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Association between Factor XIII Activity and Clinical Course in Pediatric Patients with Immunoglobulin A Vasculitis

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BACKGROUND: Immunoglobulin A vasculitis is a systemic form of vasculitis that predominantly affects children. Factor XIII activity is decreased in some cases, and several reports have shown an association between abdominal pain and decreased factor XIII activity. However, the clinical significance of decreased factor XIII activity in pediatric immunoglobulin A vasculitis has not been fully elucidated. This study aimed to identify the association between factor XIII activity and the clinical course of pediatric patients with immunoglobulin A vasculitis. METHODS: Forty-four pediatric patients, admitted to Kita-Harima Medical Center with a clinical diagnosis of immunoglobulin A vasculitis between October 1, 2013 and September 30, 2022, were retrospectively reviewed, and 22 patients were analyzed. The patients' background characteristics and clinical course were compared between the normal and decreased factor XIII activity (<70%) groups. RESULTS: The group with decreased factor XIII activity showed a significantly increased duration of hospitalization (14 [6–36] vs. 7 [5–13] days, $p = 0.01$), total glucocorticoid dose (prednisolone 22.7 [4.9–55.5] vs. 10.1 [3.4–19.6] mg/kg, $p = 0.02$), and duration of glucocorticoid administration (19 [4–85] vs. 10 [3–15] days, $p = 0.03$). Correlational analyses showed that these three parameters were negatively correlated with factor XIII activity. CONCLUSIONS: Factor XIII activity was negatively correlated with the duration of hospitalization, total glucocorticoid dose, and duration of glucocorticoid administration. Factor XIII activity is not only associated with abdominal symptoms but also may be a marker to predict the overall trajectory of acute-phase treatment in pediatric patients with immunoglobulin A vasculitis.

INTRODUCTION

Immunoglobulin A vasculitis (IgAV) is a systemic form of vasculitis caused by immunoglobulin A deposition in the blood vessel walls and is most commonly observed in children [1]. The main symptoms include purpura, arthritis, abdominal pain, and renal dysfunction, which often resolve spontaneously [1]. However, there are cases of prolonged symptoms that require long-term treatment [2].

Recent reports have shown that abdominal symptoms of IgAV are negatively correlated with factor XIII activity [3–6], and factor XIII concentrates are effective for treating severe abdominal symptoms in cases where glucocorticoids are ineffective [2]. However, few studies have described the other aspects of the clinical significance of factor XIII activity in pediatric IgAV [7, 8]. Since pediatric IgAV has a diverse clinical course, clarifying the clinical profiles associated with decreased factor XIII activity may provide new insights into the significance of factor XIII measurements.

This study aimed to clarify the association between factor XIII activity and the clinical course of pediatric patients with IgAV.

MATERIAL AND METHODS

Study Design and Patient Selection

This single-center, retrospective, observational study was conducted at Kita-Harima Medical Center, a secondary providing hospital in Hyogo Prefecture, Japan. Pediatric patients aged ≤15 years who were admitted to the hospital with a clinical diagnosis of IgAV between October 1, 2013 and September 30, 2022 were included. Patients who did not meet the diagnostic criteria of the European College of Rheumatology for IgAV [9], those with unmeasured factor XIII activity, and those whose subsequent course and data were difficult to follow owing to transfer during hospitalization were excluded.

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Data collection

Medical records of the patients were retrospectively reviewed to collect data on their background characteristics and clinical course. Background characteristics included age, sex, prior infection, and blood and urine laboratory findings on admission. Clinical course data included the presence or absence of abdominal pain, arthritis or arthralgia, or purpura; the duration from initial onset to final confirmation of each symptom; urinalysis findings (highest and most recent values); duration of hospitalization; presence or absence of glucocorticoid administration; dose (prednisolone equivalent); duration of administration; analgesic use that persisted for >24 h after the start of glucocorticoid administration; presence or absence of factor XIII concentrate administration; and analgesic use that persisted for >24 h after the completion of factor XIII concentrate administration. When rehospitalization occurred within two weeks after discharge from the hospital, it was considered a continuation of treatment for the same condition, and the sum of the initial hospitalization period and the rehospitalization period was defined as the hospitalization period. Although arthralgia was defined as joint pain without joint swelling or limitation of movement in the diagnostic criteria for IgAV [9], limb pain with no swelling and an unclear location was also treated as arthralgia in this study.

Laboratory findings included the following measurements: white blood cells, platelets, albumin, sodium, C-reactive protein, complement 3, D-dimer, and factor XIII activity. Urinary findings included qualitative hematuria, qualitative proteinuria, and quantitative proteinuria. Qualitative hematuria and proteinuria were defined as occult blood (+) and protein (+) or higher, respectively, using dipstick urinalysis. A protein/creatinine ratio ≥0.15 g/gCr was defined as quantitative proteinuria.

Factor XIII activity <70% was defined as a decrease. Patients were divided into groups with normal and decreased factor XIII activity. The background characteristics and clinical course of the two groups were compared. When multiple values were available for factor XIII activity, the lowest value was selected for the analysis in order to avoid treating cases in which retests revealed decreased factor XIII activity as normal group cases. The Japanese medical insurance covers the administration of factor XIII concentrates for improving symptoms in IgAV patients with factor XIII activity ≤90% (not 70%). In accordance with this insurance coverage, factor XIII concentrates were administered as required. For cases in which glucocorticoids or factor XIII concentrates were administered, we also investigated the indications for their administration.

Statistical Analysis

Nominal variables were expressed as numbers (%) and continuous variables as median [range]. Comparisons between the two groups were made using Fisher's exact probability test for nominal variables and Mann-Whitney U test for continuous variables. Statistical significance was set at p-value <0.05, and all analyses were performed using EZR version 1.61 (Jichi Medical University, Saitama, Japan). For items that were significantly different between the two groups, Spearman's rank correlation coefficient was used to analyze the correlation with factor XIII activity.

Ethics

This study was conducted in accordance with the Ethical Guidelines for Medical and Biological Research Involving Human Subjects and approved by the Ethics Committee of the Kita-Harima Medical Center (Approval No. 04-47). The need for informed consent was waived due to the observational nature of the study, and the opportunity to refuse participation in the study was provided using the opt-out method described on the hospital's website.

RESULTS

During the study period, 44 pediatric patients clinically diagnosed with IgAV were admitted. We excluded six patients who did not meet the diagnostic criteria for IgAV [9], 14 patients whose factor XIII activity was not measured, and two patients who were transferred to other tertiary hospitals during hospitalization. The remaining 22 patients were included in the analysis. Of these, nine were classified as having normal factor XIII activity (hereafter referred to as "normal group") and 13 as having decreased factor XIII activity ("decreased group") (Figure 1).

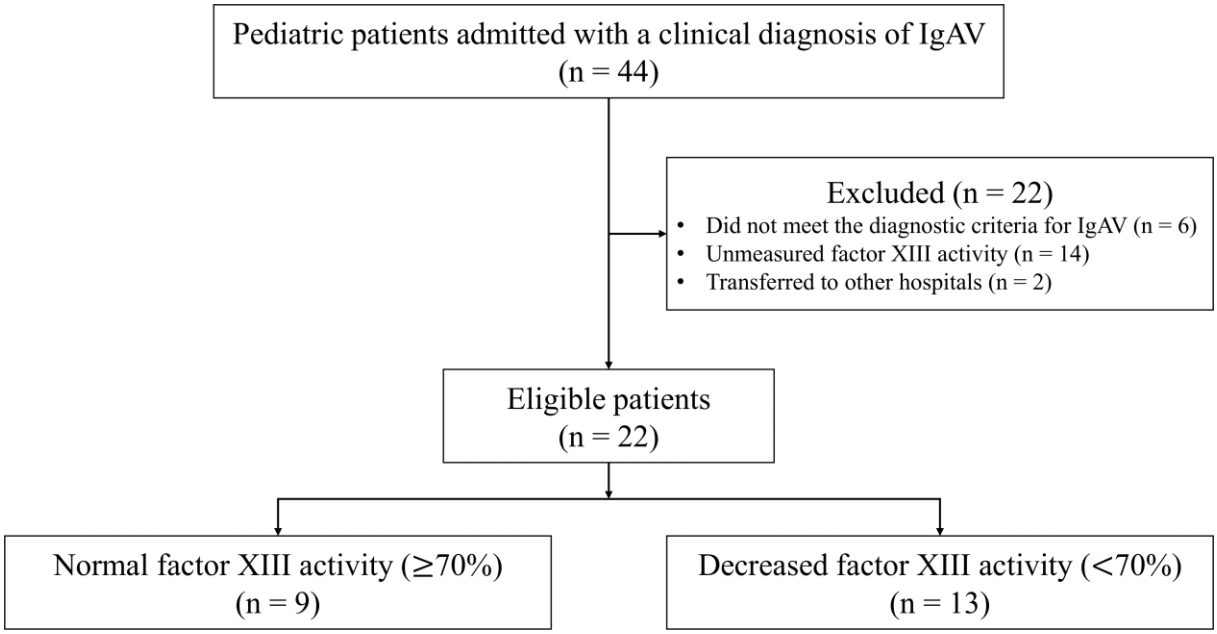

Figure 1. Patient selection flowchart.
IgAV, immunoglobulin A vasculitis.

The background characteristics of the patients are shown in Table I, and there were no significant differences between the two groups other than factor XIII activity. The clinical course of the patients is shown in Table II. The most common clinical symptom was purpura, followed by abdominal symptoms. Purpura was the symptom with the longest duration, followed by abdominal pain. Half of the patients had at least one qualitative urinalysis abnormality. Glucocorticoids were required in 90% of the patients, and the most common indication was abdominal pain. Six patients (30%) required analgesics after glucocorticoid administration, while five patients received factor XIII concentrates. Abdominal pain was the most common indication for factor XIII concentrate administration, and only one patient required analgesics after factor XIII concentrate administration (Table II, III).

Table I. Background characteristics of pediatric patients diagnosed with immunoglobulin A vasculitis

Parameters	Overall n = 22		Normal group n = 9		Decreased group n = 13		*p*
Age, years	6.4	[1.9–12]	6.5	[5.1–11.6]	6.2	[1.9–12]	0.89
Male sex	14	(63.6)	7	(77.8)	7	(53.8)	0.38
Prior infection	10	(45.5)	3	(33.3)	7	(53.8)	0.42
Laboratory findings on admission							
Blood tests							
Alb, g/dL	4	[2.3–5]	4.1	[3.8–4.7]	3.9	[2.3–5]	0.38
C3, mg/dL (n = 6)	137	[119–152]	133	[133–133]	141	[119–152]	1
CRP, mg/dL	0.58	[0.03–5.47]	0.56	[0.03–1.47]	0.76	[0.04–5.47]	0.29
D-dimer, μg/mL (n = 14)	4.1	[0.5–18.2]	3.7	[0.9–18.2]	4.1	[0.5–14]	0.95
Na, mmol/L	137.2	[131.2–140.6]	136.5	[135.4–140.6]	137.7	[131.2–140.4]	0.42
Plt, 10^4/μL	33.7	[20.5–60.2]	30.6	[20.5–60.2]	35.1	[25.4–47.3]	0.27
WBC, 10^2/μL	111.7	[29.4–321]	131.6	[29.4–224.1]	111.3	[75.2–321]	0.95
Factor XIII activity, %	65	[15–115]	89	[75–115]	56	[15–68]	<0.001
Urinalysis							
Qualitative hematuria	2	(9.1)	2	(22.2)	0	(0)	0.16
Qualitative proteinuria	3	(13.6)	2	(22.2)	1	(7.7)	0.54
Quantitative proteinuria (n = 4)	1	(25)	1	(50)	0	(0)	1

Nominal variables are presented as numbers (%) and continuous variables as median [range].
Alb, Albumin; C3, Complement 3; CRP, C-reactive protein; Na, Sodium; Plt, Platelet; WBC, White blood cell.

Table II. Clinical course of pediatric patients diagnosed with immunoglobulin A vasculitis

Parameters	Overall n = 22		Normal group n = 9		Decreased group n = 13		*p*
Symptoms							
Purpura	22	(100)	9	(100)	13	(100)	NA
Arthritis or arthralgia	17	(77.3)	7	(77.8)	10	(76.9)	1
Abdominal pain	19	(86.4)	8	(88.9)	11	(84.6)	1
Duration of symptoms							
Purpura, days	21.5	[5–319]	22	[5–67]	21	[7–319]	0.84
Arthritis or arthralgia, days (n = 17)	8	[1–38]	9	[1–21]	7	[1–38]	0.49
Abdominal pain, days (n = 19)	11	[1–97]	5	[1–97]	11	[1–37]	1
Urinalysis							
Qualitative hematuria or proteinuria detected more than once	11	(50)	3	(33.3)	8	(61.5)	0.39
Highest value							
Qualitative hematuria	8	(36.4)	2	(22.2)	6	(46.2)	0.38
Qualitative proteinuria	9	(40.9)	3	(33.3)	6	(46.2)	0.67
Quantitative proteinuria (n = 11)	5	(45.5)	2	(66.7)	3	(37.5)	0.55
Most recent value							
Qualitative hematuria	2	(9.1)	0	(0)	2	(15.4)	0.49
Qualitative proteinuria	2	(9.1)	0	(0)	2	(15.4)	0.49
Quantitative proteinuria (n = 11)	2	(18.2)	0	(0)	2	(25)	1
Treatment							
Duration of hospitalization, days	10.5	[5–36]	7	[5–13]	14	[6–36]	0.01
Glucocorticoids related items							
Glucocorticoid administration	20	(90.9)	7	(77.8)	13	(100)	0.16
Initial dose, mg/kg/day* (n = 20)	1.46	[0.88–2.93]	1.49	[0.96–2]	1.42	[0.88–2.93]	1
Maximum dose, mg/kg/day* (n = 20)	1.74	[0.88–2.93]	1.49	[0.96–2.38]	1.81	[0.88–2.93]	0.53
Total dose, mg/kg* (n = 20)	14.7	[3.4–55.5]	10.1	[3.4–19.6]	22.7	[4.9–55.5]	0.02
Duration of administration, day (n = 20)	14.5	[3–85]	10	[3–15]	19	[4–85]	0.03
Analgesic use that persisted for >24 h after the start of administration (n = 20)	6	(30)	1	(14.3)	5	(38.5)	0.35
Factor XIII related items							
Factor XIII concentrate administration	5	(22.7)	1	(11.1)	4	(30.8)	0.36
Analgesic use that persisted for >24 h after the completion of administration (n = 5)	1	(20)	0	(0)	1	(25)	1

Nominal variables are presented as numbers (%) and continuous variables as median [range].

NA, not applicable. *Prednisolone equivalent dose.

Table III. Indication for administration of glucocorticoids and factor XIII concentrates in pediatric immunoglobulin A vasculitis patients

Indication for administration	n (%)	
Glucocorticoids (n = 20)		
Abdominal pain	17	(85)
Arthritis or arthralgia	2	(10)
Purpura enlargement only	1	(5)
Factor XIII concentrates (n = 5)		
Glucocorticoid-resistant abdominal pain and purpura enlargement	2	(40)
Abdominal pain only	1	(20)
Purpura enlargement only	1	(20)
Prevention of relapse of arthralgia and purpura	1	(20)

Variables are presented as numbers (%).

A comparison of the normal and decreased groups showed no significant differences in the presence or duration of symptoms or urinalysis results. Compared with the normal group, the decreased group had a significantly longer hospital stay (Figure 2A; 7 [5–13] vs. 14 [6–36] days, $p = 0.01$). The initial glucocorticoid dose, maximum daily dose, and analgesic use that persisted for >24 h after glucocorticoid administration did not differ significantly

between the two groups. However, the total glucocorticoid dose (10.1 [3.4–19.6] mg/kg vs. 22.7 [4.9–55.5] mg/kg, $p = 0.02$) and duration of glucocorticoid administration (10 [3–15] days vs. 19 [4–85] days, $p = 0.03$) were significantly higher in the decreased group (Figure 2B–C). No significant differences were observed between groups in the number of patients who received factor XIII concentrates.

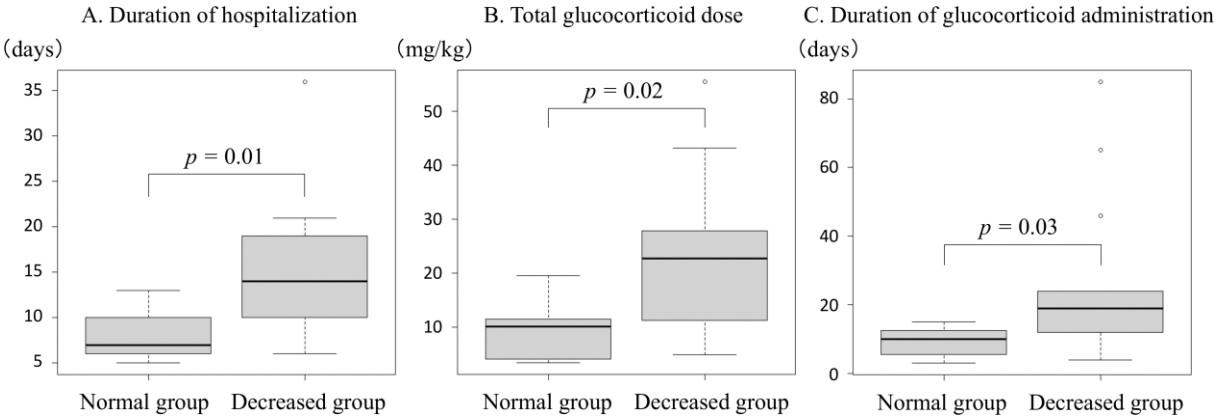

Figure 2. Boxplots of the duration of hospitalization (A), total glucocorticoid dose (B), and duration of glucocorticoid administration (C) in the normal and decreased factor XIII activity groups. The center line of the boxplot represents the median, while the top and bottom of the box represent the third and first quartiles. The upper and lower horizontal lines represent the 90th and 10th percentiles, respectively. ○ denotes outliers.

The duration of hospitalization, total glucocorticoid dose, and duration of glucocorticoid administration, which differed significantly between groups, were negatively correlated with factor XIII activity (Figure 3A–C).

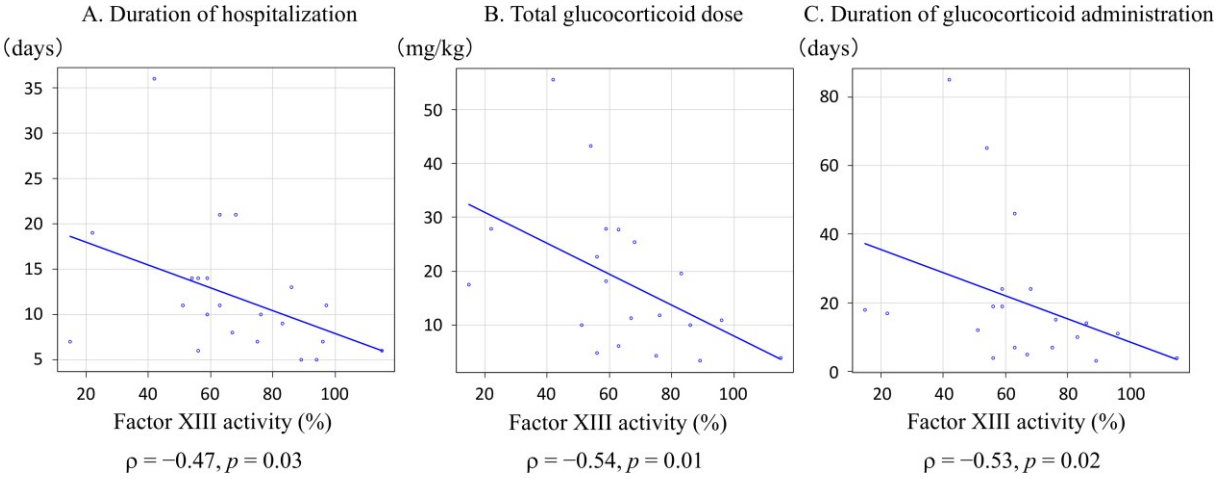

Figure 3. Scatterplot showing correlations between factor XIII activity and the following variables: duration of hospitalization (A), total glucocorticoid dose (B), and duration of glucocorticoid administration (C). The given ρ values indicate Spearman's rank correlation coefficient.

DISCUSSION

The present study revealed that decreased factor XIII activity was associated with prolonged hospitalization and increased total glucocorticoid dose and duration. These findings are relevant considering the lack of detailed reports examining the association between factor XIII activity and clinical course, other than for abdominal symptoms.

Factor XIII catalyzes fibrin cross-linking and plays an important role in thrombogenesis and wound healing [10]. Decreased factor XIII activity in IgAV may be due to degradation by leukocyte proteases or consumption around the affected vessels [11], likely reflecting disease activity. Therefore, patients with decreased factor XIII activity are presumed to have more severe disease and longer hospitalization periods; however, few studies have demonstrated this, which highlights the value of this study.

Glucocorticoids are often administered to treat the abdominal symptoms of pediatric IgAV patients [12]. In the present study, abdominal symptoms accounted for 85% of the reasons for glucocorticoid administration (Table

III). It has also been reported that patients with decreased factor XIII activity tend to develop glucocorticoid-resistant abdominal symptoms [2]. Therefore, it was presumed that the decreased group would be less responsive to glucocorticoids. However, in the present study, there were no significant differences between groups in the maximum daily dose or analgesic use that continued after glucocorticoid administration, which could be an indicator of glucocorticoid resistance. However, a significant increase in the total glucocorticoid dose and duration of administration was observed. It is reasonable to assume that an increase in the duration of administration directly leads to an increase in the total dose. In the decreased group, a longer duration of glucocorticoid administration may have occurred due to multiple relapses after dose reduction or careful dose reduction by the physician in charge, leading to an increase in the total dose. It is also possible that physicians may have decided to manage patients based on factor XIII activity levels.

Previous reports have shown that factor XIII concentrate administration contributes to the improvement of abdominal symptoms [2, 13]. However, it is unclear whether factor XIII replacement therapy is effective in decreasing the duration of hospital stay, total glucocorticoid dose, and duration of glucocorticoid administration. In this study, only 4 of the 13 patients in the decreased group received factor XIII replacement therapy, and there was no significant difference in replacement therapy between the normal and decreased groups. Further investigations are required to determine the significance of aggressive replacement therapy in patients with decreased factor XIII activity.

Urinalysis findings were abnormal in 11 patients (50%). However, there were no significant differences either in the qualitative or quantitative results between groups (Table II), and only one patient in the decreased group ultimately required renal biopsy (data not shown). Contrary to the results of the present study, previous reports have shown that decreased factor XIII activity is associated with the development of purpura nephritis [7, 8]. These previous studies were conducted at tertiary hospitals, and the different backgrounds and severity of the patients in our secondary hospital may have contributed to the different findings.

Although a previous report [11] assessed abdominal pain quantitatively, quantitative assessment of abdominal pain in pediatric IgAV management is not common. Thus, this assessment method [11] was not used in our medical records, nor was it assessed on commonly used pediatric pain scales such as the Wong-Baker Faces Pain Rating Scale [14] and the Faces Pain Scale Revised [15]. Therefore, abdominal pain could only be extracted as yes-no binary data in this study. Quantified symptom data are essential for future studies. It is desirable that the quantitative evaluation method of symptom severity using this previously reported method [11] or the pain scales [14, 15] will be generalized in IgAV management.

This study had several limitations. First, the sample size was small because of the single-center design and the limited number of cases in which factor XIII activity was measured. Therefore, it was inappropriate to compare multiple parameters, and the comparison items should have been initially limited. However, there have been few reports on the clinical significance of factor XIII activity in previous studies, except for abdominal pain, making it difficult to narrow down the comparison parameters in advance. Second, the severity of symptoms could not be quantified from medical records. Therefore, we could not rule out the possibility that differences in symptom severity between groups may have been a confounding factor in the results of this study. Third, this was a retrospective study, and the treatment strategy for each patient was at the discretion of the attending physician. Therefore, the criteria for admission and discharge, the method of glucocorticoid use, and the timing and frequency of factor XIII activity measurements were also left to the discretion of the attending physician; thus, the management methods were not unified. Fourth, the exclusion of transferred patients resulted in a selection bias due to the inability to examine severe cases that required transfer to a tertiary hospital. Furthermore, factor XIII activity was not routinely measured in pediatric IgAV admissions at our institution. This was also related to the first and third limitations mentioned above and further contributed to an additional selection bias. These limitations undermine the credibility of our findings. However, the lack of evidence-based appropriate management protocols for pediatric IgAV is not a problem unique to our institution, but one that all pediatricians must overcome. This study may be significant not only for its results but also for highlighting many of the current problems that make it difficult to conduct high-quality research in the field of pediatric IgAV as the limitations of this study. Further prospective studies involving a larger number of patients and uniform illness severity are needed in the future, using a unified management protocol.

In conclusion, among our pediatric patients with IgAV, those with decreased factor XIII activity had a significantly increased duration of hospitalization, total glucocorticoid dose, and duration of glucocorticoid administration compared to those with normal activity. Factor XIII activity is not only associated with abdominal symptoms but also may be a marker to predict the overall trajectory of acute-phase treatment in pediatric patients with IgAV.

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CONFLICT OF INTEREST

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