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Clinical Usefulness of Systemic Inflammatory Markers as Diagnostic and Prognostic Indicators for Restless Leg Syndrome

Sistemik İnflamatuar Belirteçlerin Huzursuz Bacak Sendromu İçin Tanısal ve Prognostik Göstergeler Olarak Kullanırlılığı

Buse Çağla Arı,[1] Esma Kobak Tur[2]

[1]Department of Neurology, Bahçeşehir University Faculty of Medicine, Pendik VM Medical Park Hospital, İstanbul, Turkey
[2]Department of Neurology, Fatih Sultan Mehmet Training and Research Hospital, İstanbul, Turkey

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Correspondence:
Dr. Buse Cağla Arı. Bahçeşehir Üniversitesi Tıp Fakültesi, Pendik VM Medical Park Hastanesi, Nöroloji Anabilim Dalı, İstanbul, Turkey
Phone:
+90 216 579 81 95
e-mail:
juvelia@gmail.com

ABSTRACT

Objectives: Iron depletion and dopamine dysfunction are the best-recognized mechanisms in the pathophysiology of restless leg syndrome (RLS). A novel perspective has risen that inflammation plays a part; however, the evidences remain limited. We investigated the potential roles of systemic inflammatory markers in the disease.

Methods: This cross-sectional study contains 70 patients and 50 healthy controls. We recorded the demographic data from patients' filed archives. RLS was diagnosed by the International Classification of Sleep Disorders Diagnostic Criteria, The severity of disease was evaluated by the International RLS Study Group Rating Scale and patients were divided into four subgroups as "mild (1–10),""moderate (11–20),""severe (21–30)" and "very severe (31–40)" We obtained the blood samples from the medial cubital vein regarding an 8-h of fasting. Red cell distribution width (RDW), platelet-to-lymphocyte (PLR), neutrophil-to-lymphocyte (NLR), and C-reactive-protein-to-albumin (CAR) ratios were estimated and compared with controls.

Results: We detected no difference in gender and age among the groups. The mean NLR was 3.42±2.2 in patients and 1.44±0.64 in controls (p=0.001), PLR was 200.54±180.67 in patients and 63.39±13.76 in controls (p=0.001), and RDW was 50.06±4.27 in patients and 45.43±4.28 in controls (p=0.001). All of them were are statistically higher in patients. RDW was predictive at 37.4 with a 85.7% sensitivity and 40.0% specificity. NLR was at 2.33 with a 58.57% sensitivity and 96%, PLR was predictive at 95.34 with a 65.71% sensitivity and 98% specificity.

Conclusion: PLR, NLR, and RDW are statistically higher in patients, which supports the hypothesis that there is a relationship between peripheral inflammation and RLS. Moreover, PLR, NLR, and RDW may be used as biomarkers to predict the disease. Additional investigations are needed to understand the nature of the disease.

Keywords: C-reactive protein-to-albumin; neuroinflammation; neutrophil-to-lymphocyte; platelet-to-lymphocyte; red cell distribution width; restless leg syndrome.

ÖZET

Amaç: Huzursuz Bacak Sendromu (HBS) patofizyolojisinde demir eksikliği ve dopamin disfonksiyonu en iyi bilinen mekanizmalardır. Enflamasyonun rol oynadığına dair yeni bir bakış açısı ortaya çıkmasına rağmen kanıtlar sınırlıdır. Bu çalışmada, sistemik inflamatuar belirteçlerin hastalıktaki potansiyel rollerini araştırmayı hedefledik.

Yöntem: Bu kesitsel çalışma 70 hasta ve 50 sağlıklı kontrol içermektedir. Hastaların demografik verileri dosyalanmış arşivlerinden kaydedildi. HBS, Uluslararası Uyku Bozuklukları Tanı Kriterleri Sınıflandırması (ICSD-3) ile teşhis edildi ve şiddeti Uluslararası Huzursuz Bacak Sendromu Çalışma Grubu Derecelendirme Ölçeği (IRLSSG) ile değerlendirildi. Hastalar "hafif (1-10)", "orta (11-20)", "şiddetli (21-30)" ve "çok şiddetli (31-40)" olmak üzere dört alt gruba ayrıldı.

8 saatlik açlığı takiben medial kübital venden kan örnekleri alındı. Kırmızı hücre dağılım genişliği (RDW), trombosit-lenfosit (PLR), nötrofil-lenfosit (NLR) ve C-reaktif-protein-albümin (CAR) oranları hesaplandı ve kontrol grubu verileri ile karşılaştırıldı.

Bulgular: Gruplar arasında cinsiyet ve yaş açısından fark tespit edilmedi. Hastalarda ortalama NLR 3.42±2.2 ve kontrollerde 1.44±0.64 (p=0.001), PLR hastalarda 200.54±180.67 ve kontrollerde 63.39±13.76 (p=0.001) ve RDW hastalarda 50.06±4.27 ve kontrol grubunda 45.43±4.28 saptandı (p=0.001). Tüm belirteçler hasta grubunda istatistiksel olarak daha yüksekti. RDW, %85.7 duyarlılık ve %40.0 özgüllük ile 37.4'te öngörücüydü. NLR %58.57 duyarlılık ve %96 ile 2.33'te, PLR %65.71 duyarlılık ve %98 özgüllük ile 95.34'te öngörücüydü.

Sonuç: PLR, NLR ve RDW'nin hastalarda istatistiksel olarak daha yüksek olması, periferik inflamasyon ile HBS arasında bir ilişki olduğu hipotezini desteklemektedir. Ayrıca, PLR, NLR ve RDW, hastalığı öngörmek için biyobelirteçler olarak kullanılabilir. Hastalığın doğasını anlamak için ek araştırmalara ihtiyaç vardır.

Anahtar sözcükler: C-reaktif protein-albümin oranı; nöroinflamasyon; nötrofil-lenfosit oranı; platelet-lenfosit oranı; kırmızı hücre dağılım genişliği; huzursuz bacak sendromu.

Restless leg syndrome (RLS) is defined as an involuntary need to move the lower extremities or other body parts with an unpleasant feeling. This urge becomes more prominent at night due to immobility, and a temporary relief arises after the physical activity.[1,2] This prolonged situation leads to sleep disturbances and insomnia, therefore, it decreases the quality of life.[2,3] Even though its pathophysiology has still not entirely been discovered, iron depletion, hormonal fluctuations, dopamine D3 receptor dysfunctions, and genetic susceptibility have been considered as some of the underlying mechanisms.[2,4]

In recent years, a novel opinion has become widespread that systemic inflammation plays a part in the pathophysiology and the researchers have noticed an increased association among post-inflammatory processes and RLS.[5,6] Even though none of the following notions have been conclusively proven to date, it has been hypothesized that hepcidin decreases the iron levels during the inflammation, attacks the central nervous system, and potentiates the genetic adaptations of RLS-related genes.[7,8] We have the knowledge that serum platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein-to-albumin ratio (CAR), and red cell distribution width (RDW) measurements effectively mirror the inflammatory activity.[9,10] Therefore, we inspected serum inflammatory markers of NLR, PLR, RDW, and CAR values in patients with RLS based on the observations.[9] This research is designed to explore their potential roles on the disease severity and to determine their usability as diagnostic biomarkers in the early-stage.

Methods

Subjects

We evaluated the age and sex-matched 205 individuals between April 2019 and April 2020 for this cross-sectional study. Two neurologists diagnosed the patients as RLS according to the International Classification of Sleep Disorders Diagnostic Criteria.[11] We achieved the demographic data from patients' filed records. Disease severity was assessed by the Turkish version of the International RLS Study Group Rating Scale,[12] and patients were divided into four subgroups as "mild (1–10)," "moderate (11–20)," "severe (21–30)" and "very severe (31–40)." Patients were divided into two groups according to RLS onset over and under 5 years as an experimental design.[13] We excluded the patients with iron or ferritin deficiency, with a diagnosis of a neurological, rheumatological, renal, metabolic, infectious, or cardiovascular diseases, or under treatment with anti-inflammatory drugs, neuroleptics, antidepressants, and steroids. Individuals with body mass index (kg/m^2) above 25, have a history of smoking or using illicit drugs and alcohol, and have focal lesions on basal ganglia on neuroimaging were also not included. According to the exclusion criteria, we ultimately included seventy individuals in the patient group and fifty healthy individuals in the control group. The evaluation process was demonstrated in Figure 1.

We obtained the blood samples from the medial cubital vein regarding an 8-h of fasting. Laboratory data of C-reactive protein (CRP) and albumin concentrations were run by ADVIA 1800 (Siemens Healthcare Diagnostics, Tokyo, Japan) and hematology parameters by Mindray BC6800 (Shenzen, Mindray Bio-Medical Electronics, Co., Ltd). Values of albumin were stated in grams per deciliter (g/dL), CRP was milligrams per deciliter (mg/dL), and platelet, neutrophil, and lymphocyte were stated as microliter (µl). The NLR, PLR, and CAR were estimated by dividing neutrophil to lymphocyte, platelet to lymphocyte, and CRP to albumin values. Siirt University Ethical Committee permitted the study with the number of 2020/1303.

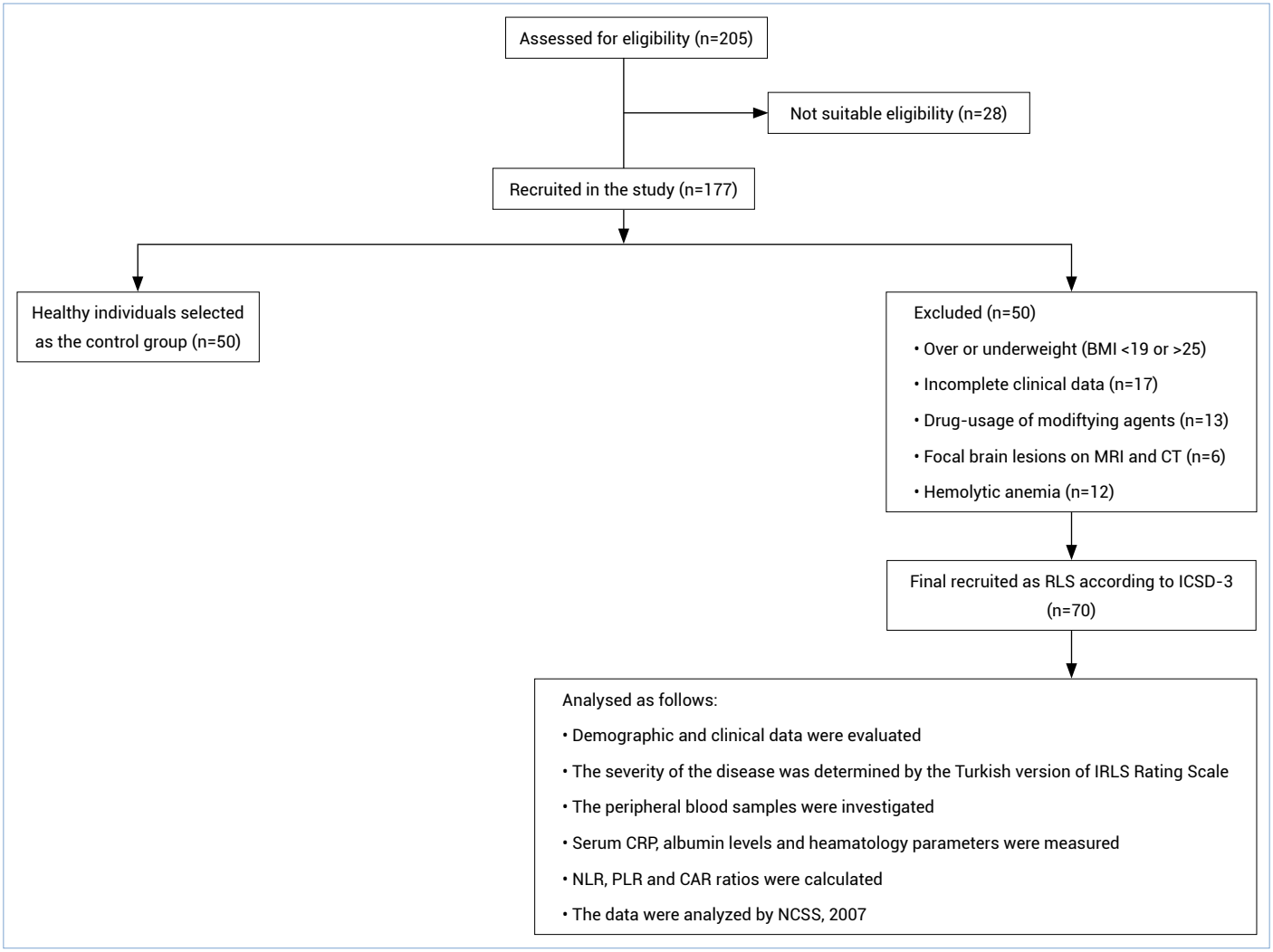

Figure 1. RSTROBE diagram for the evaluation of the individuals.

Statistical Analysis

For data processing and statistical evaluation, Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) software was initiated. Average, standard deviation, median, mean, frequency, percentage, minimum, and maximum ratios were selected for descriptive statistics. We analyzed the normality of the quantitative variables with the Shapiro – Wilk test. Student t-test was chosen for comparing normally-distributed quantitative variables among two groups. Mann–Whitney U test evaluated the non-normal distributed quantitative data. For comparing more than two groups of non-normally distributed data, Kruskal – Wallis and Dunn-Bonferroni tests were preferred. The Pearson Chi-square test, Fisher's exact test, and Fisher-Freeman-Halton exact test were assessed to compare qualitative data. We tested the correlation between RLS Scale scores and the disease's duration with Spearman's Correlation Analysis. Diagnostic screening tests [sensitivity, specificity, positive predictive value, and negative predictive value] and receiver operating characteristic (ROC) analysis were preferred to determine the predictive values of RDW, NLR, and PLR. The results are significant at the p=0.05 value.

Results

We conducted the research with 120 individuals. Among them, 60.8% (n=73) were in female gender, and 39.2% (n=47) were in male gender. The female ratio was 56.8% (n=41) in the patient group and 50% (n=25) in the control group. The mean age was 43.40±15.70 years in patients and 42.4±9.66 years in controls (p=0.708). No statistical significance was detected between the patient and the control group on age and sex (p>0.01, p>0.05). The mean RDW values were higher in the patient group (50.06±4.27) than the control group (45.43±4.28), significantly (p=0.001). The mean neutrophil

Table 1. Clinical and demographical features of the individuals

Features	Patients (n=70)	Controls (n=50)	p
Age (n)			[a]**0.708**
Min–Max (med)	21–78 (38.5)	22–74 (41.5)	
Av±SD	43.4±15.7	42.4±9.66	
Sex			[b]**0.548**
Female	41 (58.6)	32 (64.0)	
Male	29 (41.4)	18 (36.0)	
RDW (%)			[a]**0.001****
Min–Max (med)	41.2–59.4 (49.6)	36.1–55.7 (44.9)	
Av±SD	50.06±4.27	45.43±4.28	
CAR			[c]**0.139**
Min–Max (med)	0.01–5 (0.68)	0–1.9 (0.4)	
Av±SD	0.92±1.08	0.54±0.44	
PLR			[c]**0.001****
Min–Max (med)	47.24–945 (143.71)	44.7–108.7 (60.5)	
Av±SD	200.54±180.67	63.39±13.76	
NLR			[c]**0.001****
Min–Max (med)	0.56–15 (2.81)	0.56–4.69 (1.3)	
Av±SD	3.42±2.2	1.44±0.64	

a: Student-t test; b: Pearson Chi-square test; c: Mann Whitney U test; d: Fisher's exact test; *: P<0.05; **: P<0.01; RDW: Red cell distribution witdh; CAR: CRP-to-albumin ratio; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; SD: Standard deviation; Min: Minimum; Max: Maximum.

and platelet concentrations were statistically elevated in the patients than the controls (p=0.001). Serum red blood cell and lymphocyte concentrations were statistically decreased in the patient group (p=0.003, p=0.001, respectively). The mean PLR value were 200.54±180.67 in the patients and 63.39±13.76 in the controls, yet we noticed a significant difference (p=0.001). Ultimately, the NLR values were 3.42±2.2 in the patients and 1.44±0.64 in controls, and a statistical difference was detected between the groups (p=0.001). CRP and albumin values did not reveal a significance concerning the groups (p=0.208, p=0.147). The mean CAR levels in patients were 0.92±1.08 and 0.54±0.44 in the control group; however, we detected no difference among the groups (p=0.139). The detailed information of blood parameters of the individuals are presented in Table 1.

In patients, 41.42% (n=29) were treated with pramipexole, 8.57% (n=6) with gabapentin, 22.85% (n=16) with iron supplementation, and 12.85% (n=9) patients were drug-naïve. While comparing the patients according to their RLS Scale scores, the age and gender distributions did not reveal a significance (p=0.062, p=0.412). Serum iron, ferritin, RDW, CRP, albumin, platelet, neutrophil, lymphocyte concentrations,

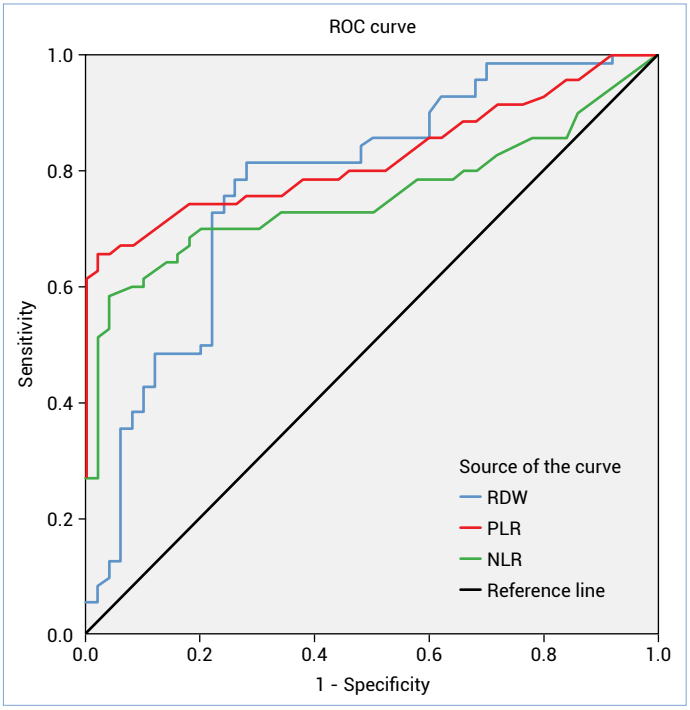

Figure 2. ROC curve of NLR and PLR according to groups.

and CAR, PLR, NLR levels did not differ significantly according to the RLS Scale scores of the patients (p=0.293, p=0.060, p=0.169, p=0.198, p=0.222, p=0.109, p=0.731, p=0.810). Finally, we revealed a positive correlation between RLS scale sores and the duration of the disease. The rest of the outcomes are shown in Table 2.

The ROC curve analyzes were performed for NLR, PLR, and RDW to predict the disease. The confidence intervals (CI) of PLR, NLR, and RDW were under 95% (95% CI: 0.669–0.844, 0.751–0.900, 0.693–0.865; respectively), and the cut-off rates were ≥2.3, ≥95.34, and ≥37.4, as shown in Table 3. The specificities were 96.00, 98.00, and 40.00; the sensitivities were 58.57, 65.71, and 85.70; and the areas under the curve were calculated as 0.757, 0.826, 0.779; respectively (p<0.001), as shown in Figure 2. The complete results of the analyses are presented in Table 3.

Discussion

The study's initial objective was to investigate the potential roles of serum inflammatory biomarkers in RLS, and to reveal the possibility of their usage as biomarkers to predict the disease. We have concluded that serum RDW, PLR, and NLR values are associated with RLS; however, we did not discover any association between RLS's severity and such parameters. We only found that as the disease's duration increases, the patients' RLS scores rise;

Table 2. The features of the patient group consistent with the severity of the disease

Features	RLS Scale Scores				p
	Mild (n=16)	Moderate (n=23)	Severe (n=24)	Very severe (n=7)	
Age (n)					[e]0.062
Min–Max (med)	21–73 (38)	25–78 (38)	25–77 (38)	39–72 (55)	
Av±SD	42.06±17.77	41.26±14.81	41.96±14.42	58.43±12.23	
Sex					[f]0.412
Female	10 (62.f5)	16 (69.6)	11 (45.8)	4 (57.1)	
Male	6 (37.5)	7 (30.4)	13 (54.2)	3 (42.9)	
Onset					
<5 years	13 (81.3)	17 (73.9)	16 (66.7)	1 (14.3)	[f]0.017*
≥5 years	3 (18.8)	6 (26.1)	8 (33.3)	6 (85.7)	
Min–Max (med)	0.3–9 (2)	0.5–7.5 (3)	0.6–9 (3.5)	1–10 (6.5)	[e]0.006**
Av±SD	2.65±2.48	3.07±2.18	4.27±2.48	6.71±3.11	
Treatment					[f]0.076
Pramipexole	7 (43.8)	5 (21.7)	13 (54.2)	4 (57.1)	
Gabapentin	1 (6.3)	7 (30.4)	6 (25.0)	2 (28.6)	
Drug-naïve	3 (18.8)	2 (8.7)	3 (12.5)	1 (14.3)	
Iron	5 (31.3)	9 (39.1)	2 (8.3)	0 (0.0)	
Iron (mg/dL)					[e]0.293
Min–Max (med)	173–282.4 (244)	178–278 (237)	86–282 (245.5)	234–275 (252)	
Av±SD	225.9±42.15	229.37±28.66	221.28±50.36	254.36±13.65	
Ferritin (mg/L)					[e]0.060
Min–Max (med)	316.3–1224.4 (761.4)	317–1433.5 (818.6)	294.4–1264.1 (444.5)	311.1–1267 (429)	
Av±SD	714.89±264.87	797.76±327.26	563.58±304.66	700.51±415.49	
RDW (%)					[e]0.169
Min–Max (med)	43.1–59 (51.7)	41.2–54.2 (48.3)	46.6–57.3 (50.2)	48–59.4 (53.4)	
Av±SD	49.59±5.29	48.64±4.17	51.05±3.3	52.37±4	
CAR					[e]0.179
Min–Max (med)	0.01–2.05 (0.59)	0.04–5 (0.87)	0.01–1.98 (0.65)	0.01–1.11 (0.11)	
Av±SD	0.76±0.62	1.47±1.57	0.64±0.58	0.43±0.5	
PLR					[e]0.604
Min–Max (med)	49.76–441.11 (129.76)	47.24–682.23 (171.34)	47.89–945 (187.27)	59.34–335 (85.44)	
Av±SD	163.38±119.96	219.98±175.86	227.71±229.93	128.45±95.84	
NLR					[e]0.932
Min-Max (med)	0.75–8.2 (1.97)	0.56–8.47 (2.81)	0.76–15 (3.15)	1.06–7.35 (1.72)	
Av±SD	3.28±2.49	3.23±1.91	3.84±3.14	2.89±2.25	
Disease duration					
	r	0.419**			
	p	<0.001*			

b: Pearson Chi-square test; e: Kruskal Wallis test; f: Fisher Freeman Halton test; r: Spearman's Correlation Coefficient; *: P<0.05; **: P<0.01; RDW: Red cell distribution witdh; CAR: CRP-to-albumin ratio; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to- lymphocyte ratio; SD: Standard deviation; Min: Minimum; Max: Maximum.

and this result supports that the disease has a progressive process. What is more, the ROC analysis led us to correlate positively with RDW, PLR, and NLR values on predicting the diagnosis. Even though the alterations in their levels do not guide us about the progression or the severity, we are determined that RDW, NLR, and PLR could be used as potential biomarkers to predict the disease at an early-period. Therefore, these markers might strongly support that they contribute to the clinical decision-making process in a short time and at a low-cost price. Consequently, our findings failed to reveal the association between the disease and CAR levels.

Table 3. ROC curve results

	Diagnostic scan					ROC curve		p
	Cut-off	Sensitivity	Specivity	Positive predictive value	Negative predictive value	Area	95% CI	
NLR	≥2.33	58.57	96.00	95.30	62.30	0.757	0.669–0.844	**0.001***
PLR	≥95.34	65.71	98.00	97.90	67.10	0.826	0.751–0.900	**0.001***
RDW	≥37.4	85.70	40.00	66.29	60.60	0.779	0.693–0.865	**0.001***

*: P<0.01; RDW: Red cell distribution witdh; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; ROC: Receiver operating characteristic; ROC: Receiver operating characteristic; CI: Confidence interval.

Epidemiological, clinical, and animal studies have provided strong evidence to support the relationship between inflammation and RLS. Likewise, studies designed about the inflammatory parameters are generally for exploring to monitor the disease progression or its response to treatment. Therefore, RLS etiology is still not explained overall; however, such mechanisms are thought to be involved in its pathophysiology. Even though the dysfunction in the ironergic and dopaminergic systems, hormonal alterations, hypoxia, and genetics variations take part, there is an increased association between RLS and post-infectious processes. According to this assumption, a novel perspective has concluded that systemic inflammation may have a role in the underlying mechanisms.[3,4,8,14]

The high prevalence of RLS in patients with systemic inflammatory diseases such as systemic lupus erythematosus, Crohn's disease, and celiac disease may indicate that inflammation is effective in the pathophysiology of RLS.[5,15] Multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and migraine are associated with RLS, but there is neither systemic nor CNS iron deficiency in the pathogenesis. In these conditions, RLS most often associated with inflammation. The pro-inflammatory interleukins (ILs), IL-6 is most often involved, but ILs 1, 2, 4, 12, 17, 18, and tumour necrosis factor (TNF)-alpha are typically high cytokines.[16] In a recent study, they compared the circulating levels of hs CRP, IL-1ß, IL-6, and TNF- alpha in patients with primary RLS and healthy control subjects. Serum IL-1ß, IL-6, and TNF-alpha levels of the patient group were statistically significantly higher than HC.[17] The higher circulating levels of inflammatory cytokines in patients with RLS may support the idea that inflammation is involved in the pathogenesis of primary RLS.

Neutrophil, lymphocyte, CRP, and albumin take the lead in inflammatory responses, and these biomarkers undergo transient fluctuations during inflammation. What is more, RDW, NLR, PLR, and CAR have been considered as obtainable indicators that would suggest significant data about the patients' inflammatory activity.[18,19] They were found to have a strong impression on differentiating the diagnosis and predicting the progression, especially in malignancies or systemic inflammatory disorders.[9,18,19] Previous studies have emerged different results on neurological conditions; for example, Patton et al.[7] and Varim et al.[20] revealed an association between the systemic inflammation and the disease; however, the study of Tak et al.[21] resulted contrarily. Nevertheless, they explained this difference by these parameters would easily be affected by individual and environmental factors.[20,21] Due to this possibility, we strictly limited our eligibility criteria while designing this study; therefore, it may be the reason why we found NLR, PLR, and RDW levels purely elevated. Consequently, our results support the involvement of systemic inflammation in the pathophysiology.

CAR has recently become a better indicator of an inflammatory response than CRP or albumin itself.[19] It has been proposed to reflect enhanced inflammatory tonus, and its increased levels suggest a poor prognosis and worse treatment outcomes in patients with systemic illnesses. Previously, CAR has been studied in several neurological illnesses and has been suggested reflecting the increased inflammatory status.[10,21] It was investigated on RLS once, resulted as reflecting the inflammation by its increased levels.[10] However, we did not detect any connection among the disease and CAR; therefore, our outcomes are not consistent with preceding studies.

The independent increase in RDW from the anemia is associated with inflammatory processes. RDW's elevation reflects the dysregulation in erythrocytes' homeostasis, disrupts the erythropoiesis, and leads to inflammation; consequently, the length of the telomeres shorten, and oxidative stress arises.[18–22] Several studies inspected the association between multisystemic diseases and RDW and revealed that anisocytosis was related to cardiac diseases, venous thromboembolism, stroke, migraine, and neurodegenerative diseases.[18,23–25] As far as we know, this is the first study investigating the relationship between RDW and RLS, and our results may guide us to conclude that the increase of RDW strongly supports inflammation in RLS pathophysiology.[18]

The weakness of this research is that the amount of individuals were quite small. However, this is the first study investigating the inflammatory markers consistent with the patients' clinical-stage differences according to the RLS Scale. Moreover, RDW is the first to be investigated in RLS's pathophysiology and indicates that these outcomes should be considered positive preliminary explorations. Consequently, more research on this topic needs to be undertaken in different populations between the disease's pathophysiology and the inflammatory markers for a clear understanding.

Conclusion

Data from several studies have identified the role of inflammation in the pathophysiology of RLS. Consistent with their results, the evidence presented in this study so far supports the idea that serum RDW, PLR, and NLR levels are associated with RLS. Overall, there seems to be some evidence to indicate that NLR, PLR, and RDW could be counted as potential biomarkers for predicting the disease.

Disclosures

Ethics Committee Approval: The Siirt University Clinical Research Ethics Committee granted approval for this study (date: 31.12.2020, number: 2020/13.03).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – B.Ç.A., E.K.T.; Design – B.Ç.A., E.K.T.; Supervision – E.K.T.; Fundings – B.Ç.A., E.K.T. Materials – B.Ç.A., E.K.T.; Data collection and/or processing – B.Ç.A., E.K.T.; Analysis and/or interpretation – E.K.T.; Literature search – B.Ç.A.; Writing – B.Ç.A., E.K.T.; Critical review – B.Ç.A.

References

1. Leschziner GD. Restless legs syndrome. In: Selsick H, editor. Sleep disorders in psychiatric patients. Berlin:Springer Heidelberg; 2018. p.175–88.
2. Trenkwalder C, Allen R, Högl B, Clemens S, Patton S, Schormair B, et al. Comorbidities, treatment, and pathophysiology in restless legs syndrome. Lancet Neurol 2018;17:994–1005.
3. Koo BB, Bagai K, Walters AS. Restless legs syndrome: Current concepts about disease pathophysiology. Tremor Other Hyperkinet Mov (NY) 2016;6:401.
4. Khan FH, Ahlberg CD, Chow CA, Shah DR, Koo BB. Iron, dopamine, genetics, and hormones in the pathophysiology of restless legs syndrome. J Neurol 2017;264:1634–41.
5. Hassan N, Pineau CA, Clarke AE, Vinet E, Ng R, Bernatsky S. Systemic lupus and risk of restless legs syndrome. J Rheumatol 2011;38:874–6.
6. Weinstock LB, Walters AS. Restless legs syndrome is associated with irritable bowel syndrome and small intestinal bacterial overgrowth. Sleep Med 2011;12:610–3.
7. Patton SM, Ponnuru P, Snyder AM, Podskalny GD, Connor JR. Hypoxia-inducible factor pathway activation in restless legs syndrome patients. Eur J Neurol 2011;18:1329–35.
8. Weinstock LB, Walters AS, Paueksakon P. Restless legs syndrome--theoretical roles of inflammatory and immune mechanisms. Sleep Med Rev 2012;16:341–54.
9. Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol 2016;26:372–6.
10. Olgun Yazar H, Yazar T, Özdemir S, Kasko Arici Y. Serum C-reactive protein/albumin ratio and restless legs syndrome. Sleep Med 2019;58:61–5.
11. Sateia MJ. International classification of sleep disorders-third edition: Highlights and modifications. Chest 2014;146:1387–94.
12. Allen RP, Picchietti DL, Garcia-Borreguero D, Ondo WG, Walters AS, Winkelman JW, et al. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: Updated international restless legs syndrome study group (IRLSSG) consensus criteria--history, rationale, description, and significance. Sleep Med 2014;15:860–73.
13. Bellei E, Monari E, Ozben S, Koseoglu Bitnel M, Topaloglu Tuac S, Tomasi A, et al. Discovery of restless legs syndrome plasmatic biomarkers by proteomic analysis. Brain Behav 2018;8:e01062.
14. Trotti LM. Restless legs syndrome and sleep-related movement disorders. Continuum (Minneap Minn) 2017;23:1005–16.
15. Becker J, Berger F, Schindlbeck KA, Poddubnyy D, Koch PM, Preiß JC, et al. Restless legs syndrome is a relevant comorbidity in patients with inflammatory bowel disease. Int J Colorectal Dis 2018;33:955–62.
16. Weinstock LB, Walters AS, Paueksakon P. Restless legs syndrome--theoretical roles of inflammatory and immune mechanisms. Sleep Med Rev 2012;16:341–54.
17. Uslu FI, Demir E, Güler EM, Koçyiğit A. Circulating levels of cytokines are increased in restless legs syndrome. Sleep Breath 2021;25:1581–5.
18. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015;52:86–105.
19. Balta S, Aparcı M, Ozturk C, Demirkol S, Celik T. Neutrophil-lymphocyte ratio as an useful mortality marker. Am J Emerg Med 2014;32:1546–7.
20. Varım C, Acar BA, Uyanık MS, Acar T, Alagoz N, Nalbant A, et al. Association between the neutrophil-to-lymphocyte ratio, a new marker of systemic inflammation, and restless legs syndrome. Singapore Med J 2016;57:514–6.
21. Tak AZA, Sengul Y. Evaluation of inflammation with neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in restless legs syndrome. Turk J Neurol 2018;24:259–63.
22. Balcioglu YH, Kirlioglu SS. C-Reactive protein/albumin and neutrophil/albumin ratios as novel inflammatory markers in patients with schizophrenia. Psychiatry Investig 2020;17:902–10.
23. Kenangil G, Ari BC, Kaya FA, Demir M, Domac FM. Red cell distribution width levels in Parkinson's disease patients. Acta Neurol Belg 2020;120:1147–50.
24. Bosman GJCGM. Disturbed red blood cell structure and function: An exploration of the role of red blood cells in neurodegeneration. Front Med (Lausanne) 2018;5:198.
25. Fava C, Cattazzo F, Hu ZD, Lippi G, Montagnana M. The role of red blood cell distribution width (RDW) in cardiovascular risk assessment: Useful or hype? Ann Transl Med 2019;7:581.