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The effect of the pretreatment systemic immune-inflammatory index and C-reactive protein-to-albumin ratio on prognosis in pediatric patients with IgA vasculitis

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ABSTRACT

Aim: Indices related to blood parameters that indicate inflammation have recently started to be used in determining prognosis for many diseases. Visceral involvement is the most important factor affecting prognosis in immunoglobulin A vasculitis (IgAV). In this study, we sought to explore the value of the systemic immune-inflammation index (SII) and the C-reactive protein-to-albumin ratio (CAR) in predicting visceral involvement in IgAV.

Material and Method: Patients diagnosed with IgAV who had gastrointestinal, renal, testicular, or central nervous system involvement were considered patients with visceral involvement. All patients with IgAV were divided into two groups, those with and without visceral involvement. The effect of SII and CAR in predicting visceral involvement was evaluated by logistic regression analysis.

Results: We found that in the summertime, the percentage of patients with visceral involvement was significantly higher than those without visceral involvement (p=0.010). The rates of the recurrence of the disease, arthralgia, arthritis, and fever were significantly greater in those with visceral involvement (p=0.032, p<0.001, p=0.027, and p=0.019, respectively). SII, CAR, and neutrophil-to-lymphocyte ratio (NLR) values were significantly higher in the patients with visceral involvement (p=0.017, p=0.046, and p=0.008, respectively). The results of the univariate analysis showed that the SII and NLR were significant predictors of visceral involvement (OR: 1.001, 95% CI: 1.000-1.001, p=0.036; OR: 1.344, 95% CI: 1.053-1.715, p=0.018, respectively). We found that NLR was of greater value than SII in terms of predicting visceral involvement.

Conclusion: SII can be a valuable indicator for predicting visceral involvement in IgAV. However, CAR was not found significant in predicting visceral involvement.

Keywords: IgA vasculitis, inflammation, prognosis

INTRODUCTION

Immunoglobulin A vasculitis (IgAV) is the most common form of systemic vasculitis in children. It mainly affects small vessels with a deposition of polyclonal Ig A complexes in vessel walls. Its clinical manifestations involve skin rash, arthralgias and/or arthritis, gastrointestinal (GI) tract symptoms, and renal symptoms. Neurological and other organ involvement can also be seen throughout the course of IgAV (1). Although the main trigger that causes the disease is unknown, factors such as infection, vaccination, and medications are implicated in individuals with genetic predisposition (2,3). The prognosis of IgAV is usually good and self-limiting while the two main types of involvement, GI (51–56%) and renal (30–54%) involvement, can seriously threaten the lives of patients (4,5). The involvement of the central nervous system (CNS), lungs, and male genital tract are also rare visceral involvements that can lead to serious complications. The most common GI symptom in IgAV is abdominal pain, which is caused by the submucosal hemorrhage and edema of the intestinal wall. The most serious GI complication is intussusception, affecting 3-4% of patients. Renal involvement may be in the form of asymptomatic microscopic hematuria, macroscopic hematuria, mild proteinuria, and nephrotic or nephritic syndrome. End-stage renal failure is seen in 2-5% of children (6). While skin and joint involvement in IgAV usually does not require immunosuppressant treatment,

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GI, renal, testicular, CNS, and other rare visceral involvement cases require treatment with corticosteroids and other immunosuppressant drugs (7,8).

Since visceral involvement is the main form of involvement determining treatment and prognosis, studies aiming to predict visceral involvement in IgAV are needed. Inexpensive and easily accessible laboratory parameters that can be used to assess the severity of systemic inflammation have been used in recent years to predict prognosis in many diseases. Neutrophils and lymphocytes, the two main cellular components of the immune system, reflect both ongoing inflammation and the activation of the immunomodulatory pathway. Like neutrophils, platelets produce important cytokines that play a role in inflammatory diseases. The neutrophil-to-lymphocyte ratio (NLR) is the most frequently reported parameter in the literature (9-11). In recent years, a new systemic immune-inflammation index (SII) (neutrophils x platelets/lymphocytes) based on lymphocyte, neutrophil, and platelet counts has been developed, and SII has been shown to be a potential prognostic indicator, especially in patients with malignancies (12). There are a limited number of studies related SII in rheumatic diseases (13-15). C-reactive protein (CRP) is a widely used acute phase protein that is regulated by proinflammatory cytokines. On the other hand, serum albumin is the most important serum protein in the human body, and inflammation causes hypoalbuminemia due to the reduced synthesis and increased catabolism of albumin (16,17). In comparison to CRP or albumin alone, the CRP-to-Albumin ratio (CAR), a newly introduced inflammation-based risk index, has been demonstrated to better reflect inflammatory status, and thus, the prognosis in patients with acute medical illness and malignancies (18,19). These indices have also been reported to predict prognosis in Behcet's disease and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (20,21).

Previous studies have used NLR to predict visceral involvement, which determines prognosis in patients with IgAV, but SII and CAR have not been evaluated. The aim of this study was to evaluate the role of these newly developed indices in predicting visceral involvement in IgAV.

MATERIAL AND METHOD

Study Design and Patient Selection

The demographic, clinical, and laboratory data of all patients diagnosed with pediatric IgAV in the Pediatric Rheumatology outpatient clinic between January 2017 and January 2020 were retrospectively obtained from patient files and the computer information system. The patients were diagnosed with IgAV according to the Ankara 2008 criteria, which were verified by the European League against Rheumatism, the Pediatric Rheumatology International Trials Organization, and the Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) (22,23). The diagnosis of IgAV is based on the presence of purpura (palpable) or petechiae (without thrombocytopenia) with lower extremity predominance (mandatory criterion) plus at least one of the following four features: (1) abdominal pain, (2) arthritis or arthralgia, (3) leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant deposition of IgA in histology, and (4) renal involvement (hematuria, red blood cell casts, or proteinuria). Recurrence was defined as the presence of a fresh episode after a period of at least 3 months without symptoms (22).

Patients with additional chronic diseases (e.g., congenital heart disease, diabetes, autoimmune disease, hematological disease), BMI>30, acute infection, medication use, and those who did not attend follow-ups regularly were excluded from the study.

The patients were divided into two subgroups according to the presence of visceral involvement. Medical records were reviewed for demographic data, clinical symptoms, time of admission, and laboratory findings.

The study was carried out with the permission of Selçuk University Ethics Committee (Date: 02.09.2020, Decision No: 2020/333). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Definitions and Data Collection

GI involvement was defined as severe abdominal pain with or without GI bleeding indicators such as positive occult blood in stool, melena, or hematochezia. Renal involvement was defined as the presence of hematuria (>5 red blood cells per high-power microscopic field in a centrifuged specimen) and/or non-nephrotic proteinuria (in spot urine, protein/creatinine ratio >0.2 or 4-40 mg/m2/per hour), or nephrotic syndrome (in spot urine, protein/creatinine ratio >2 or 40 mg/m2/per hour). IgAV involving the male genital organs was defined as the development of epididymitis, orchitis, or hematoma around the testicle and testicular torsion in ultrasound accompanied by edema and pain in the scrotum and testicle. Scrotal involvement was confirmed by ultrasound (USG) in all patients with complaints. IgAV-associated CNS involvement was defined as patients with typical rash and accompanying neurological symptoms and signs in the absence of other primary neurological diseases. Magnetic resonance imaging (MRI) and diffusion MRI were used in patients thought to have CNS involvement. GI involvement, renal involvement, and CNS involvement were considered visceral involvement (24).

The infectious trigger was defined as a viral or bacterial infection within the last 2 weeks and a drug trigger as medication used within the last 1 week.

Leukocyte count, neutrophil count, lymphocyte count, platelet count, CRP levels, albumin levels, erythrocyte sedimentation rate (ESR), urine analysis, and fecal occult blood tests at the time of admission were retrospectively recorded. NLR was calculated as the ratio of the neutrophil count to the lymphocyte count. SII was calculated using the formula: neutrophil (K/uL) count X platelet (K/uL) count / lymphocyte (K/uL) count, and CAR was calculated by the ratio of C-reactive protein (mg/L) to albumin (g/dL) (12,18,25). All blood parameters were measured in the same laboratory with a regularly calibrated device.

Statistical Analysis

The normality of the distribution of the continuous data was determined using the Kolmogorov-Smirnov test. The normally distributed continuous variables are expressed as mean±standard deviation (SD), and the non-normally distributed variables are expressed as median and interquartile range (Q1-Q3). Differences between independent variables were compared using Student's t-test or the Mann-Whitney U test. The categorical data were compared using the chi-squared ($\chi 2$) test. Logistic regression analysis was used to identify variables associated with visceral involvement in IgAV. Receiver operating characteristic (ROC) curve analysis was used to determine the sensitivity and specificity of SII to predict visceral involvement. All statistical analyses were performed using the Stata/MP 16 (Stata Corporation, College Station, Texas, USA) software. A p-value below 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics of 123 Patients with IgAV

Of the 181 screened patients, 123 satisfied the inclusion criteria and were enrolled. While visceral involvement was not detected in 70 (56.9%) patients with IgAV, visceral involvement was present in 53 (43.0%). The mean age of all patients was 8.5±3.3 years. Seventy-one patients (57.7%) were female, and 52 patients (42.3%) were male. Although summer was the most common season for the condition, with 36 (29.3%) patients, no statistically significant difference was found among the seasons (p=0.214). While 95.1% of the patients had rash only on the lower extremities, 6 patients (4.9%) had rash all over the body. Thirty-eight patients (30.9%) had arthritis. Ankle arthritis was the most common localization in 25 patients (20.3%). GI involvement was seen in 50 patients (40.7%), renal involvement was seen in 19 patients (15.4%), CNS involvement was seen in 2 patients (1.6%), and testicular involvement was seen in 1 patient (0.8%). One patient was operated on for intussusception. IgAV recurred in 2 patients (1.6%). Complete recovery was observed in all patients (with or without visceral involvement).

Comparison of Baseline Characteristics and Laboratory Indices

A comparison of the demographic, clinical and laboratory data of patients with and without visceral involvement is shown in **Table 1**. There was a significant difference between patients with visceral involvement and patients without visceral involvement in terms of the season of occurrence (p=0.018). According to the x^2 trend analysis performed to determine the origin of this difference, visceral involvement was more likely to be seen in the summer season. In the post hoc test, the number of patients with visceral involvement in the summer season was significantly higher than those without visceral involvement (Z=3, x^2 =9, p=0.010). Among the clinical findings, the rates of arthralgia, arthritis, fever, and disease recurrence were significantly higher in the group with visceral involvement compared to the group without visceral involvement (p<0.001, p=0.027, p=0.027, p=0.019, and p=0.032, respectively).

In the laboratory examinations, CRP values were significantly higher in the group with visceral involvement than in the group without (p=0.048). The mean NLR, SII, and CAR values were significantly higher in the group with visceral involvement compared to the group without visceral involvement (p=0.008, p=0.046, and p=0.017, respectively).

Hospitalization and systemic steroid use (oral and iv pulse steroid) rates were significantly higher in the group with visceral involvement, as expected (p<0.001 in 3 patients).

Prognostic value of NLR, CAR, and SII

Univariate and multivariate logistic regression analyses were performed to determine the value of the SII, CAR, and NLR parameters in predicting visceral involvement. According to the results of the univariate regression analysis, SII and NLR were effective in predicting visceral involvement (OR: 1.001, 95% CI: 1.000-1.001, p=0.036; OR: 1.344, 95% CI: 1.053-1.715, p=0.018, respectively). CAR was not significant in predicting visceral involvement. When the three indices were evaluated together in the multivariate logistic regression analysis, NLR was found to be more significant in predicting visceral involvement compared to the other indices (OR:2.286, 95% CI:1.159-4.506, p=0.017) (**Table 2**).

Table 1. Comparison of baseline characteristics and laboratory indices

Variables	All patients with IgAV n=123	IgAV without visceral involvement n=70	IgAV with visceral involvement n=53	Tp-value
Age, mean±SD	8.55±3.35	8.47±3.47	8.65±3.21	0.77
Sex				0.34
Male, (n, %)	52 (42.3%)	27 (38.6%)	25 (47.2%)	
Female, (n, %)	71 (57.7%)	43 (61.4%)	28 (52.8%)	
Seasons				0.018
Spring, (n, %)	34 (27.6%)	21 (30.0%)	13 (24.5%)	
Summer, (n, %)	36 (29.3%)	†14 (20.0%)	†22 (41.5%)	
Fall, (n, %)	32 (26.0%)	23 (32.9%)	9 (17.0%)	
Winter, (n, %)	21 (17.1%)	12 (17.1%)	9 (17.0%)	
Infectious trigger, (n, %)	72 (58.5%)	45 (64.3%)	27 (50.9%)	0.14
Drug trigger, (n, %)	21 (17.1%)	10 (14.3%)	11 (20.8%)	0.35
FMF cooccurrence, (n, %)	4 (3.3%)	1 (1.4%)	3 (5.7%)	0.19
Family history of rheumatic disease, (n, %)	1 (0.8%)	1 (1.4%)	0 (0.0%)	0.38
Family history of IgAV, (n, %)	3 (2.4%)	3 (4.3%)	0 (0.0%)	0.13
Clinical Manifestations				
Disease recurrence, (n, %)	4 (3.3%)	0 (0.0%)	4 (7.5%)	0.032
Rash				0.23
Lower extremity, (n, %)	117 (95.1%)	68 (97.1%)	49 (92.5%)	
Whole Body, (n, %)	6 (4.9%)	2 (2.9%)	4 (7.5%)	
Scrotal Rash, (n, %)	3 (2.4%)	2 (2.9%)	1 (1.9%)	0.73
Edema				0.10
Face, (n, %)	30 (24.4%)	13 (18.6%)	17 (32.1%)	
Hands-Feet, (n, %)	92 (74.8%)	57 (81.4%)	35 (66.0%)	
Arthralgia, (n, %)	75 (61.0%)	33 (47.1%)	42 (79.2%)	<0.001
Arthritis, (n, %)	38 (30.9%)	16 (22.9%)	22 (41.5%)	0.027
Myalgia, (n, %)	70 (56.9%)	38 (54.3%)	32 (60.4%)	0.50
Fever, (n, %)	4 (3.3%)	0 (0.0%)	4 (7.5%)	0.019
Hospitalization, (n, %)	33 (26.8%)	8 (11.4%)	25 (47.2%)	<0.001
Treatment				
Anti-Histaminic, (n, %)	113 (91.9%)	68 (97.1%)	45 (84.9%)	0.014
NSAID, (n, %)	85 (69.1%)	48 (68.6%)	37 (69.8%)	0.88
Pulse Steroid, (n, %)	13 (10.6%)	1 (1.4%)	12 (22.6%)	<0.001
Oral Steroid, (n, %)	17 (13.8%)	1 (1.4%)	16 (30.2%)	<0.001
Laboratory features				
CRP (mg/dl), Median (Q1-Q3)*	12 (2-11.9)	6.8 (2-11)	9.2 (2-15.7)	0.048
ESR (mm/h), Mean±SD	18.53±15.00	18.03±11.92	19.15±18.22	0.69
WBC (K/uL), Mean±SD	9.35±3.47	9.00±2.72	9.77±4.19	0.23
HB (g/dl), Mean±SD	12.85±1.22	12.95±1.17	12.74±1.29	0.36
RDW (%), Mean±SD	13.69±1.23	13.52±1.11	13.91±1.34	0.14
MPV (fL), Mean±SD	7.64±0.81	7.71±0.78	7.55±0.83	0.27
Cre (mg/dL), Mean±SD	0.41±0.13	0.41±0.12	0.41±0.14	0.86
AST (U/L), Mean±SD	29.25±26.32	26.55 ±8.38	31.54±35.46	0.65
ALT (U/L), Mean±SD	14.60±7.88	14.11±6.68	15.20±9.21	0.47
Indices				
NLR, Mean±SD	2.56±2.18	2.07±1.24	3.14±2.84	0.008
CAR, Mean±SD	4.35±8.84	2.63±3.78	6.22±11.94	0.046
SII, Mean±SD	958.51 ±970.74	749.22±621.95	1197.70±1220.24	0.017

SD: Standard deviation, NSAID: Nonsteroidal anti-inflammatory drug, FMF: Familial Mediterranean fever, WBC: White blood cell, HB: Hemoglobin, RDW: Red cell distribution width, MPV: Mean platelet volume, Cre: creatinine, AST: Aspartate amino transferase, ALT: Alanine amino transferase, ESR: Sedimentation, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, CAR: CRP to albumin ratio, SII: Systemic immune-inflammation index.
† There was a significant difference between the two groups in terms of seasonal characteristics (p=0.018). Chi-squared trend analysis revealed that this difference occurred in the summer season, and post hoc analysis showed that IgAV with visceral involvement was significantly higher in the summer season compared to patients without visceral involvement (Z=3, 2=9, p=0.010). *Mann-Whitney U test

Table 2. Independent predictors of visceral involvement in IgAV

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
Age	1.016	0.913-1.130	0.770			
Sex	1.421	0.690-2.929	0.340			
NLR	1.344	1.053-1.715	0.018	2.286	1.159- 4.506	0.017*
CAR	1.065	0.990-1.145	0.087	1.059	0.978-1.148	0.154
SII	1.001	1.000-1.001	0.036	0.998	0.998-1.000	0.119

*p<0.05, OR: Odds ratio, CI: Confidence interval

The area under the curve (AUC) value in predicting visceral involvement in IgAV was 0.703 (p=0.036, sensitivity: 80%, specificity: 46%) for SII (**Figure 1**). The cut-off value of SII was found to be 677.14. The AUC value in predicting visceral involvement in IgAV was 0.711 (p=0.027, sensitivity: 60%, specificity: 54%) for NLR (**Figure 2**). The cut-off value of NLR was found to be 1.89.

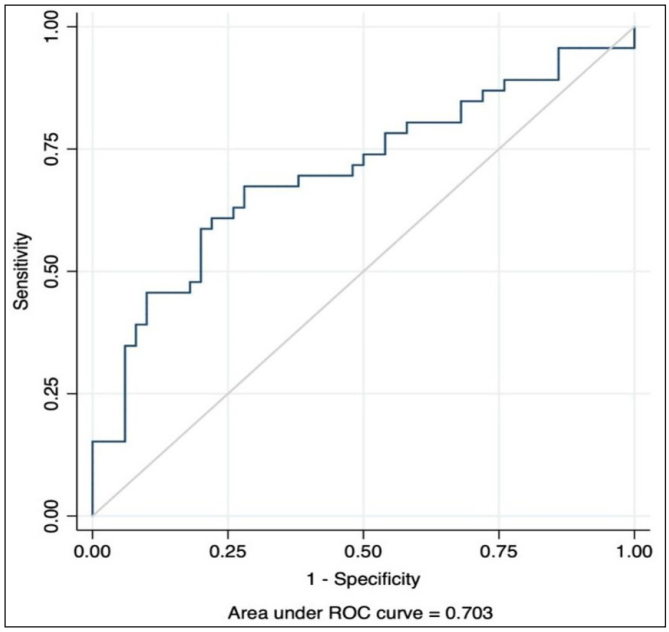

Figure 1. Receiver-operating characteristic curves of SII in predicting visceral involvement in IgAV

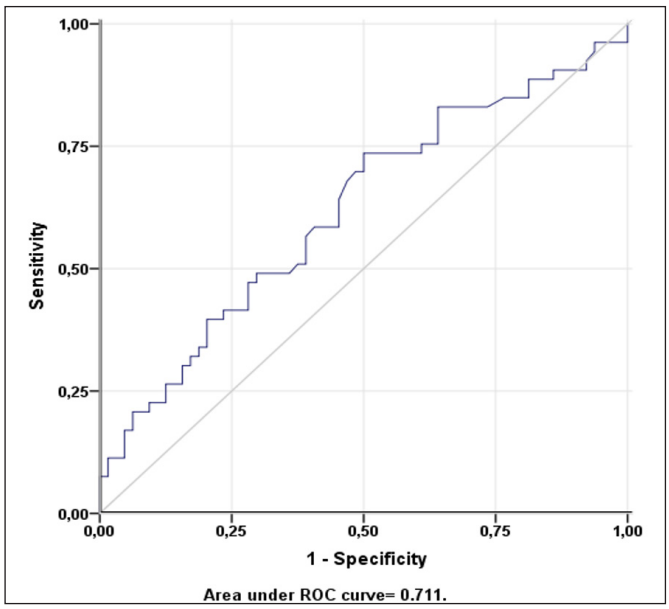

Figure 2. Receiver-operating characteristic curves of NLR in predicting visceral involvement in IgAV

DISCUSSION

IgAV is a benign form of vasculitis that is seen particularly in childhood. Although a complete cure is possible, GI system, renal system, CNS, and testicular involvement during the course of this disease can lead to the involvement of visceral organs and potential morbidity if untreated (26). It is because of this that many studies have been carried out for predicting visceral organ involvement, particularly in the GI and renal systems, using various indices and laboratory parameters. However, as far as we know, in recent studies, no assessment has been made regarding the place of SII and CAR in determining prognosis in illnesses such as cancer, MI, Behcet's Disease, and ANCA-associated vasculitis (15,19,20,27-29). We found in our study that CAR was not significantly effective in determining prognosis for visceral involvement in patients with IgAV, but SII was a significant predictor of visceral involvement. Predictability in this case, however, was weaker than the degree of predictability obtained with the more frequently used NLR parameter. At the same time, we found that visceral involvement was more prevalent in patients in the summer months. The clinical findings of fever, arthralgia, arthritis, and recurrent disease were found to be associated with visceral involvement.

It has been reported in previous studies that the prognosis of IgAV worsens with increasing age (30). In the present study, we found no significant difference in age between the patients with visceral involvement and those who had no visceral involvement. Male dominance in IgAV has been reported in many studies, although there are those that have reported the opposite (31-34). In our study, too, the female sex was predominant. However, we could not find any correlation between sex and visceral involvement in our sample.

While the pathogenesis of IgAV has not yet been discovered, it is considered that genetic predisposition and various environmental factors are instrumental in the development of the disease (35). A history of infection prior to the disease was found at a rate of 37-49% (3). In our study, this rate was much higher. Although it has been reported in some studies that the disease is more prevalent in the fall and winter seasons, our study revealed no significant difference in terms of seasonal occurrence (3,36,37).

In recent years, in fact, numerous studies have been conducted for the purpose of predicting GI and renal involvement, as these types of involvement are the main causes of morbidity in IgAV. Advanced age, persistent purpura, severe GI involvement, reduced levels of Factor XIII, and relapses have been associated with nephritis (38,39,40). A study carried out in Turkey indicated that severe GI involvement could be associated with arthralgia/arthritis, subcutaneous edema, and nephritis (3). In our study, we classified patients with renal and GI involvement and other rare visceral involvements under a single category and divided them into those with and without visceral involvement. To our knowledge, there is no other

study in the literature that has used this perspective to assess patients. Accordingly, we discovered that from a clinical point of view, fever, arthralgia/arthritis, and recurrent illness could be associated with visceral involvement.

It is believed that systemic inflammation plays a role in the pathogenesis of many diseases (12,41). Since IgAV is a disease that runs its course with IgA-related inflammation along the walls of the blood vessels, there are various studies that have worked with inflammatory markers and indices for the purpose of predicting prognosis. In previous studies, researchers have mostly focused on neutrophils and lymphocytes as it is thought that these primary inflammatory cells play an important role in the pathogenesis of IgAV (42). Neutrophils and lymphocytes are two main cellular components of the immune system and signal both ongoing inflammation and the activation of immunomodulatory pathways (43). Since neutrophils play a role in lymphocyte regulation in inflammation, NLR has been used in studying various autoimmune and inflammatory diseases (44). Moreover, when platelets are activated, they are considered to be important components of the inflammatory response that results from the secretion of many inflammatory factors such as chemokines, cytokines, and coagulation factors (45). Previous studies have shown that the NLR value is higher in patients with renal and systemic involvement in IgAV than in patients without renal and systemic involvement (3,22,44,46). In recent years, SII, which uses neutrophils, platelets, and lymphocytes together, and the CAR index, which evaluates CRP and albumin together, have attracted the attention of researchers and been used to evaluate disease pathogenesis and severity of inflammation in many diseases (15,19,21,27-29,47-50). Since CAR provides the opportunity to evaluate increased CRP and decreased serum albumin together in chronic inflammation, it has provided researchers with a two-way perspective.

SII has been found to be effective in predicting severe illness in AAV and Behcet's Disease, mortality in COVID-19, and advanced stages of colorectal cancer (21,29,48,51). Researchers have reported that CAR is helpful in predicting prognosis in myocardial infarction, sepsis, AAV, and hepatocellular cancer (19,20,29,50). On the other hand, we did not come across any study in the literature that reported the use of these indices in determining prognosis in IgAV. Since the most important factor affecting the prognosis of the disease in the short term is visceral organ involvement, this is how we approached the illness. While we found that CAR did not have a statistically significant value in predicting visceral involvement, we saw that SII was a tool that could be used to predict this condition. Because CAR indicates more likely severe and chronic inflammation, it may not be an effective predictor in IgAV, a disease that presents with visceral involvement in the acute stage. To be able to make the right decisions, there is a need for more studies to be conducted in this yet untouched area. The results of our study showed that NLR was superior to SII in predicting visceral involvement, and we found NLR to be the strongest indicator. Although SII, which is an indicator of three parameters of inflammation, did not yield the results we expected, and since ours is the first study on this subject as far as we know, it is reasonable to consider that more studies in the field will in time reveal the actual value of SII.

The present study had a few limitations. Most importantly, it was a retrospective, single-center study. Therefore, a large-scale prospective validation study is required to validate the results of this study.

CONCLUSION

Indices that are calculated through the use of simple inflammation markers are increasingly being used to determine prognosis in many illnesses. SII is a tool that has only newly begun to be employed, and therefore, its prognostic value has not been exactly understood yet. In IgAV, the most important factor affecting prognosis is visceral involvement. SII may be a valuable predictor of visceral involvement. Since there is no previous study on this subject, more comprehensive studies need to be conducted to unveil the value of this index.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Ethics Committee (Date: 02.09.2020, Decision No: 2020/333).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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