-227.

17. Osei-Bimpong A, Meek JH, Lewis SM. ESR or CRP? A comparison of their clinical utility. Hematology. 2007;12(4):353-357.

18. Assasi N, Blackhouse G, Campbell K, et al. Comparative Value of Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) Testing in Combination Versus Individually for the Diagnosis of Undifferentiated Patients With Suspected Inflammatory Disease or Serious Infection: A Systematic Review and Economic Analysis. Ottawa (ON) 2015.

19. Arbel Y, Finkelstein A, Halkin A, et al. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis. 2012;225(2):456-460.

20. Fletcher DD, Lawn ND, Wolter TD, et al. Long-term outcome in patients with Guillain-Barre syndrome requiring mechanical ventilation. Neurology. 2000;54(12):2311-2315.