The Turkish Journal of Pediatrics 2024; 66: 599-607
https://doi.org/10.24953/turkjpediatr.2024.4797

Original Article

Exploring the predictive factors in the gastrointestinal involvement of patients with immunoglobulin A vasculitis

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ABSTRACT

Background. Immunoglobulin A vasculitis (IgAV), the most common systemic vasculitis in children, typically presents with gastrointestinal (GI) symptoms in about half of cases. This study aimed to analyze the clinical and laboratory findings of patients with IgAV regarding GI involvement.

Methods. We compared the GI involvement data of the patients diagnosed with IgAV.

Results. Of the 210 patients (60.5% female and 39.5% male), 101 had GI involvement, with abdominal pain being the predominant symptom (n=98). White blood cell, neutrophil, monocyte, and platelet counts, C-reactive protein, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI) were significantly elevated in patients with GI involvement ($p<0.001$, $p<0.001$, $p=0.01$, $p=0.005$, $p=0.002$, $p<0.001$, $p=0.03$, $p=0.001$, $p<0.001$, $p<0.001$, respectively). The cutoff values for SII (>1035.7), SIRI (>1.65), NLR (>2.73), and MLR (>0.28) were determined, yielding respective sensitivities of 46%, 59%, 47%, and 53%, specificities of 83.1%, 69.1%, 81.3%, and 71.9%. Corresponding areas under the curve were 0.658, 0.668, 0.649, and 0.634, respectively (all $p<0.001$).

Conclusion. Although IgAV is a self-limiting disease, GI involvement can lead to serious consequences. Systemic inflammatory indices such as SII and SIRI may be indicative in identifying patients with GI involvement.

Key words: immunoglobulin A vasculitis, gastrointestinal involvement, Henoch-Schönlein purpura.

Immunoglobulin A vasculitis (IgAV), formerly known as Henoch-Schönlein Purpura (HSP), is the most common systemic vasculitis in children with an incidence ranging from 3 to 27 per 100,000.[1] The disease is characterized by the deposition of immunoglobulin A (IgA) containing immune complexes and complement components in the small vessel walls.[1,2] While it can occur at any age, it's more commonly seen in childhood with the highest frequency between the ages of 4 and 6.[3] Diagnosis is made based on classical signs and symptoms.[4] For the diagnosis of IgAV, the mandatory criterion was purpura or petechiae that were prominent on the lower extremities and without thrombocytopenia or coagulopathy. Other criteria included abdominal pain, arthritis (acute in any joint), arthralgia, renal involvement (proteinuria, hematuria), and the presence of IgA deposition demonstrated by biopsy criteria.

Gastrointestinal (GI) symptoms are present in approximately half of the cases of IgAV. A spectrum of clinical presentations is observed, ranging from mild symptoms such as nausea,

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Received 31st May 2024, revised 23rd Aug 2024, accepted 30th Sep 2024.

The study was presented as an oral presentation at the 3rd Panoramic View to Rheumatology Symposium, in May 2024 in Sakarya, Türkiye.

abdominal pain, and vomiting to more severe findings including GI bleeding, intestinal ischemia, and intussusception.[5] In prior studies, various parameters including lymphocyte count, neutrophil count, platelet count, hemoglobin level, mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and mean platelet volume-to-platelet count ratio (MPR) have been assessed in patients exhibiting GI system (GIS) involvement.[6-8] Accordingly, inflammatory markers such as NLR, MLR, PLR, systemic inflammation response index (SIRI), and systemic immune-inflammation index (SII) have emerged as valuable predictors of vascular diseases.[6,9,10] Particularly in the context of cardiovascular pathologies, oncological pathologies, chronic kidney disease, and more recently in COVID-19 patients, these markers have demonstrated their predictive potential.[11,12] In our study, we have further investigated the predictive role of systemic inflammatory indices such as SII and SIRI regarding GIS involvement. This study aims to evaluate the clinical and laboratory features of patients with IgAV and assess the role of laboratory parameters in predicting the course of GIS involvement.

Materials and Methods

This cross-sectional retrospective study was conducted between August 2020 and January 2024. A total of 211 patients aged between 0-18 with a diagnosis of IgAV were included. The diagnosis of IgAV was determined using the Ankara 2008 criteria endorsed by the European League Against Rheumatism, Pediatric Rheumatology International Trials Organization, and Pediatric Rheumatology European Society.[4]

Demographic information (age, gender, age at diagnosis), clinical findings (skin, musculoskeletal system, gastrointestinal system, renal, neurological, pulmonary involvement), laboratory findings (white blood cell count [WBC], absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, hemoglobin level, platelet count, C-reactive protein [CRP] level, albumin level, complement 3 [C3] and complement 4 [C4] levels, anti-dsDNA, extractable nuclear antigen [ENA] panel, anti-nuclear antibody [ANA] values, and results of *MEFV* [Mediterranean FeVer] gene analysis) were retrospectively reviewed and recorded from patients' files. Systemic involvements were assessed up until the last visit of the patients.

Abdominal involvement was defined as the presence of any of the following symptoms: 1) abdominal pain, 2) vomiting, 3) hematemesis, 4) melena, 5) hematochezia, and 6) intussusception.

Patients were considered to have renal involvement if they exhibited at least one of the following findings: 1) hematuria (>5 red blood cells/high power field), 2) red blood cell casts in urinary sediment, 3) nephritic proteinuria (4-40 mg/m^2/hour), 4) hypertension (blood pressures ≥95th percentile for gender, age, and height), 5) nephrotic proteinuria (>40 mg/m^2/hour), 6) renal insufficiency.

Patients were classified as experiencing a relapse if they developed a new disease-related symptom after a period of at least 3 months without any symptoms.[13]

The NLR is determined by dividing the neutrophil count by the lymphocyte count, whereas the PLR is calculated by dividing the platelet (PLT) count by the lymphocyte count. Moreover, the MLR is derived by dividing the monocyte count by the lymphocyte count. The SII is computed by multiplying the neutrophil count by the platelet count and then dividing it by the lymphocyte count. Similarly, the SIRI is obtained by multiplying the neutrophil count by the monocyte count and then dividing it by the lymphocyte count. The study was approved by the Kocaeli University Ethics Committee.

Statistical analysis

The database was constructed using SPSS 29.0 (IBM Corp., Armonk, NY, USA) and MedCalc 14.0 (MedCalc Software, Ostend, Belgium). The adequacy of the variables'

normal distribution was assessed both visually (through histograms and probability plots) and analytically (Kolmogorov-Smirnov Shapiro-Wilk tests). Quantitative data were presented as means ± standard deviation or median (range). Categorical variables were compared using either the chi-square test or Fisher's exact test. Continuous data were compared using either the Student's t-test or the Mann-Whitney U test. ROC analysis was employed to determine the discerning threshold (cut-off) values among significant parameters for GIS involvement in patients with IgAV. Area under the curve (AUC), sensitivity, specificity, and cut-off values were calculated by the receiver operating characteristic (ROC) analysis. Results were deemed statistically significant when the p-value was less than 0.05 (two-tailed).

Results

Baseline characteristics of patients

A total of 211 patients diagnosed with IgAV were screened. One patient was excluded from the study due to a concomitant diagnosis of hemolytic anemia. Furthermore, three patients were also omitted from the study due to the lack of baseline laboratory parameters. Finally, data from 207 patients were analyzed. Of these patients, 60.5% were female (n=127) and 39.5% were male (n=83). The median age at diagnosis for patients was 78.5 months (range: 19-202 months). Among them, 34.8% (n=73) presented in autumn, 28.6% (n=60) in winter, 21.9% (n=46) in spring, and 14.8% (n=31) in summer. Within the four weeks preceding the onset of the disease, 108 patients (51.4%) had a history of upper respiratory tract (URT) infection, while 8 patients (3.8%) had a history of acute gastroenteritis (AGE).

Baseline clinical findings are given in Table I. All patients presented with purpuric rashes, with bullae observed in 3 patients (1.4%). In 19.1% of the patients (n=41), only cutaneous involvement was noted. Gastrointestinal involvement was present in 48.1% (n=101), and renal involvement was detected in 16.7% (n=35) of cases. The most common symptom related to GIS involvement was abdominal pain in 98 patients (46.7%), followed by nausea and vomiting in 37 patients (17.6%), bowel wall edema in 23 patients (11%), intussusception in 8 patients (3.8%), hematochezia in 7 patients (3.3%), and melena in 1 patient (0.5%). No cases of perforation were identified.

Upon evaluation for renal involvement, 2 patients (1%) were found to have hypertension, while 25 patients had proteinuria. Among these patients, 19 (9%) exhibited proteinuria at nephritic levels, and 6 (2.9%) had proteinuria at nephrotic levels. Hematuria was detected in 15 patients, with microscopic hematuria in 13 patients (6.2%) and macroscopic hematuria in 2 patients (1%).

Five patients were diagnosed with relapsing HSP. One patient presented with purpuric rash and nephritic-level proteinuria six months after the initial diagnosis. During follow-up, her nephritic proteinuria regressed within six months. The remaining four patients presented solely with purpuric rashes at 7 months, 1 year, 6 years, and 8 years after the initial diagnosis, respectively.

The baseline laboratory parameters are summarized in Table II. Out of 39 patients, *MEFV* analysis was conducted. Among them, 3 patients carried the E148Q heterozygous variant, 2 had the V726A heterozygous variant, 2 had the M680I heterozygous variant, and 1 had the M694V heterozygous variant. One patient had the R408Q/P369S compound heterozygous mutation, and 1 patient had the M694V homozygous mutation.

Assessing the predicting factors in gastrointestinal involvement

When comparing patients with and without GIS involvement, there were no significant differences observed regarding gender and the season of presentation (Table I). In terms of clinical findings other than arthralgia, there

Table I. Comparing clinical findings among patients with immunoglobulin A vasculitis based on gastrointestinal system involvement

Clinical and demographic findings	All patients (n=207), n (%)	Patients with GIS involvement (n=100), n (%)	Patients without GIS involvement (n=107), n (%)	p values
Gender				0.77
Female	127 (60.5)	60 (59.4)	67 (61.5)	
Male	83 (39.5)	41 (40.6)	42 (38.5)	
Seasonal pattern				0.2
Spring	46 (21.9)	23 (22.8)	23 (21.1)	
Summer	31 (14.7)	17 (16.8)	14 (12.8)	
Fall	73 (34.8)	39 (38.6)	34 (31.2)	
Winter	60 (28.6)	22 (21.8)	38 (34.9)	
History of infection for the last 4 weeks				
URT infection	108 (51.4)	36 (35.6)	72 (66.1)	**<0.001**
AGE	8 (3.4)	7(6.9)	1(0.9)	**0.03**
Location of skin lesions				
Buttocks and lower extremities alone	194 (92.4)	92 (91.1)	102 (93.6)	0.67
Buttocks, lower and upper extremities, and trunk	16 (7.6)	9 (8.9)	7 (6.4)	0.67
General	9 (4.3)	5 (5)	4 (3.7)	0.64
Joint manifestations				
Arthralgia	102 (48.6)	37 (36.6)	65 (59.6)	**0.001**
Arthritis	58 (27.6)	23 (22.8)	35 (32.1)	0.16
Hand-foot dorsum edema	91 (43.3)	39 (38.6)	52 (47.7)	0.21
Renal involvement				0.10
Nephritic proteinuria	19 (9)	13 (12.9)	6 (5.5)	
Nephrotic proteinuria	6 (2.9)	4 (4)	2 (1.8)	
No proteinuria	185 (88.1)	84 (83.1)	101 (92.7)	
Renal involvement				0.33
Microscopic hematuria	13 (6.2)	6 (5.9)	7 (6.4)	
Macroscopic hematuria	2 (1)	2 (2)	0 (0)	
No hematuria	195 (92.8)	93 (92.1)	102 (93.6)	

AGE, acute gastroenteritis; GIS, gastrointestinal system; URT, upper respiratory tract infection.

were no differences. Patients without GIS involvement showed a significantly higher frequency of arthralgia (p=0.001). There was no association between the presence of proteinuria and/or hematuria and GIS involvement.

Regarding laboratory findings, patients with GIS involvement showed elevated levels of WBC, absolute neutrophil count, monocyte count, platelet count, and CRP (p<0.001, p<0.001, p=0.01, p=0.005, p=0.002, respectively). Moreover, parameters such as NLR, PLR, MLR, SII, and SIRI were also significantly higher in patients with GIS involvement (p<0.001, p=0.03, p=0.001, p<0.001, p<0.001, respectively). The capacity of NLR, PLR, MLR, SII, and SIRI to foresee the GIS involvement was analyzed using the ROC curve. The best cut-off value for SII level was >1035.7 (sensitivity 46%, specificity 83.18%, AUC=0.658, 95% confidence interval

Table II. Comparing laboratory parameters among patients with immunoglobulin A vasculitis based on gastrointestinal system involvement

Laboratory parameters	All patients (n=207)	Patients with GIS involvement (n=100)	Patients without GIS involvement (n=107)	p values
White blood cell, ×10³/μL	10.38 (4.10-36.12)	11.81 (4.10–36.12)	9.5 (4.81–21.74)	**<0.001**
Neutrophil count, ×10³/μL	5.97 (1.43-33.38)	7.0 (1.76-33.88)	5.2(1.43-16.17)	**<0.001**
Lymphocyte count, ×10³/μL	2.9 (1.00-11.41)	2.74 (1.00-11.41)	3.08(1.43-7.5)	0.14
Monocyte count, ×10³/μL	0.74 (0.12-2.20)	0.84 (0.12-2.1)	0.71 (0.26-2.2)	**0.01**
Hemoglobin, g/dL	12.37 ± 1.32	12.52 ± 1.44	12.23 ± 1.20	0.12
Platelet count, × 10³/μL	373 (194-681)	406 (194-681)	356 (197-681)	**0.005**
NLR, %	2.00 (0.28-20.79)	2.47 (0.6-20.79)	1.72 (0.28-6.46)	**<0.001**
PLR, %	126.61 (49.3-536.2)	132.9 (49.3-536.2)	116.88 (50.7-250.3)	**0.03**
MLR, %	0.24(0.1-0.7)	0.28(0.1-0.7)	0.22(0.1-0.7)	**0.001**
C-reactive protein, mg/L	7.4 (0.3-133)	10.1 (0.3-133)	5.45 (0.3-71.8)	**0.002**
Albumin, g/dL	4.28 (2.50-6.52)	4.2 (2.5-5.01)	4.3 (3.5-6.52)	**0.02**
C3, g/L (n=77)	1.34 ± 0.24	1.31 ± 0.26	1.36 ± 0.21	0.35
C4, g/L (n=77)	0.25 (0.12-0.43)	0.25 (0.12-0.41)	0.22 (0.12-0.43)	0.9
SII	738.02 (72.5-13219.4)	924.14 (196.7-13219.4)	630.74 (72.5-3590.8)	**<0.001**
SIRI	1.45 (0.1-15.7)	1.97 (0.2-15.7)	1.14 (0.1-9.4)	**<0.001**

Data presented as mean ± standard deviation (for hemoglobin and C3, normally-distributing data), or median (min-max). C3, C3 complement; C4, C4 complement; GIS, gastrointestinal system; MLR, monocyte/lymphocyte ratio; NLR, neutrophil/ lymphocyte ratio; PLR, platelet/lymphocyte ratio; SII, neutrophil x platelet/ lymphocyte count; SIRI, neutrophil x monocyte/ lymphocyte count.

[CI] 0.589-0.723, p<0.0001), for SIRI was > 1.65 (sensitivity 59%, specificity 69.16%, AUC=0.668, CI 0.599-0.732, p<0.0001), for NLR was > 2.73 (sensitivity 47%, specificity 81.31%, AUC=0.649, CI 0.580-0.714, p=0.0001), for MLR was >0.28 (sensitivity 53%, specificity 71.96%, AUC=0.634, CI 0.564-0.699, p=0.0007) (Fig. 1).

Mild patients were treated with non-steroid anti-inflammatory drugs (NSAIDs), while those who did not respond to NSAIDs or required hospitalization received steroids. Among 101 patients with GIS involvement, 75 (74.3%) were treated with steroids, and the remaining 26 (25.7%) used only NSAIDs. The parameters were compared between patients treated with steroids and those not treated with steroids (Table III). Only SIRI was found to be significantly elevated in patients treated with steroids (2.26 vs. 1.51, p=0.02).

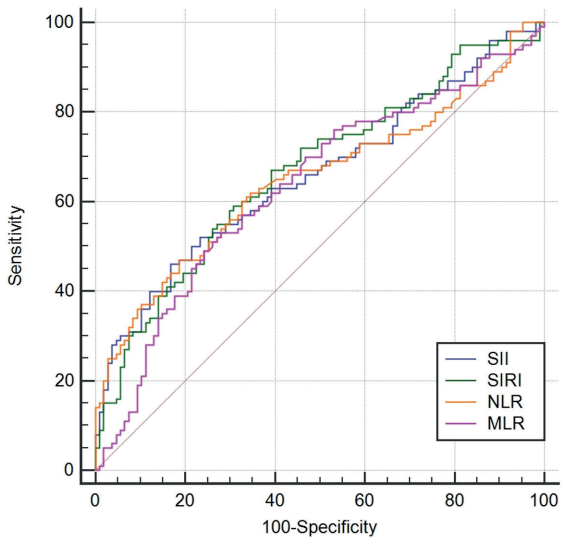

Fig. 1. Receiver operating characteristic curve of laboratory parameters. The best cut-off values were as follows: For SII level, >1035.7 (area under the curve [AUC] = 0.658); for SIRI, >1.65 (AUC = 0.668); for NLR, >2.73 (AUC = 0.649); and for MLR, >0.28 (AUC = 0.634).

MLR, monocyte/lymphocyte ratio; NLR, neutrophil/ lymphocyte ratio; SII, neutrophil x platelet/ lymphocyte count; SIRI, neutrophil x monocyte/ lymphocyte count.

Table III. Comparing parameters among patients treated with steroids and those not treated with steroids

Laboratory parameters	Patients treated with steroids (n=75)	Patients treated without steroids (n=26)	P values
White blood cell, ×10³/μL	12.22 (4.1-36.12)	9.89 (4.77-19.0)	0.06
Neutrophil count, ×10³/μL	7.82 (1.83-33.88)	6.39 (1.76-16.06)	0.09
Lymphocyte count, ×10³/μL	2.56 (1.0-11.41)	2.81 (1.04-7.44)	0.92
Monocyte count, ×10³/μL	0.86 (0.16-2.1)	0.73 (0.12-1.64)	0.17
Hemoglobin (g/dL)	12.51 ± 1.54	12.53 ± 1.10	0.95
Platelet count, ×10³/μL	410.5 (194-681)	384.5 (267-584)	0.43
NLR, %	2.68 (0.66-20.79)	2.07 (0.6-9.73)	0.12
PLR, %	133.22 (49.3-536.2)	130.87 (63.4-355.8)	0.83
MLR, %	0.29 (0.1-0.7)	0.23 (0.1-0.6)	0.06
C-reactive protein, mg/L	12.6 (0.3-133)	7.7 (0.5-26.1)	0.07
Albumin, g/dL	4.19 (2.5-5.01)	4.33 (3.53-4.71)	0.11
SII	1005.35 (196.7-13219.4)	853.90 (200-4516.3)	0.19
SIRI	2.26 (0.2-15.7)	1.51 (0.2-7.2)	0.02

Data presented as mean ± standard deviation (for hemoglobin, normally-distributing data), or median (min-max).
MLR, monocyte/lymphocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SII, neutrophil x platelet/ lymphocyte count; SIRI, neutrophil x monocyte/ lymphocyte count.

Discussion

Although IgAV is a self-limiting disease, GI and renal involvement may lead to serious consequences. In our study, we investigated markers that could predict GI involvement in patients with IgAV. Among the 207 patients examined, inflammatory markers at presentation were found to be higher in those with GI involvement. This study constitutes the initial examination of inflammatory biomarkers, notably SII and SIRI, concerning GI involvement in pediatric patients diagnosed with IgAV. Systemic inflammatory indices, such as SII and SIRI, exhibited significant elevation in patients with GI involvement, suggesting their potential utility in detecting such involvement.

IgAV shows a male predominance, with reported male-to-female ratios ranging from 1.2:1 to 1.8:1[1,14,15], although two studies[16,17] conducted in Korea have indicated a slight female predominance. Correspondingly, in our study, the female gender was more predominant (1.53:1). IgAV tends to occur especially in the autumn and winter months, which suggests a link with infections.[1,2] The incidence of URT infections before the onset of IgAV has been reported in the literature to range from 36% to 63%.[18-20] In the present study, a history of recent URT infections within the last month was present in 51.4% of patients, with 34.8% presenting in the autumn and 28.6% in the winter period. A study conducted in Taiwan documented a heightened incidence of GI involvement in children who did not have a history of URT infections before the onset of IgAV.[10] Likewise, in our study, individuals lacking GI involvement exhibited a greater prevalence of a history of URT infections ($p<0.001$). While earlier research has established a link between URT infections and nephritis, additional studies are warranted to elucidate the relationship between URT infections and GI involvement in these cases.[20]

Recent studies have investigated the correlation between organ involvement and various laboratory parameters in individuals diagnosed with IgAV. The neutrophil-to-lymphocyte ratio has been widely used to define the severity

of inflammation. In the study conducted by Gayret et al.[21] in which 119 HSP patients and 40 healthy children participated, NLR levels were significantly increased in IgAV patients, and PLR and platelet values were significantly higher in patients with GI bleeding compared to those without GI bleeding. Correspondingly, Makay et al.[6] observed a significant elevation in NLR among pediatric IgAV patients with GI bleeding compared to those without. In the aforementioned study, logistic regression analysis identified mean platelet volume (MPV) and NLR as two significant factors correlated with GI bleeding in patients. The optimal NLR threshold for predicting GI bleeding was determined to be 2.82, with a sensitivity of 81.0% and specificity of 76.0%. Another study has shown that IgAV patients with GI bleeding have significantly higher NLR compared to those without GI bleeding. The optimal cut off NLR for predicting GI bleeding was determined to be 2.05 with 93% sensitivity and 62% specificity.[22] In the present study, NLR and PLR values were found to be significantly higher in individuals with GIS involvement ($p<0.001$, $p=0.03$). The predictive threshold for NLR in anticipating GIS involvement was determined to be >2.73 (sensitivity 47%, specificity 81.3%, AUC=0.649, CI: 0.580-0.714, $p=0.0001$).

In a recent study, Suszek et al.[23] showed that the MLR serves as a valuable marker for evaluating the activity of systemic lupus erythematosus. Moreover, other studies[24,25] suggested that MLR could potentially serve as an indicator of disease activity in Takayasu arteritis and rheumatoid arthritis. Nevertheless, there is limited research examining the correlation between MLR and the severity of IgAV in pediatric patients. For instance, Yuan et al.[26] conducted a study involving 115 children diagnosed with IgAV and 95 healthy children. They found GI involvement in 29.5% of the patients and renal involvement in 10.4%. In children with IgAV, the neutrophil count, as well as the levels of NLR and MLR, were notably elevated in those with GI involvement compared to those without it. Logistic regression analysis identified the MLR as the sole significant risk factor for GI involvement among the parameters studied in this cohort of patients with IgAV. Moreover, a threshold MLR value of 0.245 effectively differentiated children with IgAV who had GI involvement from those who did not (AUC 0.694, with a sensitivity of 52.9% and specificity of 77.8%). The elevated MLR level could arise from an increase in monocyte counts or a decrease in lymphocyte counts. Monocytes serve as a fundamental source of pro-inflammatory mediators in various types of vasculitis. Lymphocytes have been demonstrated to play a broader role in regulating the inflammatory response at each stage of vasculitis. Furthermore, a decreased lymphocyte count has been linked to the progression of IgA vasculitis in rat and rabbit models.[27]

The utilization of SII and SIRI as a novel identifier has exhibited correlations with disease severity and prognosis in both cancer patients and individuals afflicted with inflammatory diseases. Some researchers contend that the SII offers a more comprehensive and balanced evaluation of the body's immune response and inflammation dynamics.[10,20] In a study conducted on children with Kawasaki Disease in China, a positive correlation between SII and the development of coronary artery lesions was observed. It has been demonstrated that elevated SII levels increase the risk of coronary artery lesions. Furthermore, a strong correlation between SII and CRP was found.[10] Lee et al.[9] have also examined the levels of SIRI in predicting the prognosis and mortality of ANCA-associated vasculitis. Patients with ANCA-associated vasculitis who had a SIRI ≥ 2847.9 mm^3 exhibited a significantly increased risk of mortality compared to those with a SIRI < 2847.9 mm^3.[9] In our study, for the first time, SII and SIRI parameters were assessed in patients with IgAV. It was observed that

these parameters were notably elevated in individuals with GI involvement. Additionally, SIRI was significantly higher in the group with severe GIS involvement. Further studies are required to establish the routine use of these novel biomarkers in clinical practice.

Our study had certain limitations including a retrospective design and a small sample size. However, the study is strengthened by the use of SII and SIRI parameters in patients with IgAV for the first time.

Consequently, organ involvement holds crucial significance in patients with IgAV. Utilizing simple and cost-effective markers can aid in its detection. This study aims to provide a clearer delineation of the demographic and clinical characteristics, as well as laboratory markers, associated with GI involvement in IgAV.

Ethical approval

The study was approved by Kocaeli University Ethics Committee (date: 18.01.2024, number: 2024-24).

Author contribution

Study conception and design: NŞ, HES; data collection: BÖ; analysis and interpretation of results: BÖ, NŞ, HES; draft manuscript preparation: BÖ, HES. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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