Original article

Renal involvement in Henoch-Schönlein vasculitis: Frequency and Risk Factors in Egyptian Children.

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ABSTRACT

Introduction: Henoch-Schoenlein Purpura (HSP) is the most common vasculitis in children. It is a self-limited disease. Nephritis is one of the most serious complications, and many risk factors have been related to its prognosis.

Aim of the study: This study aimed to determine the frequency and risk factors for renal affection in Egyptian children with Henoch-Schoenlein Purpura.

Methods: This retrospective study included 100 pediatric patients diagnosed with HSP. Selected medical data and laboratory results were obtained by reviewing patients' records.

Results: The study included 100 pediatric patients diagnosed with HSP. Among them, 26% had renal involvement. Ten patients (38%) had non-nephrotic proteinuria, two patients (8%) had nephrotic-range proteinuria, six patients (23%) had isolated hematuria, and eight patients (31%) developed nephritis. Still, renal failure was not detected in any of our patients. The mean age was significantly higher in patients with renal involvement compared to the non-renal affection group with a median age range of 10 (5.8-12) years and 7 (5-10) years, respectively. Infection as a triggering factor was significantly higher in the renal affection group than in the non-renal group. No other statistically significant differences between the two groups as regards other clinical and laboratory data were detected.

Conclusion: Renal affection was found in 26% of Egyptian HSP pediatric patients. Age and infection as a triggering factor might be risk factors for renal involvement.

KEYWORDS

Henoch-Schönlein Purpura, Nephritis, Renal failure

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INTRODUCTION

Children are primarily affected by Henoch-Schönlein purpura (HSP), a systemic vasculitis that affects small vessels [1]. It can impact the kidneys, gastrointestinal system, joints, and skin. The severity of renal damage is the determining factor for the long-term prognosis. The long-term prognosis is determined by the severity of renal HSP [4]. Children have a lower risk for renal progression than adults (30%– 50% vs 70%–80%)[5][6]. However, the predictive factors for such progression in children are poorly known [7].

METHODS

Study Design and Participants: This was a retrospective study that included 100 pediatric patients diagnosed with HSP. Data were selected from the files of patients being followed at the rheumatology clinic, Tertiary University Specialized Pediatric Hospital, Faculty of Medicine. The inclusion criteria were children aged 1-14 years who were diagnosed with HSP according to the European League Against Rheumatism/Pediatric Rheumatology European Society (EULAR/PRES) [8]. Cases associated with another systemic disease, e.g., HSP with familial Mediterranean fever, were excluded.

Ethical consideration: We abide by The diagnosis of HSP, at least one of the following symptoms must be present: (i) acute, diffuse, or colicky abdominal pain; (ii) immunoglobulin A deposition in affected tissue biopsy; (iii) arthritis or arthralgia; and (iv) renal involvement (hematuria or proteinuria) in addition to palpable purpura (without affection [2]. Approximately 30-50% of HSP patients show symptoms of renal affection. Although these symptoms are usually mild, some patients have renal failure or nephrotic syndrome [3].

Children presenting with either hematuria alone or mild proteinuria also have a good prognosis, whereas the higher the degree of proteinuria, the worse the outcome is. Therefore, the progression of renal disease contributes to the outcome of the Declaration of Helsinki and obtained the study protocol approval by the Research Ethics Committee, Faculty of Medicine, Cairo University. The approval number is [MS-96-2022]. A parent or eligible guardian provided documented informed consent for all included subjects. The protection of personally identifiable data was guaranteed.

Sample size: The sample size was calculated using the Med Calc program version 11.3.0.0 and according to the total known population of HSP following in the Rheumatology clinic at our Tertiary University Specialized Pediatric Hospital. By adjusting the confidence interval to 95%, the margin of error accepted to be 5%, and the power of the test to be 80%, the sample size needed was found to be 100 patients.

Data Collection: Data was retrieved by reviewing medical records. The collected clinical data included demographics and a history of presenting symptoms that guided the thrombocytopenia and coagulopathy)[8]. Additional clinical information, such as medication use and clinical symptoms over the entire duration of the illness, disease course as regards recurrence were also gathered.

Routine laboratory tests: Routine lab data were retrieved from patients' files,

such as complete blood cell count (CBC), Erythrocyte sedimentation rate (ESR), serum creatinine, urine analysis, and ASOT titer.

Statistical Analysis: Data entry and coding were done using Microsoft® Excel® 2016, then transferred to IBM® SPSS® v25 to be analyzed. The conformity of the distributions of the quantitative variables to the normal distribution was checked (Shapiro-Wilk test). Accordingly, the appropriate statistical methods were used (mean ±SD/ median, IQR) and tests (independent-t or Mann-Whitney U test). Qualitative data were expressed as frequency (n) and percent, and Chi-squared or Fisher's exact tests were used to compare qualitative variables.

RESULTS

A total of 100 HSP pediatric patients were already diagnosed clinically. They were recruited from the Rheumatology Clinic at Tertiary Children's University Hospital. The mean age was 7.81 ± 3.8 years; most of the patients (78%) were less than 10 years old and with female predilection (51%). Autumn and winter showed higher rates of presentation (33% each). The median disease duration was 4 weeks, ranging from 1 -28 weeks.

Twenty-three patients suffered from a preceding potential trigger event which was upper respiratory tract infections (URTI) in 13 patients (13%) (including pharyngotonsillitis, otitis media, and rhinitis), urinary tract infection 1-2 weeks before disease onset in 5 children, gastroenteritis in 4 patients, and one patient had appendicitis 2 weeks before the onset as shown in **Figure 1**.

There were different initial presentations among the studied cohort, most of them (78 cases) (78%) presented initially with a rash mainly on the lower extremities and buttocks of which 44 patients (56%) developed rash as the only presenting symptom while remaining 34 cases who presented with rash as a main complaint had also other manifestations. Nine patients (9%) were initially presented with joint manifestations, including 2 cases that had arthralgia and 7 cases that had arthritis. Nine cases (9%) presented initially with abdominal manifestations including abdominal pain in 6 cases (6%), bleeding per rectum was the presenting symptom in 2 cases (2%) and 1 case had a combined abdominal pain and arthritis. Other presenting manifestations included lower limb edema (around the ankle) in 1 case (1%), generalized edema in 1 case (1%), hematuria in 1 case (1%), and orchitis in 1 case (1%), as shown in **Figure 2.**

Regarding clinical manifestations along the course, 96 patients (96.0%) had palpable purpura, 65 patients (65%) had gastrointestinal tract (GIT) involvement, joint involvement occurred in 60 patients (60%) (42 patients had arthritis while 18 patients had arthralgia), 26 patients (26%) had renal involvement, and 38 patients (38%) had combined two or more systems as shown in **Table 1.**

A variety of renal symptoms were present in the renal affection group (26 patients with renal involvement); Ten patients (38%) had non-nephrotic proteinuria, two patients (8%) had nephrotic-range proteinuria, six patients (23%) had isolated hematuria, and eight patients (31%) developed nephritis; however, none suffered from renal failure, as shown in **Figure 3**.

In the renal affection group, age was statistically significantly higher in the renal affection group (n=26 patients) compared to the non-renal affection group (p-value=0.037), with a median age range of 10 (5.8-12) years and 7 (5-10) years, respectively as well as infection as a triggering factors was significantly higher in the renal affection group than the other group (P value = 0.007). The female sex was more predominant, with a prevalence rate of 61.5% in the renal affection group, although not statistically significant. Furthermore, 16 out of 26 patients with renal affection were from urban areas (61.5%), but no statistically significant differences were observed.

By comparing the laboratory data of patients with renal involvement and those without renal affection, the ESR was insignificantly higher in patients with renal affection. Furthermore, there was no difference regarding other laboratory data, including high total leucocytic count (>15,000), high PLT count (>50,000), and high ASOT titer (≥200mg/dl) between the two groups, as shown in **Table 2.**

Renal affection in HSP was independent of any other symptom or multisystem affection, as well as symptom recurrence. Purpura predominated in approximately 92.3% of patients of the renal affection group, followed by GIT pain in 65%, arthritis in 42%, and GIT bleeding in 15% of this group; none of these symptoms were statistically significant. In addition, 23.1% of the renal affection group experienced symptoms of recurrence compared to 28.4% in the other group, as shown in **Table 3**.

27 patients in the entire investigated group experienced recurrence in the form of rash, joint, GIT, or a combination of two or more symptoms. The renal affection course was regressive because only one patient experienced recurring isolated hematuria. The recurrence period ranged from 0.5 to 72 months after disease onset, with a median of 2.1 months, and there was no statistically significant difference between the renal affection group and the non-renal group as regards the recurrence of the disease.

Ninety patients (90%) in the study group began treatment; 71 received it early (with symptom onset), while 19 received it later. Nine patients received non-steroidal anti-inflammatory medicines (NSAIDs), sixteen patients had combination treatment (NSAID and steroids), and sixty-five patients received only steroids in a dose of 1-2 mg/kg/day, tapering over 2 -12 weeks. **Figure 4** shows the proportion of patients who used various treatment lines. The majority of the renal affection group (71.4%) received treatment early in the disease course (with symptom onset), and there was no statistically significant difference between both groups (P value=0.060) regarding early treatment.

DISCUSSION

Renal involvement in HSP is a major determinant of chronic renal failure in children, and the severity of its damage is the main long-term prognostic factor **[9]**.

The study aimed to detect renal affection frequency and risk factors in Egyptian children suffering from HSP. In our study, we found that 26% of cases with HSP had renal involvement. Similarly, *Ekinci et al*. reported the same incidence of 26.2% **[10]**. In contrast, some studies revealed a higher incidence of about 30-50% **[1][3]**. This can be attributed to a variety of factors such as race and region involved as well as the study type (retrospective or prospective).

Table 1: Clinical manifestations of the study group

	Clinical manifestations	N	Percent
Skin involvement	Palpable purpura	96	96%
GIT involvement	Abdominal Pain	65	65%
	GIT bleeding	15	15%
	Vomiting	24	24%
Joint involvement	Arthritis	42	60%
	Arthralgia	18	
Renal involvement	Isolated hematuria	6	26%
	Non-nephrotic range proteinuria	10	
	Nephritis	8	
	Nephrotic range proteinuria	2	
Multisystem affection		38	38%

GIT: Gastrointestinal tract, Multisystem affection; combined two or more systems.

Table 2: Comparisons of demographic characteristics and laboratory parameters between patients with and without renal involvement.

		Renal affection		Total	P-value
		No (n=74)	Yes (n=26)	(n =100)	
Demographic data					
Age					
Mean+ SD		39 7.4+3	9+3.6	49	0.037**
Min-Max		1.5-13	38.5%2-14	49.0%	
Median (IQR)		7(5-10)	10(5.8-12)	51	
Gender					
Male	**N**	39	10	49	0.211*
	%	52.7%	38.5%	49%	
Female	**N**	35	16	51	
	%	47.3%	61.5	51.0%	
Residence					
Rural	**N**	32	10	42	0.671*
	%	43.2%	38.5%	42.0%	
Urban	**N**	42	16	58	
	%	56.8%	61.5%	58.0%	
Season					
Autumn	**N**	27	6	33	0.083
Spring	**N**	14	12	26	
Summer	**N**	6	2	8	
Winter	**N**	27	6	33	
Triggering factor (Infections)					
Yes	**N**	12	11	33	**0.007**
	%	16.2%	42.3%	33%	
No	**N**	62	15	77	
	%	83.8%	57.7%	77%	
Laboratory Data					
WBC Count (Thousands/cmm)					
≤ 15,000	**N**	65	21	86	0.511***
	%	87.8%	80.8%	86%	
>15,000	**N**	9	5	14	
	%	12.2%	19.2%	14.0%	
PLT Count (Thousands/cmm)					
≤500,000	**N**	63	18	81	0.072***
	%	85.1%	69.2%	81.0%	
>500,000	**N**	11	8	19	
	%	14.9	30.8	19.0 %	
ASOT (mg/dl)					
Normal	**N**	48	19	67	0.444*
	%	64.9%	73.1%	67.0%	
High	**N**	26	7	33	
	%	35.1%	26.9%	33%	

Table 2: Comparisons of demographic characteristics and laboratory parameters between patients with and without renal involvement **(Continued)**					
		Renal affection		**Total**	**P Value**
		No (n=74)	**Yes (n=26)**	**(n =100)**	
ESR (mm/hr)					
Normal	**N**	22	6	28	0.516*
	%	29.7%	23.1%	28.0%	
High	**N**	52	20	72	
	%	70.3%	76.9%	72.0%	
Hb (gm/dl)					
Mean (SD)		11.3 (1.4)	11.5 (1.5)		0.558*
Normal	**N**	61	23	84	0.552
	%	82.4%	88.5%	84%	
Low	**N**	13	3	16	
	%	17.6%	11.5%	16%	

SD: Standard deviation, IQR; Interquartile range, PLT; platelets, WBCs; white blood cells, ASOT; Anti streptolysin O titer, ESR; erythrocyte sedimentation rate, Hb; Hemoglobin. * Chi^2 test ** Mann-Whitney U test ***Fisher's exact test

Table 3: Comparison of clinical characteristics between patients with and without renal involvement

Symptoms along the course of the disease			**Renal affection**		**Total (n=100)**	**P-value**
			No (n=74)	**Yes (n=26)**		
Purpura	**Yes**	**N**	72	24	96	0.277**
		%	97.3%	92.3%	96.0%	
	No	**N**	2	2	4	
		%	2.7%	0.7%	4.0%	
GIT (pain)	**Yes**	**N**	49	16	65	0.667*
		%	66.2%	61.5%	65.0%	
	No	**N**	25	10	35	
		%	33.8%	38.5%	35.0%	
Joint (arthritis)	**Yes**	**N**	31	11	42	0.618*
		%	41.9%	42.3%	42.0%	
	No	**N**	43	15	58	
		%	58.1%	57.7%	58.0%	
GIT (bleeding)	**Yes**	**N**	8	7	15	00.060**
		%	10.8%	26.9%	15.0%	
	No	**N**	66	19	85	
		%	89.2%	73.1%	85.0%	
Rare (orchitis)	**Yes**	**N**	1	2	3	0.165**
		%	1.4%	7.7%	3.0%	
	No	**N**	73	24	97	
		%	98.6%	92.3%	97.0%	
Multisystem affection	**Yes**	**N**	27	11	38	0.599*
		%	36.5%	42.3%	38.0%	
	No	**N**	47	15	62	
		%	63.5%	42.3%	62.0%	
Outcome (recurrence)	**Yes**	**N**	21	6	27	0.600*
		%	28.4%	23.1%	27.0%	
	No	**N**	53	20	73	
		%	71.6%	76.9%	73.0%	
Early treatment (steroids only or combined treatment) *	**Yes**	**N**	49	22	71	0.060*
		%	66.2%	84.6	71%	
	No	**N**	25	4	29	
		%	33.8%	15.4	29%	

GIT: Gastrointestinal tract, Recurrence; Rash, joint complaints, GIT complaints, haematuria or a combination of two or more systems, combined treatment; non-steroidal anti-inflammatory drugs & Steroids*Chi^2 test, **Fisher's exact test

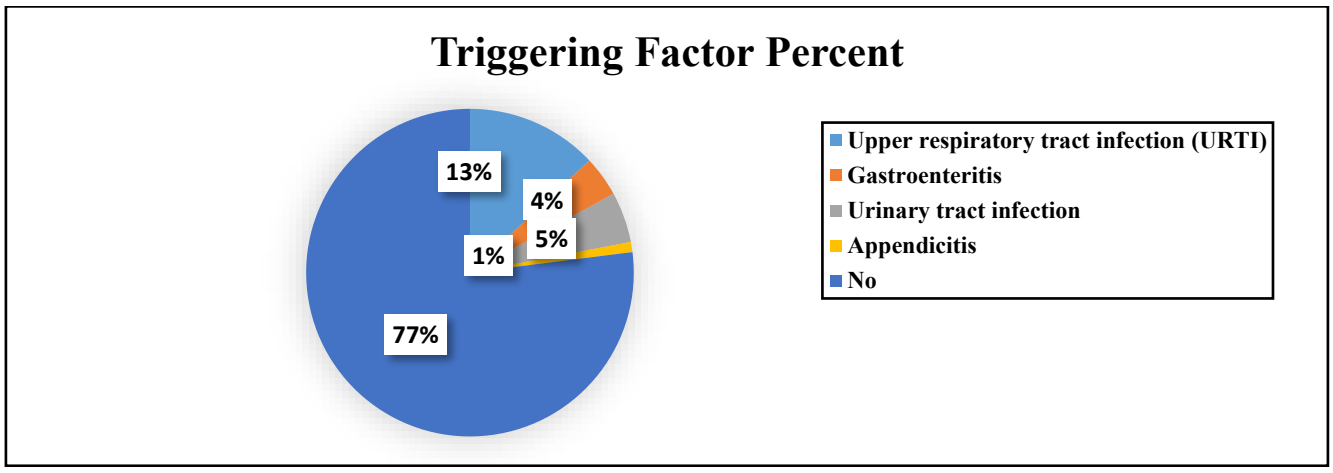

Figure 1: The percentage of different triggering factors among studied cases

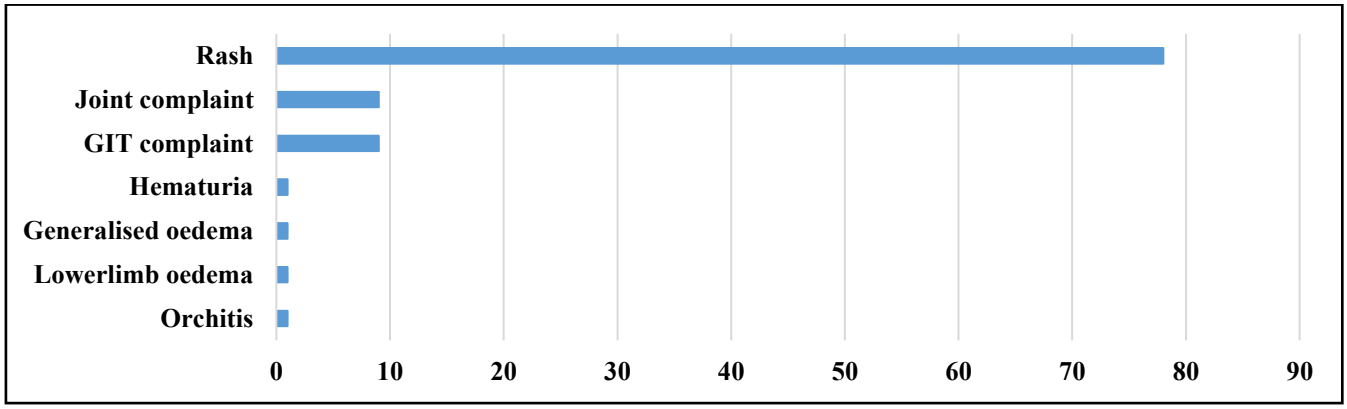

Figure 2: Different initial presentation percentages among the cases studied.

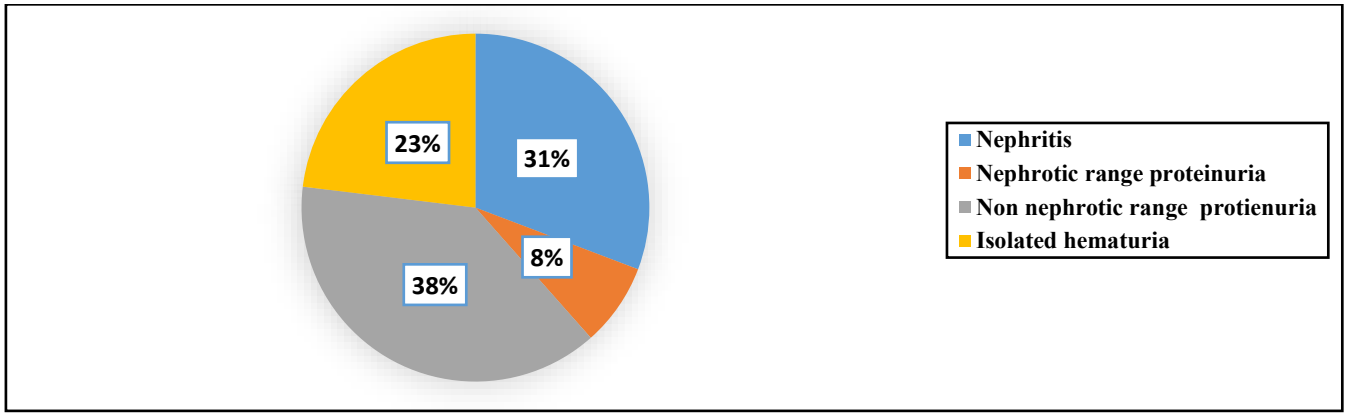

Figure 3: Different Renal Presentations among the renal affection group.

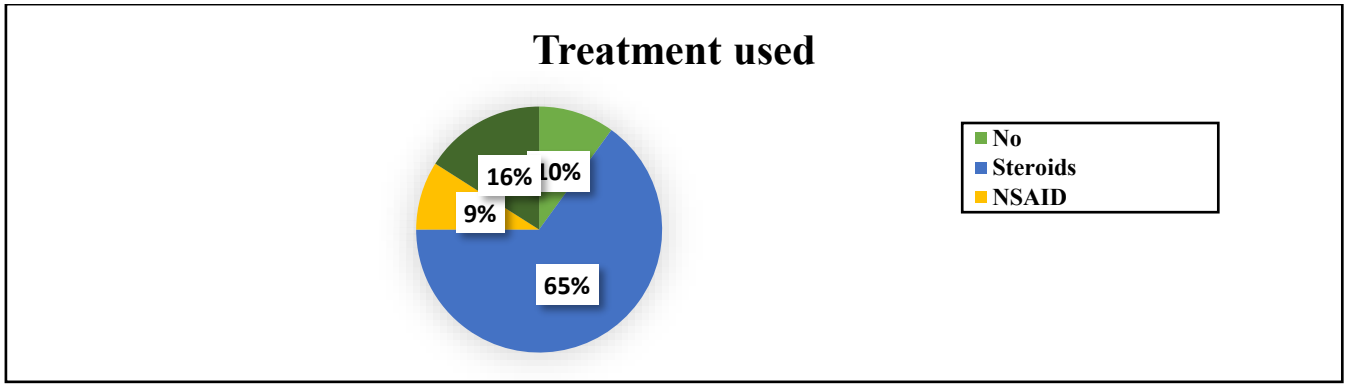

Figure 4: Different treatment lines among the studied group.

In our study, the mean age was 7.81 ± 3.8 years. We identified age as one of the factors associated with Henoch-Schönlein purpura nephritis (HSPN). A higher mean age of 9±3.6 years among patients with renal involvement was detected, similar to another study that revealed that children over 10 years of age were more likely to develop HSPN. [11]. On the contrary, both *Sano et al.* and *Jauhola et al*. concluded that ages older than 4 years and 8 years, respectively, were associated with an increased risk of renal involvement [12] [13]. According to our results, infection as a triggering factor was statistically significantly higher in the renal affection group. *Gonzalez et al*, suggested that upper respiratory tract infection, especially streptococcal infection related to high ASO, precedes HSPN [14].

Furthermore, other studies demonstrated that female patients carried a 3.21-fold greater risk for renal affection. [7] Even though HSPN had more male predilection [11][15]. However, our results did not show a significant connection between HSPN and a particular gender. Additionally, no evidence of a significant relationship between renal involvement and onset during a particular season was found. However, a different study concluded that HSPN frequently occurs in winter and spring [16]. This may be due to HSP being more frequently triggered by upper respiratory tract infections, which are more common during these seasons. According to our data, there is no discernible relationship between renal involvement and residency compared to a different study that postulated that renal involvement might be linked to a rural area's weak economy, lack of medical resources, and inadequate medical understanding, children from rural regions were more likely than those from urban areas to experience it [17].

Clinical presentations could be indicative of the long-term outcome. The risk of long-term renal impairment is low (1.6%) in patients having isolated hematuria or proteinuria but is much higher (19.5%) in cases initially presenting with nephritic or nephrotic syndrome [18]. Our study revealed that 6 patients (23%) had isolated hematuria, 8 (31%) developed nephritis, and proteinuria whether non-nephrotic range (10 cases, 38%) or nephrotic range (2 cases, 8%); however, renal failure was not recorded to have affected any of our patients. These results are comparable to another study conducted by Kiliç et al., who found that 15.1% (n=28) of patients had renal involvement, including hematuria (13 cases) and proteinuria (5 cases); however, neither nephritic, nephritic/nephrotic syndrome, or renal failure were observed [19].

Prior research by *Kim et al.* [7] and *Wang et al.* [17] found no correlation between different clinical symptoms of HSP and the occurrence of renal affection which is in agreement with our results, while other studies suggested that some symptoms such as severe GIT manifestations, persistent purpura, or the occurrence of relapse encountered higher incidence of renal affection in children with HSP [11] [4].

Laboratory tests have also been investigated; however, no significant link was found between any of these values and renal involvement. A meta-analysis found that renal involvement was associated with the following: Total leucocytic count (TLC) >15 × 10^9/L and platelet count >500 × 10^9/L. Also, upper respiratory tract infection, especially streptococcal infection, evidenced by elevated ASOT, precedes HSPN [11].

Recurrence or relapse of the disease is

not a risk factor for renal involvement, according to the results of our study. However, a meta-analysis of 13 studies involving 2,398 children conducted by *Chan et al.* identified 20 potential and 13 significant risk factors for renal involvement in HSP, of which relapse was one[11]. *Wang et al.* further verified that one of the independent risk factors for renal involvement and severe kidney disease in HSP is recurrence [17].

The debatable use of Glucocorticoids for HSP treatment is attributed to the fact that they do not prevent renal affection [20]. Unlike the results of another meta-analysis, which showed that early corticosteroid treatment significantly decreased the incidence of persistent renal disease, our data showed no statistically significant difference between early corticosteroid use and renal involvement [21].

LIMITATIONS OF THE STUDY

Our study has some limitations. The major limitations of this study are its retrospective nature and the fact that we included children during the acute phase of the disease; hence, we might have overlooked the late-onset changes. So, multicenter prospective studies including a larger number of patients are required.

RECOMMENDATIONS

Although HSP is a self-limiting disease, Close follow-up is recommended for HSP patients, especially those with an older age of onset and those with a history of preceding infection.

CONCLUSION

We concluded that HSP is a self-limited disease, and only a small portion may develop renal involvement. Older age at the onset of HSP and infection as a triggering factor might be independent risk factors of renal involvement. In addition, renal involvement in HSP is independent of any other disease symptoms.

ABBREVIATIONS

ASOT	Anti-streptolysin O titer.	**HSP**	Henoch-Schönlein Purpura.
CBC	Complete blood cell count.	**HSPN**	Henoch-Schönlein Purpura nephritis.
ESR	Erythrocyte sedimentation rate.	**IQR**	Inter-quartile range.
EULAR/PRES	European League Against Rheumatism /Pediatric Rheumatology European Society.	**SD**	Standard deviation.
		SPSS	Statistical Package for the Social Sciences.
		TLC	Total leukocytic count.
GIT	Gastrointestinal tract.	**URTI**	Upper respiratory tract infections.

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AUTHORS' CONTRIBUTIONS.

The submitted manuscript is the work of the author & co-author. All authors have contributed to authorship, have read, and approved the manuscript.

H.T Osman and M.M Aziz contributed to the study conception and design.

M.O. Aboudeif and E. F. Eryan performed material preparation, data collection, and analysis.

The first draft of the manuscript was written by Eman F. Eryan and all authors commented on the previous version of the manuscript. All authors read and approved of the final manuscript.

STATEMENTS

Ethical approval and written consent to participate

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of the Research Ethics Committee, Faculty of Medicine, Cairo University and informed written consent was obtained in every case from their legal guardians.

Consent for publication

The contents and material of the manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material

"Not applicable"

Conflict of interest

Non-existing Conflict of interest.

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