

## Abnormal urinalysis on day 7 in patients with IgA vasculitis (Henoch–Schönlein purpura)

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### ABSTRACT

Rare progression to renal failure imposes a burden on children with IgA vasculitis (Henoch–Schönlein purpura, HSP). An abnormal urinalysis on day 7 (7d-UA) may be a surrogate marker for persistent nephritis, but this has not been established. We retrospectively analyzed the risk factors for persistent nephritis in a cohort of 138 children. Of 35 children with abnormal 7d-UA, 24 (69%) had an abnormal urinalysis 6 months after the diagnosis of HSP, which was significantly more than 6 of 103 children (6%) with normal 7d-UA ( $P < 0.0001$ ). The negative predictive values for normal urinalysis and negative proteinuria 6 months after diagnosis were 0.94 (95% confidence interval [CI], 0.90–0.97) and 0.98 (95% CI, 0.95–0.99), respectively. When children with abnormal urinalysis 6 months after diagnosis were compared with those without, the following factors were significantly associated: age at diagnosis, abnormal urinalysis at diagnosis, abnormal 7d-UA, complement C3, steroid treatment, and presence of abdominal pain. However, multivariate analysis revealed that abnormal 7d-UA was the only significant risk factor for abnormal urinalysis 6 months after diagnosis (odds ratio 54.3, 95% CI 15.3–275,  $P = 1.89 \times 10^{-6}$ ). Abnormal 7d-UA may be an independent risk factor for persistent nephritis, but this should be confirmed in a prospective study.

**Key Words:** IgA vasculitis, Henoch–Schönlein purpura, abnormal urinalysis, complement C3, multivariate analysis

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### INTRODUCTION

Immunoglobulin (Ig) A vasculitis (Henoch–Schönlein purpura, HSP) is one of the most common forms of systemic vasculitis in children, presenting with palpable purpura or petechiae with lower limb predominance, arthralgia/arthritis, abdominal pain, and renal disease.<sup>1, 2)</sup> The central pathogenesis of HSP is a vasculitis with IgA immune complex depositions that predominantly

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affect small vessels;<sup>3)</sup> however, the precise cause of HSP has not been uncovered. HSP is self-limited in most cases and the prognosis for HSP is favorable overall; however, the mean HSP relapse rate is as high as 36% (range 15–66%) in prospective studies and 17% (range 3–35%) in retrospective studies, respectively.<sup>4)</sup> Additionally, the development of end-stage renal failure imposes a burden on children with HSP;<sup>5–9)</sup> 1.8% of patients with HSP progress to renal failure.<sup>10)</sup>

The risk factors for progression to renal failure in HSP include older age (>8 years of age) and the existence of an abnormal urinalysis at diagnosis.<sup>4)</sup> The retrospective analysis of a cohort of 102 children with HSP showed that a normal urinalysis on day 7 had a 97% negative predictive value (95% confidence interval [CI] 90–99%) in predicting a normal renal outcome.<sup>11)</sup> In addition, none of the children with a normal urinalysis 6 months after diagnosis progressed to end-stage renal failure, which was concluded after a systematic review.<sup>12, 13)</sup>

Some abnormalities of laboratory findings are often observed at the diagnosis of HSP, despite their lack of specificities.<sup>14)</sup> IgA, erythrocyte sedimentation rate, C-reactive protein (CRP), antistreptolysin O titer, fibrinogen degradation products (FDP), and D-dimer are often elevated and Factor XIII is often decreased during the course of HSP.<sup>4, 14, 15)</sup> Nevertheless, none of these markers or blood cell counts seem to be predictive of the onset of glomerulonephritis as a single marker.<sup>4, 14)</sup>

The urinalysis on day 7 seems to be a sensitive marker for renal outcome, but the usefulness of 7d-UA has not been established in comparison with other clinical and laboratory findings including urinalysis on the day of diagnosis. We conducted a multicenter retrospective analysis of children with HSP in order to elucidate the early risk factor(s) for abnormalities in urinalysis 6 months after the diagnosis of HSP.

## METHODS

### *Study design and patients*

In this multicenter, retrospective study, children under 16 years of age diagnosed with HSP from January 2007 to December 2011 at 11 Nagoya University Affiliated Hospitals were enrolled. The inclusion criteria were selected according to the EULAR/PRINTO/PRES criteria for HSP.<sup>2)</sup> We collected the clinical data of all children who were admitted with abnormalities of 7d-UA from 11 affiliated hospitals. We also collected data of all children who were admitted without abnormalities of 7d-UA from four of 11 affiliated hospitals as a control group, as these four hospitals covered most of the children with abnormal 7d-UA included in our study.

The first questionnaire was sent to 11 institutions and asked about the number of inpatients with the diagnosis of HSP. The response rate was 100%, and we sent the second questionnaires to 11 institutions that had inpatients with a diagnosis of HSP. We asked about the manifestations of HSP, including any skin, joint, or gastrointestinal symptoms, and renal symptoms at the diagnosis of HSP along with the complete blood cell count, FDP, D-dimer, Factor XIII, CRP, albumin, blood urea nitrogen (BUN), serum creatinine, IgG, IgA, IgM, complement C3, C4, and CH50. In addition, data were collected regarding treatment at the institutions, the number of relapses, and urinalysis results at 6 months after diagnosis of HSP. There were no missing data as for symptoms, treatment, and urinalysis results at diagnosis, 6–8 days, and 6 months after diagnosis; however, 1%–18% of patients had missing data for blood tests.

### *Definition*

An abnormality of urinalysis was defined as 5 or more erythrocytes per high power field in early morning urine sedimentation (hematuria), or early morning urine protein 30 mg/dL or

more (proteinuria). The day of the diagnosis of HSP was defined as the day of admission to the affiliated hospitals. The urinalysis at diagnosis (1d-UA) was defined as the result of urinalysis on the day of the diagnosis of HSP. The urinalysis on day 7 (7d-UA) was defined as the urinalysis taken 6–8 days after the diagnosis of HSP. The urinalysis 6 months after diagnosis (6m-UA) was defined as the urinalysis taken 21–27 weeks after the diagnosis of HSP.

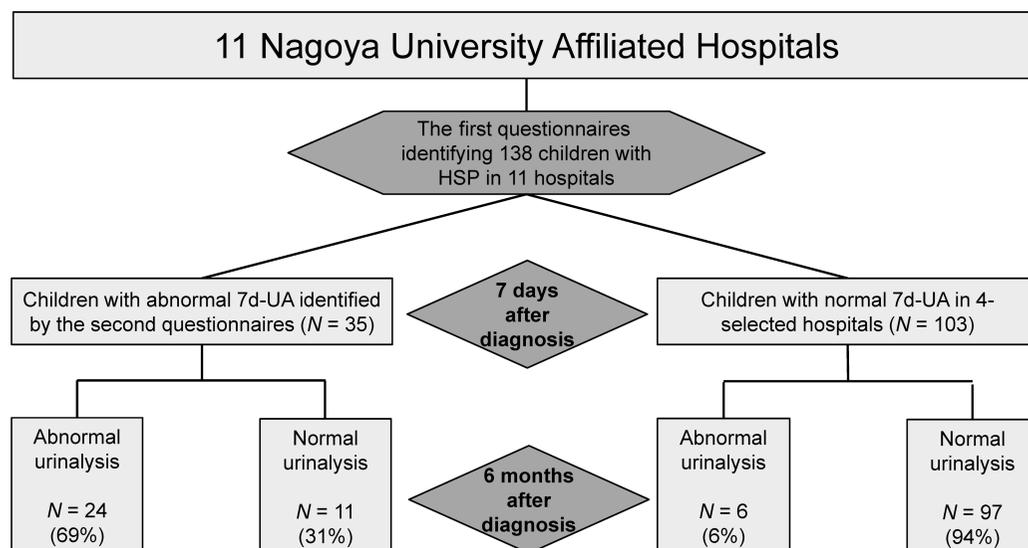
#### Statistics and institutional reviews

Categorical variables were compared using Fisher's exact tests. Continuous variables were compared using the two-sided student's *t* tests. The bidirectional stepwise logistic regression model was used for a multivariate analysis. *P*-value threshold of 0.25 was utilized to enter and remove effects from the model. Results of the multivariate regression analysis were presented as odds ratios (OR) with 95% CI. *P* < 0.05 was considered to indicate statistical significance. All statistical analyses were conducted using JMP Pro 11.0.0 (SAS Institute Inc., Cary, NC). This retrospective study was approved by the ethics committee of Nagoya University Graduate School of Medicine.

## RESULTS

#### Patient characteristics in the cohort

A total of 138 children with HSP were eligible for the study. Of those, 35 children had an abnormal 7d-UA and 103 children had a normal 7d-UA (Fig. 1 and Table 1). Of the 35 children with an abnormal 7d-UA, 25 (71%) had both hematuria and proteinuria, 5 (14%) had



**Fig. 1** The patients' recruitment in the IgA vasculitis (Henoch-Schönlein purpura) cohort.

The primary questionnaire identified 138 children with IgA vasculitis (Henoch-Schönlein purpura, HSP) who were admitted to 11 institutions consisting Nagoya University Affiliated Hospitals. The secondary questionnaire identified 35 children with an abnormal urinalysis 7 days after the diagnosis of HSP (7d-UA). All children in the cohort were followed at least 6 months after diagnosis. This retrospective study was approved by the ethics committee of Nagoya University Graduate School of Medicine.

**Table 1** Patient characteristics of the cohort

<i>N</i> = 138	Abnormal 7d-UA		Normal 7d-UA		<i>P</i>
Patients, <i>n</i> (male/female)	35 (21/14)		103 (52/51)		0.433
Age (years), median (range)	6.0 (3–12)		6.0 (0–15)		0.470
Symptoms at diagnosis, <i>n</i> (%)					
Skin	34	(97%)	100	(97%)	1.00
Gut	17	(48%)	51	(50%)	1.00
Joint	22	(64%)	66	(64%)	1.00
Abnormal UA at diagnosis, <i>n</i> (%)	13	(37%)	20	(19%)	0.0409
Abnormal UA 6 months after diagnosis, <i>n</i> (%)	24	(69%)	6	(6%)	<.0001
Hematuria only	3	(9%)	4	(4%)	0.370
Proteinuria only	1	(3%)	1	(1%)	0.444
Hematuria and proteinuria	20	(57%)	1	(1%)	<.0001
Laboratory data at diagnosis, mean (SD)					
White blood cell count ( $\mu$ L)	10157	(2770)	10985	(5900)	0.346
C-reactive protein (mg/dL)	0.8	(0.99)	1.1	(1.1)	0.301
Albumin (g/dL)	4.1	(0.4)	4.1	(0.4)	0.432
Blood urea nitrogen (mg/dL)	12.1	(3.6)	12.3	(3.5)	0.717
Serum creatinine (mg/dL)	0.33	(0.073)	0.33	(0.097)	0.973
FDP ( $\mu$ g/mL)	47	(108)	17	(17)	0.154
D-dimer ( $\mu$ g/mL)	8.8	(8.4)	6.7	(7.7)	0.307
Factor XIII (%)	81	(32)	90	(31)	0.210
IgG (mg/dL)	1088	(217)	1098	(306)	0.878
IgA (mg/dL)	205	(63)	200	(86)	0.783
IgM (mg/dL)	104	(36)	113	(46)	0.334
C3 (mg/dL)	132	(20)	120	(16)	0.00544
C4 (mg/dL)	31	(8.6)	31	(11)	0.870
CH50 (/mL)	49	(8.6)	49	(13)	0.993

Abbreviations: 7d-UA, urinalysis 7 days after diagnosis.

hematuria only, and 5 (14%) had proteinuria only. The median age at diagnosis was 6.0 years (range, 3–12 years) in the abnormal 7d-UA group, which was not significantly different from the normal 7d-UA group (median 6.0 years, range, 0–15 years;  $P = 0.433$ ). The percentage of organ involvement at diagnosis was not significantly different between the abnormal and normal 7d-UA groups (Table 1). Almost all children had skin symptoms at diagnosis. One child with an abnormal 7d-UA and three with normal 7d-UA had no skin involvement at diagnosis, but they presented with petechiae later in the course, and thus, fulfilled the EULAR/PRINTO/PRES criteria for HSP.

All children in the cohort were followed for at least 6 months after diagnosis. The percentage of abnormal 6m-UA was significantly higher in children with abnormal 7d-UA in comparison with children with normal 7d-UA ( $P < 0.0001$ ; OR 35.3, 95% CI, 11.9–105.0; Fig. 1 and Table 1). The sensitivity and specificity of 7d-UA predicting abnormal 6m-UA were 0.80 (95% CI, 0.66–0.89) and 0.90 (95% CI, 0.86–0.92), respectively. The positive and negative predictive values of 7d-UA were 0.69 (95% CI, 0.57–0.77) and 0.94 (95% CI, 0.90–0.97), respectively.

Three children in abnormal 7d-UA group (9%) and 4 children in normal 7d-UA group (4%) had hematuria only, respectively, and this was not statistically significant ( $P = 0.370$ ; Table 1).

The proportion of proteinuria 6 months after diagnosis was significantly higher in children with abnormal 7d-UA (20 children with both proteinuria and hematuria and 1 boy with proteinuria only) in comparison with children with normal 7d-UA (1 girl with both proteinuria and hematuria and 1 boy with proteinuria only) ( $P < 0.0001$ ; OR 75.8, 95% CI, 16.0–358.5; Table 1). The sensitivity and specificity of 7d-UA predicting proteinuria 6 months after diagnosis were 0.91 (95% CI, 0.76–0.98) and 0.88 (95% CI, 0.85–0.89), respectively. The positive and negative predictive values of 7d-UA were 0.60 (95% CI, 0.50–0.64) and 0.98 (95% CI, 0.95–0.99), respectively.

Nephrotic-range proteinuria was observed in 3 children with abnormal 7d-UA and no children with normal 7d-UA developed large proteinuria 6 months after diagnosis. No children in this cohort developed end-stage renal failure by 6 months. Of 30 children with abnormal urinalysis 6 months after diagnosis, 6 children (20%) underwent renal biopsy and all had a histological diagnosis of HSP nephritis. All 6 had abnormal 7d-UA. The grades in the International Study of Kidney Disease in Children grade was II in 2 children and IIIb in 4 children.

Regarding laboratory tests at diagnosis, the serum C3 level was significantly higher in children with an abnormal 7d-UA than in children with a normal 7d-UA (mean 132 mg/dL, standard deviation [SD] 20 in abnormal 7d-UA group vs. mean 120 mg/dL, SD 16 in normal 7d-UA group;  $P = 0.005$ ; Table 1), although the mean C3 was within a normal limit in both groups. No significant differences were found in the results of other tests, including white blood cell count, CRP, albumin, FDP, D-dimer, Factor XIII, IgG, IgA, IgM, C4, and CH50, between children with or without abnormal 7d-UA, respectively.

#### *Comparison of children with or without abnormal urinalysis 6 months after diagnosis of HSP*

We hypothesized that 7d-UA could be utilized as a sentinel marker for persistent abnormal urinalyses, especially persistent proteinuria, and we compared clinical symptoms and laboratory testing between children with or without an abnormal 6m-UA. At 6 months, 30 children (19 boys and 11 girls) had abnormal urinalyses and 108 children (54 boys and 54 girls) had normal urinalyses (Table 2). The median age at diagnosis was significantly higher in children with an abnormal 6m-UA than in those without (median 6.5 years, range, 3–15 years vs. median 6.0 years, range, 0–12 years;  $P = 0.0202$ ). The organ involvement at diagnosis was not significantly different between the two groups. However, the percentages of children with abnormal 1d-UA and 7d-UA were significantly higher in children with an abnormal 6m-UA than in those without (53% vs. 16%,  $P < 0.0001$  for 1d-UA and 80% vs. 10%,  $P < 0.0001$  for 7d-UA, respectively). No significant differences were found in the results of the laboratory tests between children with or without abnormal 6m-UA, except for serum C3 level, which was significantly higher in children with an abnormal 6m-UA than in those without (mean 135 mg/dL, SD 30, vs. mean 120 mg/dL, SD 17;  $P = 0.0088$ ; Table 2), although the mean C3 was within a normal limit in both groups. Some symptoms and interventions during the treatment for HSP have been presumed to be involved in persistent abnormal urinalysis. The percentages of children who received steroid treatment during the initial manifestation of HSP, and those with the presence of abdominal pain were significantly higher in children with an abnormal 6m-UA (60% vs. 38%,  $P = 0.0378$  and 70% vs. 46%,  $P = 0.0243$ , respectively; Table 2). The presence of hematochezia was not significantly different between the groups.

We also compared clinical characteristics between children with or without proteinuria 6 months after diagnosis. In consistent with the findings in children with abnormal urinalysis, which included children with hematuria only, the percentages of children with abnormal 1d-UA and 7d-UA were significantly higher in children with proteinuria 6 months after diagnosis than

**Table 2** Comparison of patient characteristics 6 months after diagnosis

<i>N</i> = 138	Abnormal 6m-UA		Normal 6m-UA		<i>P</i>
Patients, <i>n</i> (boys/girls)	30 (19/11)		108 (54/54)		0.220
Age (years), median (range)	6.5 (3–12)		6.0 (0–15)		0.0202
Symptoms at diagnosis, <i>n</i> (%)					
Skin	29	(97%)	105	(97%)	1.00
Gut	16	(53%)	52	(48%)	0.682
Joint	18	(60%)	70	(65%)	0.671
Abnormal 1d-UA, <i>n</i> (%)	16	(53%)	17	(16%)	<.0001
Abnormal 7d-UA, <i>n</i> (%)	24	(80%)	11	(10%)	<.0001
Laboratory data at diagnosis, mean (SD)					
White blood cell count (/μL)	10226	(2561)	10953	(5663)	0.514
C-reactive protein (mg/dL)	1.2	(1.3)	1.1	(1.3)	0.587
Albumin (g/dL)	4	(0.35)	4.1	(0.41)	0.188
Blood urea nitrogen (mg/dL)	12.9	(3.5)	12.3	(3.5)	0.247
Serum creatinine (mg/dL)	0.35	(0.094)	0.34	(0.097)	0.246
FDP (μg/mL)	18	(15)	16	(16)	0.669
D-dimer (μg/mL)	9.2	(8.1)	6.7	(7.5)	0.211
Factor XIII (%)	84	(32)	90	(32)	0.476
IgG (mg/dL)	1118	(245)	1106	(301)	0.645
IgA (mg/dL)	214	(74)	201	(83)	0.0847
IgM (mg/dL)	105	(37)	112	(45)	0.431
C3 (mg/dL)	135	(30)	120	(17)	0.00878
C4 (mg/dL)	31	(10)	30	(11)	0.787
CH50 (/mL)	52	(7)	49	(13)	0.340
Steroid administration after diagnosis, <i>n</i> (%)	11	(48%)	48	(42%)	0.0378
Presence of abdominal pain after diagnosis, <i>n</i> (%)	15	(65%)	56	(49%)	0.0243
Presence of hematochezia after diagnosis, <i>n</i> (%)	7	(30%)	18	(16%)	0.188

Abbreviations: 1d-UA, urinalysis at the diagnosis; 7d-UA, urinalysis 7 days after diagnosis; 6m-UA, urinalysis 6 months after diagnosis; SD, standard deviation.

in those without (52% vs. 18%,  $P = 0.0021$  for 1d-UA and 91% vs. 11%,  $P < 0.0001$  for 7d-UA, respectively; Table 3). No significant differences were found in other clinical findings and the results of the laboratory tests between children with or without proteinuria 6 months after diagnosis.

#### *Multivariate analysis of risk factors for abnormal urinalysis 6 months after diagnosis of HSP*

We defined the role of 7d-UA for predicting abnormal 6m-UA in the setting of multivariate analysis. Covariates included age  $\geq 6.5$  years, abnormal 7d-UA, abnormal 1d-UA, steroid administration, presence of abdominal pain, and C3  $\geq 125$  mg/dL. Of those factors, age, presence of abdominal pain, abnormal 1d-UA, and abnormal 7d-UA were selected after the bi-directional stepwise logistic regression modelling. The analysis revealed that the single most significant and independent predictor of abnormal 6m-UA after diagnosis of HSP was abnormal 7d-UA (OR 54.3, 95% CI 15.3–275,  $P = 1.89 \times 10^{-6}$ ; Table 4).

**Table 3** Comparison of children with or without proteinuria 6 months after diagnosis

<i>N</i> = 138	With proteinuria		Without proteinuria		<i>P</i>
Patients, <i>n</i> (boys/girls)	23 (14/9)		115 (59/56)		0.495
Age (years), median (range)	6.0 (3-12)		6.0 (0-15)		0.373
Symptoms at diagnosis, <i>n</i> (%)					
Skin	22	(96%)	112	(97%)	0.522
Gut	12	(52%)	56	(49%)	0.822
Joint	14	(61%)	74	(64%)	0.814
Abnormal 1d-UA, <i>n</i> (%)	12	(52%)	21	(18%)	0.0021
Abnormal 7d-UA, <i>n</i> (%)	21	(91%)	14	(12%)	<.0001
Steroid administration after diagnosis, <i>n</i> (%)	18	(60%)	41	(38%)	0.648
Presence of abdominal pain after diagnosis, <i>n</i> (%)	21	(70%)	50	(46%)	0.175
Presence of hematochezia after diagnosis, <i>n</i> (%)	8	(27%)	17	(16%)	0.135

Abbreviations: 1d-UA, urinalysis at the diagnosis; 7d-UA, urinalysis 7 days after diagnosis.

**Table 4** Multivariate analysis of risk factors for abnormal urinalysis 6 months after diagnosis

Variables	Odds ratio	95% confidence interval	<i>P</i>
Age $\geq 6.5$ years	1.81	0.516–6.81	0.0634
Presence of abdominal pain after diagnosis	2.91	0.777–12.5	0.146
Abnormal 1d-UA	8.71	2.35–42.4	0.0533
Abnormal 7d-UA	54.3	15.3–275	0.00000189

Abbreviations: 1d-UA, urinalysis at the diagnosis; 7d-UA, urinalysis 7 days after diagnosis.

Similarly, we defined the role of 7d-UA for predicting proteinuria 6 months after diagnosis of HSP. The multivariate analysis revealed that the statistically significant independent predictors of proteinuria 6 months after diagnosis were 1d-UA (OR 4.9, 95% CI 1.9–12.9,  $P = 0.017$ ) and 7d-UA (OR 75.6, 95% CI 16.0–358,  $P = 1.66 \times 10^{-7}$ ), respectively.

## DISCUSSION

Renal involvement is frequently observed in HSP; 85% of patients have renal involvement within a month after the onset of HSP, and as many as 97% of patients within 6 months in a systematic review of 1133 children with HSP.<sup>10</sup> Most of them are self-limited, but 7% of children develop nephritis and/or nephrosis, and 1.8% of children develop end-stage renal failure. Importantly, children with persistent hematuria and/or proteinuria only develop renal failure, although the possibility is low compared with children having an ongoing nephritis or nephrosis. The regular follow-up policy over a certain duration after a diagnosis of HSP is rationalized by the observation that none of the children without persistent hematuria or proteinuria 6 months after diagnosis develop end-stage renal failure.<sup>10</sup> Our data suggested that children with an abnormal 7d-UA may develop persistent renal involvement, especially persistent proteinuria, and that these patients may need pre-emptive therapy to suppress the progression to renal failure, or at least, an abnormal 7d-UA may awaken attention for careful observation.

The high negative predictive value of normal 7d-UA predicting negative proteinuria 6 months

after diagnosis may have a role in shortening the follow-up period of HSP, which is further supported by our observation that no children with normal 7d-UA developed prolonged large proteinuria. A meta-analysis showed that long term renal impairment never developed after normal urinalysis, and follow-up of renal symptoms up to 6 months was suggested.<sup>10</sup> In a prospective study, the incidence rate of nephritis 2 months after diagnosis was 2%, and follow-up of all HSP patients up to 2 months was recommended.<sup>16</sup> Our study indicates that 7 days follow up of UA may be able to sufficiently predict persistent nephritis, the negative predictive values for normal urinalysis and negative proteinuria being 0.94 (95% CI, 0.90–0.97) and 0.98 (95% CI, 0.95–0.99), respectively. From our findings, quantified urinalysis and urine sedimentation test are recommended for the first 1 week for all children with HSP.

Our study had some limitations, including its retrospective nature. A retrospective study by questionnaires can result in biases due to the incompleteness or inaccuracy of data. However, the return rate of questionnaires reached 100%, and the missing data including laboratory results were few. Our cohort did not include children with HSP who were seen only in outpatient setting, and thus, may have included patients with more severe forms of HSP, which may result in a biased perspective of HSP. In Japan, the hospitalization threshold is not generally high for sick children, and nearly 80–90% of children with a definitive diagnosis of HSP in our cohort were seen through an inpatient service. Additionally, the incidence of nephritis or nephrosis may be higher in more severe forms of HSP, and our findings about the predictive role of 7d-UA for abnormal 6m-UA and proteinuria 6 months after diagnosis may be generalized to children with all severity of HSP.

In conclusion, abnormal 7d-UA may be an independent risk factor for abnormal 6m-UA, although this should be confirmed in a prospective study. Children with HSP may be stratified by the results of 7d-UA, which could contribute to an early intervention with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers<sup>17</sup>) to prevent end-stage renal failure in children with HSP.

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